Acta Pharmaceutica Sinica B 2025;15(5):2323−2350

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

www.elsevier.com/locate/apsb
www.sciencedirect.com

REVIEW

The neuroscience of cancer: Focus on neuropeptidergic systems

Zikai Dong[a,b], Yongfei Wang[a,b], Weilin Jin[a,b,*]

[a]*Institute of Cancer Neuroscience, Medical Frontier Innovation Research Center, the First Hospital of Lanzhou University, the First Clinical Medical College of Lanzhou University, Lanzhou 730000, China*
[b]*The First Clinical Medical College of Lanzhou University, Lanzhou 730000, China*

Received 3 July 2024; received in revised form 9 December 2024; accepted 3 January 2025

KEY WORDS

Cancer neuroscience;
Drug repurposing;
Comorbidity;
GPCRs;
Neuropeptides;
Targeted therapy;
Tumor microenvironment;
Tumor macroenvironment

Abstract Tumors are complex, highly heterogeneous diseases that place an enormous burden on the world's healthcare systems. Updating understanding of tumor initiation and progression is critical and the current breakthrough lies in cancer neuroscience, which focuses on the crosstalk between neural components and tumors. Neuropeptides are a class of highly potent peptides, that perform the physiological functions of neurotransmitters, neuromodulators, and endocrine hormones. Currently, many studies have shown that many cellular components of the tumor microenvironment express neuropeptides and their receptors and that neuropeptides may play an important role in their cellular communication. In addition, neuropeptides and their receptors affect cancer hallmarks such as proliferation, invasion and metastasis, angiogenesis, immune escape, metabolic reprogramming, and others. More importantly, neuropeptides may also affect some tumor comorbidities such as insomnia, depression, anorexia, cancer pain, and others. Targeting neuropeptides in combination with new therapeutic strategies may significantly advance anti-tumor therapy, not only for treating the tumor itself but also for improving the patient's quality of life.

*Corresponding author.
E-mail address: ldyy_jinwl@lzu.edu.cn (Weilin Jin).

Peer review under the responsibility of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences.

https://doi.org/10.1016/j.apsb.2025.03.025

1. Introduction

Cancer remains intractable due to its complex pathogenesis and highly plastic progression, which places a significant economic and social burden[1]. Researchers make plenty of effort to handle this dilemma. One of the advances has been updating knowledge about tumor development and progression: we are becoming aware that the nervous system significantly impacts tumors[2]. High intratumoral nerve density correlates with worse outcomes in some solid tumors such as prostate cancer, head and neck cancer, pancreatic cancer, and breast cancer[3−6]. The crosstalk between cancer and nerves, termed cancer neuroscience, attracts researchers. Recently, Borniger[7] summarized corresponding fields comprehensively and proposed an innovative mode of their interaction. It is believed that the nervous system plays an important role in the sensation of tumors and the integration of cancer-related signals. Finally, the nervous system reciprocally influences systemic physiology relevant to cancer. Tumors, as homeostatic challenges, also affect and even reshape the nervous system. This process is based on the action of signaling molecules. For example, tumors could secrete several cellular factors such as nerve growth, brain-derived neurotrophic factors, glial cell-derived neurotrophic factors, and several guidance molecules to promote axonogenesis and innervation[8−11]. In turn, intratumoral nerves could release neurotransmitters, neuropeptides, neural hormones, and other substances to promote cancer progression. Researchers have now had some success in understanding the effects of neurotransmitters on tumors[12]. As for neuropeptides, due to their sheer number and complexity, they still need to be deeply studied.

Sufficient evidence exists to show that peptidergic innervation exists in tumors. For example, Neuropeptide Y (NPY)-immunoreactive nerves can be observed in colorectal cancer, renal cell carcinomas, nephroblastoma, and adrenal cortical tumors[13−15]. Tumors also express neuropeptide receptors on their surface or even secrete neuropeptides in an autocrine means. Accumulating evidence supports that activation of neuropeptide receptors can significantly affect cancer behavior. They participate in tumor proliferation, immunoregulation, invasion, metastasis, and angiogenesis, and somehow influence cancer-related microbiomes, *via* paracrine, autocrine, and endocrine means, which is context-dependent[16]. The complicated functions they play in tumor development have troubled researchers to a great extent. How to understand the paradoxical role of neuropeptides is likewise a challenge. In that case, in the so-called tumor macroenvironment, neuropeptides may play a broader role as signaling molecules, influencing the progression of the tumor disease alone and participating in the development of tumor comorbidities. Solid evidence supports that the dyshomeostasis of neuropeptides leads to the aberrant situation of the whole body, resulting from the significant roles of neuropeptides in the homeostatic regulation of physiological functions.

Considering the important role of neuropeptide signaling, targeting the neuropeptide system may be one of the important manners of tumor therapy. An interesting direction could be the repurposing of these compounds to target neuropeptide receptors. It has been shown that aprepitant, an antagonist of the neurokinin-1 receptor (NK1R), significantly hinders tumor development[17]. In this review, we provide a detailed summary of how peptidergic nerves communicate with tumors and the sophisticated mechanisms by which neuropeptides regulate cancer progression and cancer comorbidities. We also present some discussion on the therapeutic promise of neuropeptides and their receptors, especially their importance in targeted therapies.

2. Characteristics of neuropeptides and their receptor

We can term a molecule a neuropeptide when it fulfills the following characteristics: (1) It's a small peptide molecule. (2) It's produced and secreted by neurons or works on neurons. (3) It plays a role in the regulation of the nervous system, serving as neurotransmitters or hormones[18]. According to traditional beliefs, neuropeptides are the class of signaling molecules like the classical neurotransmitters to mediate the communication among neurons, glial cells, and peripheral cells[19]. But compared with the classic ones, neuropeptides could long-lastingly mediate neural processing. As concepts have evolved, many peptides are not synthesized by neurons that are also classified as neuropeptides because they could also regulate activities of the central nervous system. In a later section, we will briefly describe the synthesis, secretion, classification, and function of neuropeptides, as well as some other features, especially those that significantly differ from neurotransmitters.

2.1. *Synthesis, secretion, and deactivation*

Typically, neuropeptides range in size from about 3 to 100 amino acids, and about 75% of neuropeptides are no larger than 30 amino acids. Unlike monoamine neurotransmitters which are mainly derived from multiple chemical modifications of amines, the synthesis of neuropeptides travels a longer travel. The synthesis is generally divided into two steps: precursor peptide synthesis and mature peptide modification. Precursor peptides undergo a series of processes in the endoplasmic reticulum, including shearing, phosphorylation, acetylation, and sulphation to produce mature peptides. A case in point is proopiomelanocortin (POMC)-derived peptide. POMC, a precursor polypeptide, carries the amino acid sequences of many small polypeptides, such as adrenocorticotropic hormone, endogenous opioid β-endorphin, and melanocyte-stimulating hormone (MSH)[20,21]. The capacity of POMC to synthesize a multitude of neuropeptides or hormones is a consequence of the actions of various enzymes, such as prohormone convertase 1/2/3, and carboxypeptidase E[22].

Neuropeptides are stored in large dense-core vesicles (LDVs) in nerve endings, in contrast with classical neurotransmitters stored in small synaptic vesicles. However, most of the neurons contain both two vesicles. This phenomenon is called the co-existence of neuropeptides and small-molecule neurotransmitters which was first observed by Vincent et al[23]. The existence of this condition lies in the diversity of rich neurotransmitter regulation. Compared with small synaptic vesicles, LDVs will only be released at higher firing rates. So, when a presynaptic neuron is firing at a low frequency, only the neurotransmitter will be released. While it's overexcited, both neuropeptides and neurotransmitters will be secreted into the synaptic cleft and subsequently bind to their receptors on postsynaptic neurons. In this situation, neuropeptides could regulate the drastic effect made by neurotransmitters.

The mechanism of deactivation also differs between the classic neurotransmitters and neuropeptides. Neurotransmitters such as norepinephrine (NE) and dopamine (DA), are deactivated by specific enzymes and by reuptake into the presynaptic terminal. As for neuropeptides, presynaptic neurons rarely reuptake them, and they are frequently degraded by specific peptidase enzymes.

2.2. *Classification of neuropeptides and receptors*

To date, there are nearly 2500 kinds of vertebrate neuropeptides recorded by various databases[24]. Due to the large number of

neuropeptides, it is difficult to classify them into different families using an individual taxonomic approach. Currently, neuropeptides are categorized into small or large families based on genetic similarity, molecular similarity, functional similarity, or homology to the site of production[25]. According to Hökfelt et al.[26], some of the long-length established families so far include the hypothalamic hormones, hypothalamic releasing and inhibiting hormones, tachykinins family, opioid peptides family, NPY and related peptides family, VIP-glucagon family, and others. The current categorization is tedious and cumbersome, and it is worth considering whether there is a more sensible means.

In general, neuropeptides bind to their corresponding receptors to exert their functions, most of which are G-protein coupled receptors (GPCRs). Based on structural and functional characteristics, the large number of GPCRs can be roughly grouped into the following families: class A, class B, class C, and class F[27]. Class A GPCRs, also termed the rhodopsin-like family, are the most abundant and studied superfamily[28]. Opioid receptors, somatostatin receptors, galanin receptors, bombesin receptors, and others all belong to the class A family. Class B GPCRs can be further subdivided into secretin (B1), with a large extracellular structural domain, and adhesive (B2), with a unique long N-terminal motif and an autoproteolytic-inducing structural domain[29]. Class B family contains fewer receptors than class A, including vasoactive intestinal peptide (VIP) receptors, calcitonin receptors, and the other eleven receptors. As for the class C family, the glutamate family consists of γ-aminobutyric acid B receptors, calcium-sensing receptors, metabotropic glutamate receptors, sweet and amino acid taste receptors, and serval orphan receptors[30]. Class C family has some unique features distinguished from others. First, despite the universal structure of GPCRs, the class C family has an extracellular domain that comprises a Venus flytrap module and a cysteine-rich domain[31]. The large extracellular domain contains the orthostatic binding site for ligands, while in the 7TM region, only allosteric binding sites are found. The fact that they function only as homodimers or heterodimers is another unique feature of the class C family[31]. To date, there are no known neuropeptide receptors that belong to this family. Class F GPCRs are composed of 10 frizzled receptors and one smoothened receptor, distinguished by shared CRD regions and engagement in the Wnt and Hedgehog signaling pathways[32]. Of course, there are no neuropeptide receptors belonging to this family. As the research progressed, a new family of GPCRs, class F, was identified, consisting mainly of taste 2 receptors. It was isolated because its sequence similarity to the existing family was less than 20%[27].

Despite the large number of GPCRs and the complexity of their classification, they share a similar core structure: seven transmembrane α-helices that weave in and out of the membrane. Upon binding to corresponding ligands, the GPCR exposes intracellular sites that interact with the G protein heterotrimer containing the α, β, and γ subunits[33]. It catalyzes the detachment of GDP attached to the Gα subunit and its displacement by GTP, thus causing the dissociation of Gα from the G$\beta\gamma$ subunit. The Gα and G$\beta\gamma$ subunits complex subsequently stimulate several downstream effectors and finally lead to signaling cascades. It's believed that neuropeptides and their counter GPCRs are involved in various biological activities in both normal physiological and pathological conditions.

2.3. *Signaling pathways of neuropeptide receptors*

Neuropeptides not only serve as neurotransmitters but also hormones, exerting plenty of functions such as cell survival, proliferation, secretion, and motility. These functions are based on complex signal transduction mediated by neuropeptide receptor activation (Fig. 1).

Serval neuropeptide receptors are coupled to the Gα_q subunit, leading to the activation of phospholipase C, which mainly sociates calcium elevation and protein kinase C (PKC) activation. PKC subsequently promotes phosphorylation of serine/threonine proteins[34].

A greater number of neuropeptide receptors are coupled to Gα_s subunit, whose activation subsequently stimulates adenylyl cyclase (AC) synthesis of cyclic adenosine monophosphate (cAMP). The transitory cAMP flux could regulate numerous cellular processes *via* two major downstream machinery: protein kinase A (PKA) and guanine nucleotide exchange protein activated by adenylyl cyclase (EPAC)[35,36]. PKA, a tetrameric enzyme, could phosphorylate the serine and threonine in substrates[37]. For example, PKA could phosphorylate calmodulin-dependent protein kinase kinase-2 (CAMKK2) and subsequently inactivate it, whose functions mainly link to energy hemostasis[38]. The more important function of PKA is to phosphorylate transcription factors such as the cAMP response element binding protein/activating transcription factor (CREB/ATF) family. Activated CREB and ATF1 could attach to the cAMP response element (CRE) present in the promoter region of target genes and trigger transcription[39].

cAMP could also bind to the cAMP-nucleotide binding-B domain (CNBD-B) on EPAC and lead to a conformational shift releasing the autoinhibition and exposing Cdc25-HD for the RasF-like guanine triphosphatase (Rap). Rap in turn stimulates downstream effectors such as V-Raf murine sarcoma viral oncogene homolog B1, mitogen-activated protein kinase 1 and 2 (MEK1/2), and mitogen-activated protein kinase/extracellular signal-regulated kinase 1 and 2 (ERK1/2), which is mainly associated with cell growth and proliferation[40]. The combination of ligands for several neuropeptide receptors leads to the activation of Rho proteins and further regulates the arrangement of the actin cytoskeleton, which in turn affects cell morphology, cell motility, and intercellular interactions[41]. Other types of research also confirm the gene expression regulatory functions of Rho GTPase, including the c-Fos and c-Jun oncoproteins, the serum response factor, and NFκB[42]. Current research suggests that the Rho pathway is implicated in various aspects of tumor progression, particularly behaviors related to cell motility such as invasion and metastasis[43]. Similarly, there are neuropeptide receptors coupled to α_i that act primarily by inhibiting cAMP synthesis.

When we stand at the point of the whole body, neuropeptides not only serve the role of neurotransmitters and hormones, but they can also act as signal molecules to participate in the balance of the body's homeostasis.

2.4. *Functions of neuropeptidergic system*

Neuropeptides play the following roles in human physiological activities: (1) neurotransmitters, which are involved in signaling between neurons in the central nervous system; (2) neuromodulators, which indirectly regulate the release of transmitters from synaptic endings to increase or decrease their effect in transmitting information; (3) neuroendocrine hormones, which act as signaling molecules to communicate between the central nervous system and peripheral organs, and widely regulate the physiological functions of the organism. Ultimately, neuropeptide is a signaling molecule and, due to its closed loop, the information it transmits is not unidirectional. Neuropeptides can likewise be used

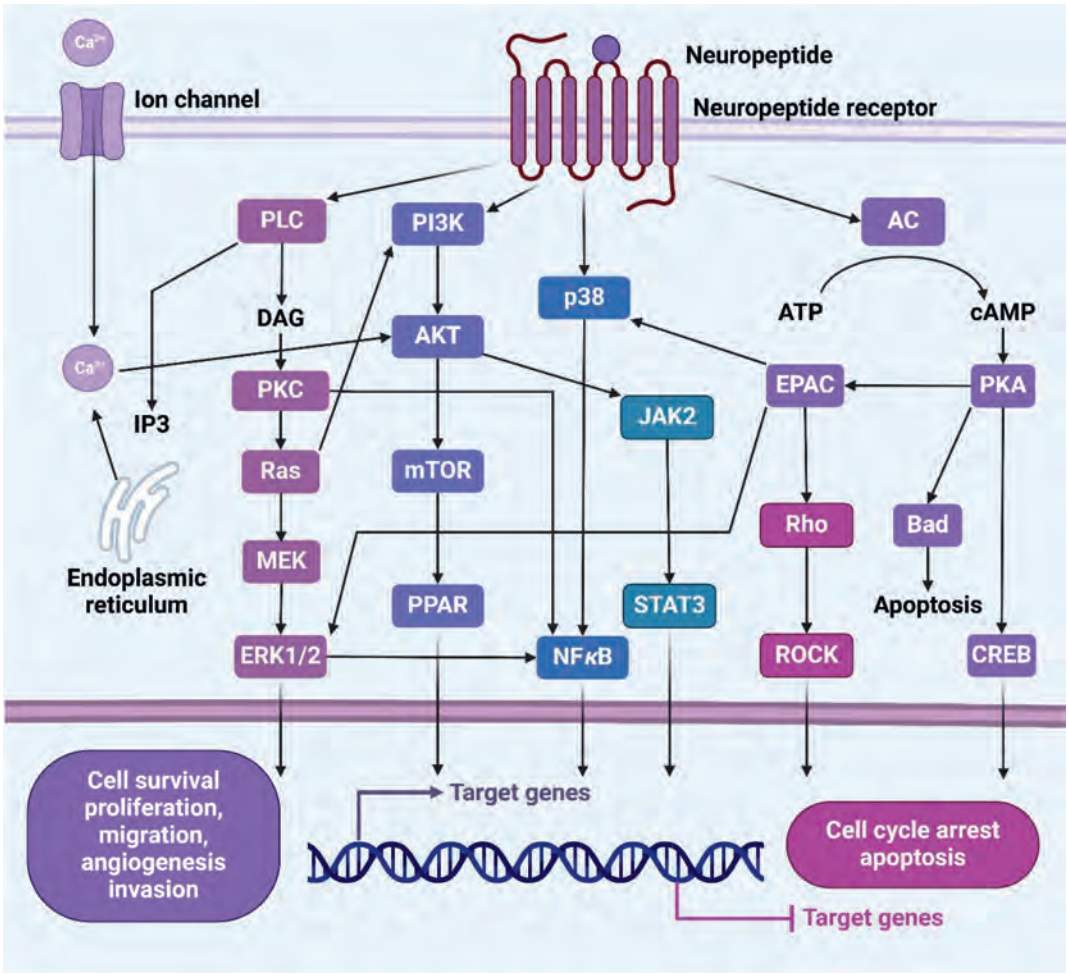

Figure 1 Signaling pathways transduced by neuropeptide receptors. The prime signaling pathways are activated by neuropeptides and the corresponding receptors involved in cellular behaviors. Activation of neuropeptide receptors regulates the production of the second messengers such as cAMP, DAG, IP3, and Ca^{2+}, which subsequently activate several cytokines and induce gene regulation. PKA/CREB, Ras/MEK, PI3K/AKT, NFκB, and intracellular Ca^{2+} are considered in cell survival, proliferation, drug resistance, and apoptosis. Rho/ROCK are involved in cell motility and metastasis. JAK/STAT pathways are also involved in metastasis and angiogenesis. Abnormal levels of neuropeptides may stimulate or inhibit these cascades, inducing aberrant cellular behaviors. This figure was created using BioRender (https://biorender.com/).

as signals from peripheral organs to eventually enter the brain through the blood−brain barrier (BBB) and influence brain function. In what follows we will take some examples to demonstrate the effects of the neuropeptide system on several physiological functions, with an emphasis on multi-organ communication.

Food intake is a vital and complex behavior that is regulated by various neuropeptides. So, it will be a good example to clarify the neuropeptide's mode of action. Research confirms that two main neuropeptide systems are involved in the control of food intake: NPY and POMC, the former exerting a strong orexigenic effect and the latter counteracting it[44]. Arcuate nucleus (ARC) is the region most crucial to the control of feeding and energy balance and there are vast NPY and POMC neurons located in it. NPY from the ARC neurons stimulates the feeding process and reduces energy expenditure in the following ways: (1). NPY acts straightly on postsynaptic Y1R expressed on adjacent POMC neurons and inhibits their functions; (2) NPY acts on a different set of postsynaptic Y1R and Y5R-expressing neurons located in PVH and promotes their neural activity; (3) GABA and AgRP, co-released neurotransmitters of NPY, could also inhibit activation of POMC neurons. NPY neurons are projected to plentiful nuclei such as the bed nucleus of the stria terminalis, dorsomedial hypothalamic nucleus, and lateral septal nucleus and induce their neural activities[45]. More importantly, melanocortin receptor agonist shows no subsequent influence on the electrical activities of NPY neurons, suggesting the dominance of NPY neurons in feeding regulation[46]. What's more, these NPY neurons are highly controlled by various peripheral factors including ghrelin, leptin, insulin, peptide YY, glucagon-like peptides, and others, most of which are neuropeptides[45].

Neuropeptides are involved in the gut−brain axis, referring to the bidirectional communication between the gut and brain[47]. The gut hormones PYY and PP and the enteric neuropeptide NPY regulate digestion[48]. Meanwhile, gut microbiota could influence the gut−brain axis *via* NPY and PPY[49]. Neuropeptides also play an important role in other physiological activities such as sleep, cognition, cardiovascular activity, and chronic inflammation, which we will discuss in more detail in the following section on tumor comorbidities[47,50−53].

Another important but long-time ignored function of neuropeptides is the trophic effect. Some neuropeptides were initially

noted in the central nervous system only during embryonic life, suggesting a developmental stimulus. VIP has been shown to affect growth throughout the embryo, mainly because of its ability to shorten the G1 and S phases of the neuronal cell cycle[54]. NPY could exert a trophic effect on cardiomyocytes characterized as a reduced degradation of protein and stimulation of protein synthesis[55]. Gastrin is also considered to exert trophic effects reflexing as control of gastric mucosal thickness and stimulation of some gastric cancer[56].

It is clear from the above that the neuropeptide system is a multi-functional and highly regulated signaling system, so it is worth exploring how it is altered in the case of tumor-bearing and how this affects cancer. Solid evidence supports the multifaceted functions of neuropeptides in cancer progression (Table 1)[57−80].

3. Neuropeptidergic signals influence TME

Neuropeptides contribute to cancer progression, serving as hormones to promote their proliferation or serving as hemostasis challengers against anti-tumor effects. Plenty of *in vitro* and *in vivo* experiments confirm this view. Their effect on tumors may be achieved by remodeling the tumor microenvironment (TME).

Neuropeptides influence tumors through several mechanisms, which can be categorized into three primary modalities (Fig. 2): (1) paracrine: in this mode, neuropeptides are predominantly released by interneurons and interact with specific receptors on tumor cells, thereby influencing their behavior; (2) autocrine: certain tumor cells, notably those neuroendocrine tumors (NETs) or neuroendocrine carcinomas (NEC), secrete neuropeptides that act in a paracrine fashion, suggesting a self-stimulatory role in tumor progression; (3) endocrine: neuropeptides originating from the hypothalamic−pituitary axis can traverse the circulatory system, reaching the TME and modulating its characteristics and functionality. What's more, neuropeptides, despite their origin, could also act on other non-malignant cells in TME, thereby reshaping the environment and contributing to cancer progression (Fig. 2).

3.1. Cancer stem cells

Cancer stem cell (CSC) is a minor subpopulation of non-dividing cells in neoplastic tissues, with strong self-renewal and tumorigenic potential. Succinctly, CSCs refer to a population of tumor-initiating and treatment-refractory cell populations[81,82]. An important facet of CSC studies has focused on cell−extrinsic interactions with the ambient TME. It depends on several bidirectional cellular mechanisms, such as cell-to-cell contact and ligand−receptor interactions, to drive tumor growth. When we start thinking in the context of normal physiology, nerves are tightly regulated for cell stemness. They are also considered an essential component of the human stem cell niche[83]. It is worth discussing the influence of infiltrating peptidergic neurons and neuropeptides on CSC.

Various neuropeptides are associated with cancer stem cells. Adrenomedullin (ADM) is a vasopressor and vasodilator neuropeptide, a member of the calcitonin gene-related peptide family, which binds to calcitonin receptor-like receptor (CALCRL) to exert its functions[84]. Recent studies confirm the crucial roles of ADM and CALCRL for sustaining leukemia stem cells (LSCs) in acute myeloid leukemia[85]. CALCRL is diffusely distributed in LSCs and its high expression correlates to adverse outcomes in AML. What's more, CALCRL knockdown will significantly impair leukemic growth, impair colony formation, decrease LSC frequency, and enhance the potency of chemotherapeutic agents toward AML[85,86]. Other studies also confirm that the expression of *ADM* in AML is associated with a stem phenotype, inflammatory markers, and immunosuppressive genes[87]. So it's pretty clear that the ADM system is tightly associated with leukemia stem cells but right now all knowledge is fragmented. We could not picture a clear landscape from how adrenomedullin-releasing nerves interact with leukemia and their bidirectional interactions are worthy of exploring. Endothelin (ET) and its coupled receptor-endothelin receptor (ETR) are also involved in the regulation of chemotherapy resistance of cancer stem cells[88]. Macitentan, a kind of antagonist for ETR, reduced cell growth in cell lines with $CD133^{+}$ CSC[88]. Whereas, endothelin-converting enzyme-1 (ECE1), which is essential for activation of ET, is also considered as the important and independent regulator for CSC. Researches confirm casein kinase 2 could induce phosphorylation of ECE1 and enhance its stability. ECE1 finally promotes CSC characteristics, including elevated expression of the stemness gene, chemo-resistance, self-renewal, colony, and spheroid formation[89].

Neuropeptides could also be important signal molecules between the communication of cancer stem cells and other TME components. The community accepts that adipocytes contribute to cancer initiation and progression, but the concrete molecular mechanism remains to be ill-defined[90]. Recent researches confirm that adipocytes promote the enrichment of prostate CSCs through a cycle of autocrine amplification[91]. The ability of adipocytes to secrete cathepsin B (CTSB) promotes the autocrine secretion of cholecystokinin (CCK) by tumor cells. CCK secreted by tumor cells serves two purposes: when binds to adipocytes, it further promotes the secretion of CTSB, which ultimately enhances the autocrine secretion of CCK; and when applied to tumor cells, CCK contributes to the maintenance of stemness and self-renewal[91].

3.2. Immune cells

The role of the nervous system in regulating the immune cells and immune system has long been recognized. Solid evidence also supports neuropeptides could directly regulate immune cells. For example, substance P (SP) and its corresponding receptor NK1R are universally expressed in the immune microenvironment. SP regulates immune cells and immune responses at diverse levels, from immune-cell recruitment to modulation[92].

Neuropeptides regulate immune cell migration and recruitment mainly by influencing the expression of chemokines, and adhesion molecules. For instance, SP could induce the production of chemokines, such as monocyte chemoattractant protein-1, macrophage inflammatory proteins, and interleukin-8 (IL-8)[93−96]. High concentrations of these chemokines lead to migration and recruitment of lymphocytes and monocytes. Activation of NK1R increases dendritic cell expression of the chemokine receptor CCR7, and of the adhesion molecule macrophage-1 antigen and its ligand ICAM-1[97−99]. This facilitates the targeting of these cells to lymph nodes.

Neuropeptides also contribute to immune cell proliferation. Anatomy shows that peptidergic nerves innervate the bone marrow, leading to a high concentration of SP. Lately, SP binds to NK1R on bone marrow stroma to induce interleukin-1 (IL-1) and stem cell factor[100]. Other research confirms SP could enhance bone marrow stromal stem cell proliferation *via* the WNT signaling pathway[101]. SP could stimulate T cell proliferation *via* the upregulation of interleukin-2 (IL-2)[102]. *In vivo* study shows

Table 1 Family of neuropeptides and their role in cancer progression.

Neuropeptides family	Corresponding receptors	Expression in cancer	Functions in cancer	Action modes	Signaling pathways	Ref.
Adrenomedullin Calcitonin Amylin Calcitonin-related polypeptide	Calcitonin receptor (CTR) Calcitonin receptor-like receptor (CLR) Receptor activity-modifying proteins (RAMP)	Insulinoma, pancreatic adenocarcinoma, gastric cancer, colorectal cancer, medullary thyroid cancer, prostate cancer	Cell proliferation, metastasis, cell migration	Promotion/suppression of cancer growth through autocrine and paracrine mechanisms and possibly through endocrine mechanism	MAPK/ERK PI3K/Akt	58–62
Neuropeptide Y Peptide YY Pancreatic polypeptide	Y1R Y2R Y4R Y5R	Glioma, glioblastoma, hemangioblastomas, breast cancer, cholangiocarcinoma, colorectal cancer, esophageal cancer, ewing sarcoma, gastric cancer, hemangioma, head and neck cancer, leukemia, liver cancer, lung cancer, melanoma, neuroblastoma, ovarian cancer, pancreatic cancer, parathyroid adenoma, pheochromocytoma, pituitary adenoma, prostate cancer		Promotion/suppression of cancer growth through autocrine and paracrine mechanisms	MAPK/ERK, PI3K/Akt	63–72
Enkephalins Endorphins Dynorphins	μ Opioid receptor (MOR) δ Opioid receptor, (DOR) κ Opioid receptor (KOR) Nociceptin/orphanin FQ peptide receptor (NOPR)	Ganglioglioma, glioma, meningioma, breast cancer, cervical cancer, colorectal cancer, cutaneous squamous cell carcinoma, gastric cancer, head and neck cancer, leukemia, liver cancer, lung cancer, melanoma, myeloma, neuroblastoma, ovarian cancer, pancreatic cancer, pheochromocytoma, pituitary cancer, prostate cancer, renal cancer	Apoptosis, cell growth, cell migration, cell permeability, angiogenesis, immunosuppression	Stimulation/inhibition cancer progression through autocrine, paracrine, endocrine, and exocrine	MAPK/ERK AC/CREB NFκB P38/JNK/STAT	73–76
Substance P Neurokinin A Neurokinin B	Neurokinin receptor-1 (NK1R) Neurokinin receptor-2 (NK2R) Neurokinin receptor-3 (NK3R)	Breast cancer, ovarian cancer, pancreatic cancer, thyroid cancer, prostate cancer, glioblastoma, and astrocytoma	Cell proliferation, antiapoptosis, angiogenesis, mitogenesis, metastasis	Promotion of cancer development through autocrine, paracrine, endocrine pathways, or peripheral nervous system	MAPK/ERK AC/CREB NFκB P38/JNK/STAT3	77–81

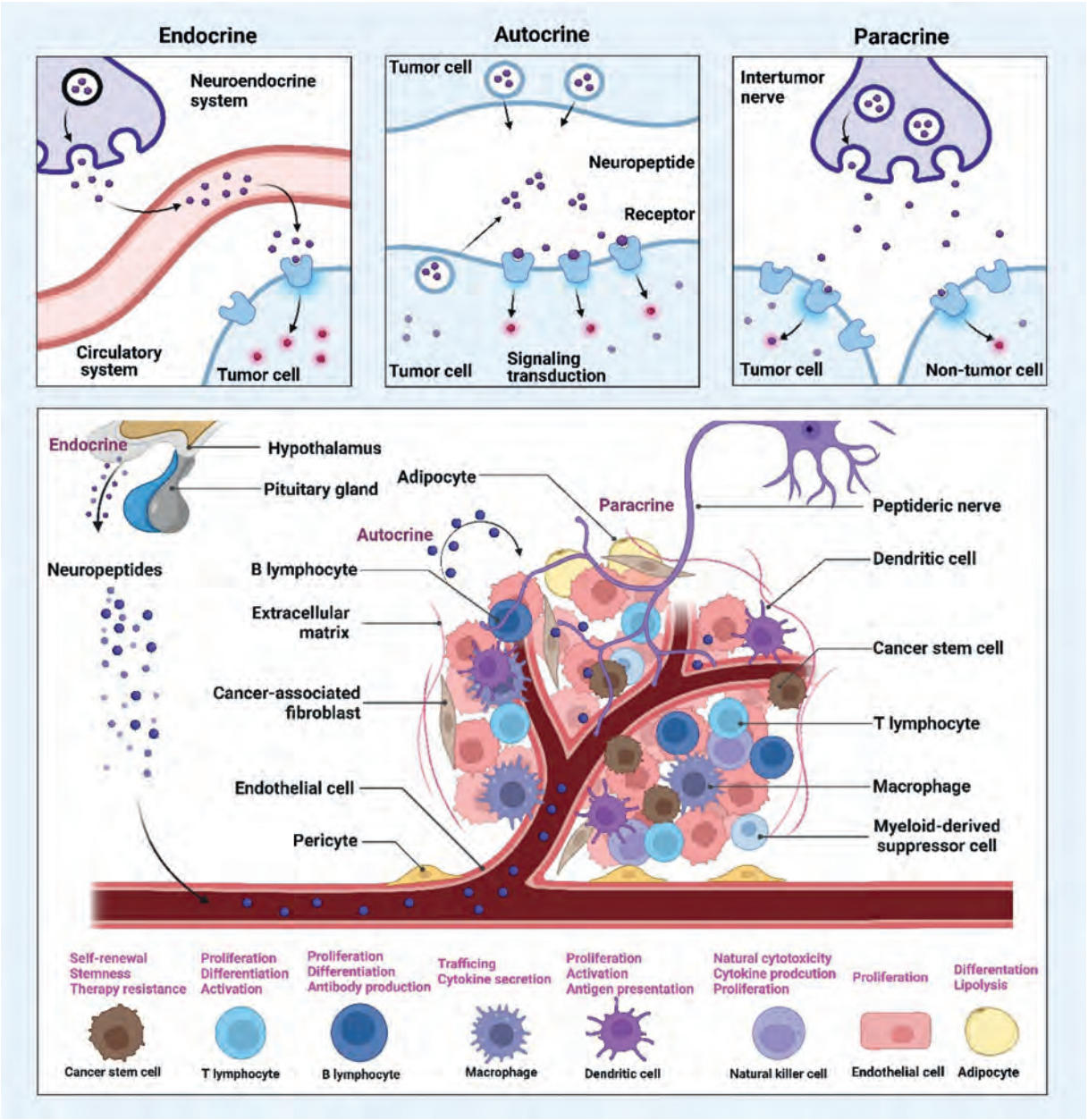

Figure 2 Neuropeptides reshape tumor microenvironment. Considering the universal expression of neuropeptide and their receptors in cellular components in TME, their regulatory functions should not be ignored. Neuropeptides may regulate these cells *via* three main means: (1) Endocrine, neuropeptides derived from other organs enter the circulating system and finally reach TME; (2) Autocrine, tumor cells can even release neuropeptides by themselves, leading to a positive feedback loop; (3) Paracrine, intratumor peptidergic nerves release neuropeptides to TME adjacently and regulate corresponding activities, whose processes are in turn regulated by other cells and their productions. Generally, neuropeptides mainly regulate the proliferation, differentiation, mobility, and specific functions of these cells. This figure was created using BioRender (https://biorender.com/).

that genetic deletion of NK1R will decrease the proliferative response of T cells[103].

Moreover, neuropeptides modulate innate immune cells' activity *via* numerous intracellular pathways. By upregulating the generation of cytotoxic-associated molecules and natural cytotoxicity receptors, SP improves the cytotoxicity of natural killer cells[104]. SP may also enhance the phagocytic activity of neutrophils and macrophages through the production of reactive oxygen intermediates (ROI) and the synthesis and release of arachidonic acid metabolites[105–108]. In mast cells, SP could trigger histamine and serotonin degranulation and release, and upregulate Toll-like receptor-2[109,110].

Neuropeptides also play a vital role in the modulation of adaptive immune cells. SP could enhance immunoglobulin secretion of B cells. Depletion of SP in mouse model by capsaicin and treatment with SP antagonist significantly decrease the number of antibody-secreting cells[111]. Neuropeptides could regulate T cell activation and helper T cell differentiations. *Via* binding to NK1R on DCs, SP can induce a Th1 and T cytotoxic (CTL)-1 bias of effector T cells in mice[112]. SP binds to NK1R on T cells and induces the production of

IFN-γ, a Th1 signature cytokine. At the same time, it does not affect the secretion of Th2 cytokines, such as IL-4 and IL-5[113]. VIP also participates in the regulation of the Th1/Th2 balance: VIP reduces IL-12 secretion and inhibits T-bet expression, thereby reducing differentiation into Th1 cells[114]. Simultaneously, VIP promotes the expression of c-MAF, GATA-3, and JUNB, which are key regulators of Th2 cells, inhibits CXCL10, and induces the expression of CCL22, which promotes Th2 cell differentiation and recruitment to inflammatory sites[115]. Another research also confirms RAMP3 has potent effects on Th differentiation. RAMP3 signaling restricted the differentiation of Th2; however, promoted Th1 cell differentiation by inducing the expression STAT1, the key regulator of the related process[116]. Considering the balance between Th1 and other types of Th cells is critical for anti-tumor response, intervention of related neuropeptide signaling may facilitate the enhancement of antitumor immunity.

The wide distribution of neuropeptides and their receptors under physiological conditions and their close relationship with the etiology, pathogenesis, or possible treatment of immune-mediated diseases have revealed them as important parts in the field of neuroimmunomodulation. In the subsequent sections, we will discuss how neuropeptide signaling reshaped the immune microenvironment under tumor-nearing situations.

3.3. *Endothelial cells and other stromal cells*

Researches confirm neuropeptides contribute to the functional regulation of endothelial cells in TME. ETs are a family of three 21-aa peptides, mediating their action by activation of Endothelin receptor A and Endothelin receptor B, which has been confirmed to influence tumor-associated endothelial cells and matrix cells. ETs could serve as mitogens and angiogenic factors. ETs regulate multiple angiogenesis processes, including endothelial cell proliferation, migration, tube formation, and vessel renewal[117]. Upregulated expression of ETs and their cognate receptors is significantly associated with microvessel density and vascular endothelial growth factor (VEGF) expression in tumor tissues. At the level of RNA, ETs will increase *VEGF* mRNA expression in a time- and dose-dependent manner. Further studies also prove that ETs could induce the release of endothelial microvessels, subsequently influencing cellular inflammation, apoptosis, and endothelial nitric oxide synthase[118].

Neuropeptides also affect some other stromal cells. For example, NPY also contributes to adipocyte differentiation and activation[119]. The browning of white adipose tissue is controlled by hypothalamic NPY neurons, what's more, white adipose tissue could also be an important source for NPY secretion[119]. Leptin, an energy-regulated peptide, is mainly produced in white adipose tissue and seldom released from the hypothalamus[120,121]. Several studies have proven that leptin directly influences lipogenesis, lipolysis, and metabolism of adipocytes[122,123]. It also exerts indirect effects through the modification of insulin action[124]. As for fibroblasts, several neuropeptides participate in the regulation of their proliferation.

In addition to these cellular components mentioned above, neuropeptides have a more pronounced effect on the tumor itself, correlating with cancer hallmarks, and the remodeling of the TME by neuropeptides underpins their influence on tumor behaviors.

4. Neuropeptide systems influence cancer hallmarks

The cancer hallmarks present a theoretical framework that provides long-lasting support for rationalizing the vast complexity of cancers and their mechanisms of occurrence. Here, we will consider several examples illustrating how neuropeptide systems influence the hallmarks (Fig. 3).

4.1. *Cancer proliferation*

Cells rely on mitogenic growth signals to switch from dormant to active proliferative states[125]. These signaling molecules bind to certain receptors, subsequently regulating the cell's proliferation behavior. The growth signals received by normal tissues are tightly controlled, no matter by whatever means. However, tumors spontaneously generate signaling molecules and overexpress the corresponding receptors, thereby maintaining a prolonged proliferative state, termed autocrine signaling[126]. As mentioned earlier, neuropeptidergic signaling shows great trophic effects. Therefore, it is not surprising that they can also influence tumor proliferation.

Taking bombesin (BBS) as an example, back in 1985, Cuttitta et al.[127] confirmed that BBS and gastrin-releasing peptide could act as autocrine growth factors in human small-cell lung cancer *via* bombesin receptor (BnR). From molecular levels, BBS caused a significant increase in Sonic Hedgehog gene transcription and protein secretion[128]. Activation of BnR could also transactivate the EGFR/HER family and its downstream signaling cascades[129]. A similar phenomenon was observed in breast cancer. Researchers confirmed SP could induce phosphorylation of HER2 Tyr1248[130]. SP treatment also induced elevation of HER-2, contributing to its overexpression[130]. BBS could also act as an autocrine growth factor in some medullary thyroid, pancreatic, gastric, colorectal, and breast cancer lines[131]. Apart from this, tumor cells can influence the release of neuropeptides by other components in the TME, thereby regulating tumor proliferation through paracrine signaling. Glioblastoma showed high expression of Y2R and researchers also observed increased intratumoral nerve fibers contained NPY by immunohistochemistry[132]. The neuron-derived NPY would finally enhance tumor proliferation.

Neuropeptides do not always exhibit a tumor-promoting effect. For example, research has shown that NPY can inhibit the proliferation and invasion of cholangiocarcinoma and the administration of NPY receptor antagonists can block the inhibitory effect[133]. Somatostatin (SST) and its analogs also exert an inhibitory effect on tumor proliferation. SST could suppress the synthesis and secretion of growth factors and indirectly affect tumor growth. They could inhibit hepatic GH-induced OGF-I production *via* SST-mediated activation of a tyrosine phosphatase leading to dephosphorylation of STAT5b and a decrease in IGF-I gene transcription[134].

4.2. *Cancer apoptosis*

Apoptosis, a type of programmed cell death, is an essential means of controlling cell counts. Accumulating evidence suggests that cancer cells could acquire resistance toward apoptosis. One common mechanism is the upregulation or activation of anti-apoptotic proteins, such as Bcl-2 and Bcl-xL. These proteins prevent the release of cytochrome *c* from mitochondria, inhibiting the formation of the apoptosome complex and subsequent activation of caspases, which are responsible for carrying out apoptosis. Additionally, cancer cells may exhibit dysregulation in signaling pathways that control apoptosis, such as the PI3K/Akt pathway. Moreover, cancer cells may hijack survival signaling pathways, such as NFκB, which promotes cell survival and inhibits apoptosis. By aberrantly activating these pathways, cancer cells can evade apoptosis and promote their survival and growth.

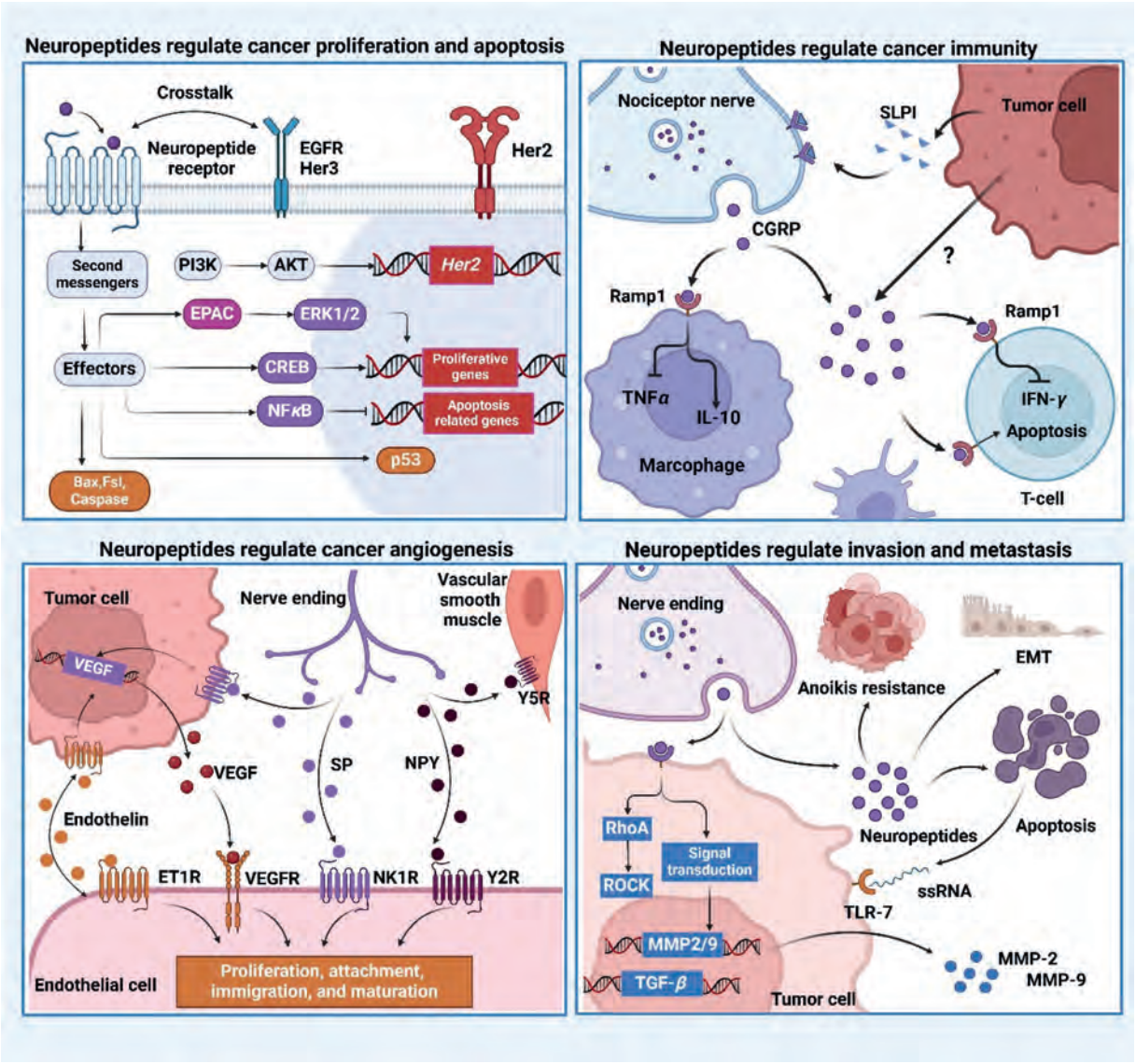

Figure 3 Neuropeptides influence cancer hallmarks. Neuropeptides regulate several cancer hallmarks, in both promotion and inhibition, which is content-dependent. Current studies suggest that neuropeptides have profound effects on tumor proliferation and apoptosis, tumor immunity, tumor invasion and migration, and tumor angiogenesis. The influence on other cancer hallmarks deserves the exploration. This figure was created using BioRender (https://biorender.com/).

The relationship between neuropeptides and apoptosis is highly complex, and different neuropeptides can have different effects on various types of tumors. Some neuropeptides have been found to promote cell apoptosis, while others may have anti-apoptotic effects. A classic case is the role of Orexin and its receptors on tumor apoptosis. More importantly, exploring orexin-induced apoptosis reveals a novel apoptotic pathway, involving immunoreceptor tyrosine-based motifs (ITIM) and the tyrosine-protein phosphatase non-receptor type 11 (SHP2)[135,136]. The interaction between orexins and OX1R in colon cancer cells induced the β/γ subunits dissociation from the Gq protein, leading to phosphorylation by Src kinases of two ITIM sites present in TM2 and TM7 of the receptor. The phosphorylated receptor then recruits and activates SHP2, which subsequently leads to the activation of p38 mitogen stress protein kinase through the RAS/MAPK signaling pathway.

Bax protein translocation in mitochondria, followed by cytochrome *c* release, which is involved in the formation of apoptotic vesicles. This leads to the activation of caspases 3 and 7, which results in cell death. The same situation could also be observed in neuroblastoma cells. These findings add a new dimension to the biological activities of these neuropeptides, which may have important implications for health and disease[137]. As we have emphasized, the actions of neuropeptides and their receptors are tumor-context dependent. Other researchers confirm that in pancreatic cancer cells, orexin A will promote cell proliferation through the Akt/mTOR pathway while inhibiting Bcl-2/caspase 9/c-myc-mediated apoptosis in contrast[138]. Methionine enkephalin (MENK), a kind of opioid peptide, enhanced the expression of opioid receptor (OGFR) and induced apoptosis of lung cancer cells by activating the Bcl-1/Bax/caspase 3 signaling pathway *in vitro* and *in vivo*. On the contrary, the regulatory effects of

MENK were impeded after the blockade of the OGFR[139]. And MENK could also promote apoptosis of cervical carcinoma *via* triggering extrinsic apoptosis signal of Fas/Caspase 3/Caspase 8 and intrinsic pathway of Bax/Caspase 9/Caspase 3[140]. What's more, the contribution of somatostatin system to mediation of apoptosis is well studied. The binding of SST to its corresponding receptors will lead to several cytotoxic and cytostatic effects and induction of CDKs. In leukemia cells, SSTR2 exhibits apoptosis independent of p53. In other cancer cells, activation of SSTR2 induces apoptosis through the PTP-1-C-mediated signaling pathway. SP has an adverse function, while usage of NK1R antagonists could induce cell apoptosis[141]. Aprepitant, a long-history NK1R antagonist, has been proven to induce apoptosis in various types of cancer and various antitumor effects[142]. Researchers found that Aprepitant resulted in Caspase 8/-9-dependent apoptotic pathway activation by modifying the expression of genes involved in apoptosis and it could also abrogate the PI3K/Akt pathway[143]. When we take into account the cross-talk between neuropeptides, the situation becomes even more complex. Feng investigated the effects of SP and serotonin (5-HT) on B16F10 melanoma cells and they found SP was able to inhibit the expression of the 5-HT2A receptor and upregulate the expression of NK1R[144]. Additionally, the pro-apoptotic effect of SP could be attenuated by 5-HT2A agonists and its receptor activation[144].

4.3. Cancer angiogenesis

Just like normal tissues, tumors need sustenance in the form of nutrients and oxygen. They also require the ability to evacuate metabolic wastes and carbon dioxide. Tumor-associated vasculature addresses these problems. Tumor vessels have many unique characteristics. They are tortuous and leaky, their diameter is irregular and their walls are thin, which could be explained by the relative paucity of pericytes, or reduced pericyte function[145]. Angiogenesis, this process is regulated by various growth factors, especially VEGF and its corresponding receptor. Recent researches confirm neuropeptides and their receptors also take part in tumor angiogenesis, not only *via* regulation of the release of VEGF but also by directly promoting endothelial proliferation, which has been previously discussed in detail.

The relationship between the tachykinin family and tumor angiogenesis is also abundantly learned. NK receptors are found in most arteries, small arterioles, capillaries, and post-capillary venules. Tachykinin binds to these receptors and thus plays a role in regulating microvascular permeability, regulating blood flow, leukocyte trafficking, and angiogenesis. Therefore, it is quite reasonable to speculate that the tachykinin system can influence tumor angiogenesis. Tachykinin and its receptor are highly expressed in tumor tissues and peritumor blood vessels in many cancer specimens. Peritumoral blood vessels of gliomas, medullary thyroid carcinomas, breast carcinomas, neuroblastomas, and colon carcinomas all upregulate the corresponding receptors at an extremely high rate[146]. SP, by binding to NK1R, was able to significantly affect the structure and function of intratumor or peritumor blood vessels, which means they can promote tumor vascular flow and stromal cell development, thus facilitating tumor metastasis. In studies of colon cancer, researchers have found that neurons are not the only source of SP. Because neurons grow too slowly, there may be no perivascular nerves adjacent to tumors, and in this case, immune cells would take over the function of neurons, which are also able to secrete tachykinin to regulate the growth of tumor blood vessels[147]. Momen Razmgah et al.[76] found that treating ovarian cancer cells A2780 with SP and aprepitant (a kind of NK1R antagonist) would influence the expression of VEGF and VEGFR. Aprepitant would significantly reduce the mRNA expression of VEGF and VEGFR genes and exogenous SP will lead to a significant increase in VEGF and VEGFR genes. As for neurokinin-B and neurokinin-3 receptor, other researchers observed that NK-B could reversibly inhibit endothelial cell vascular network assembly and opposes angiogenesis in the chicken chorioallantoic membrane[148]. Mechanistically speaking, NK-B reduced the expression of some proangiogenic factors such as VEGF while enhanced the expression of calreticulin and vasostatin to inhibit angiogenesis[148]. Wang et al.[149] designed two novel NK-B analogs: NK3R-A1 and NK3R-A2 and validated their anti-angiogenesis effect in tumors.

NPY system also shows great effects on angiogenesis on multifaceted aspects. These functions are closely related to a cleaved form of NPY, $NPY_{3\text{-}36}$. Dipeptidyl peptidase IV (DDPIV) could cleave Tyr1-Pro2 off the N terminus[150]. Compared with other forms, $NPY_{3\text{-}36}$ shows a higher affinity to Y2R and Y5R, whose pro-angiogenic functions are in the core status[151]. Y2R participates in endothelial cell growth, viability, and migration, finally inducing angiogenesis. Y5R is also associated with vascular smooth muscle (VSMC) proliferation[152]. *In vitro*, NPY could stimulate VSMC growth over a wide range, from pmol/L to nmol/L, which could be blocked by corresponding antagonists[153]. Except for proliferative regulation, NPY enhances the attachment, immigration, and capillary maturation of umbilical vein endothelial cells[154]. Several studies confirm the important role of NPY in the illness context. For example, NPY mediates angiogenesis after ischemia and leads to revascularization of ischemic tissues[155]. It is therefore interesting to consider how NPY regulates tumor vascular growth in the hypoxic−ischemic TME and whether it contributes to the revascularization of aberrant blood vessels in tumors. Our previous section also mentioned that endothelin has a significant effect on vascular endothelial cells. Recently, Harrison[156] summarized the effect of endothelin on tumor angiogenesis very well and could be a worthwhile reading reference.

It is interesting that during embryonic development, the nervous system and vascular system often develop in parallel. There exists a close interaction between the nervous and vascular systems. The growth and guidance of neurons rely on the support of the vascular system, and the interaction between neurotrophic factors and angiogenic factors plays an important regulatory role in the development of both systems. For example, angiogenic factors can influence vascular development and the formation of vascular networks, while neurotrophic factors can promote the migration and positioning of neurons. In some cases, neuropeptides can serve as the "angiogenic factors". Endothelial cells also express various kinds of neuropeptide receptors and the proliferation will be activated when specific peptides bind to them. What's more, the transcriptome of the TME reveals that endothelial cells themselves will also overexpress several neuropeptides. It's how the autocrine loop builds. There will be great treasure waiting for us behind the mysterious veil.

4.4. Cancer invasion and metastasis

One of the best-known characteristics of cancer cells is their ability to invade adjacent or distant tissues, which is termed "metastasis": tumor cells that grow in a hostile and crowded microenvironment, attempt to move and proliferate in another environment, so they initiate a series of reactions, known as the

"metastatic cascade". Firstly, they will experience serial biological and morphological changes called epithelial−mesenchymal transition (EMT), reducing their dependency on intracellular connection and increasing the ability for dissemination towards distant organs[157]. With the abundant vascularization, newly formed or pre-existing blood vessels could serve as channels for disseminating cells[158,159]. Later, tumor cells utilize a variety of motility mechanisms, chemokine gradients, and proteinases to enter and exit the circulation. After introversion, circulation, and extraversion, tumor cells lodge at secondary sites and re-establish cell connection[157,160].

When talking about the relationship between neuropeptides and tumor metastasis, there is a neuropeptide we couldn't ignore. Kisspeptin (KP), also known as KiSS-1 metastasis suppressor[161]. As the name suggests, KP plays an important role in metastasis. KP has a unique mechanism for delaying metastatic cascade that KP tends to prevent the proliferation and establishment of metastatic cells in remote sites. While other metastasis suppressors always block cell separation and emigration from the primary tumor[162]. At present, there is no direct evidence that KP-releasing nerves innervate tumors, suggesting that KP influences tumors mainly *via* endocrine means.

KP usually binds to kisspeptin receptor 1 (KISS1R), also known as GPR54 to exert its function, including suppressing motility, invasion of human cells *in vitro*, and metastasis. KISSR1 is coupled with Gq/11, which subsequently stimulates the PLC, induces intracellular calcium mobilization, and finally activates PKC to exert a broad-spectrum effect[163]. Several studies confirm that KP signaling could inhibit metastasis *via* the regulation of the MAPK/ERK pathway[163,164]. What's more, this signaling could also influence RhoA-ROCK activation, which is regarded as a crucial signaling pathway to regulate transformation and metastasis[165]. Current studies seem to emphasize the effect of KP signaling on the metastatic capacity of the tumor itself, rather than how it remodels the TME to facilitate metastasis. People first observed KP has antimetastatic action in melanoma cell lines[166]. Lee et al.[166] found KiSS-1 expression in metastatic melanoma cells and nonmetastatic melanoma cells: only the later cell was detected of KiSS-1 mRNA expression, indicating its antimetastatic role. In tumor cells, the expression level of KP is usually down-regulated, which may be related to the regulation of miR-21 as well as TCF21[167]. Researchers confirm the antimetastatic role of KP in thyroid, ovary, bladder, gastric, pancreas, and lung cancers[168].

With the depth of related studies, KP is thought to be a promoter of tumorigenesis and metastasis in some cancer types such as breast and liver cancer[169−171]. In breast cancer cells, KP signaling could induce invadopodia formation by activation of cortactin, cofilin, and membrane type I matrix metalloproteases (MMP) and finally promote TNBC cell invasion[172]. What's more, KP signaling could also transactivate EGFR to promote TNBC invasion, *via* β-arrestin2 and MMP-9 pathway[173]. Tian et al.[174] confirmed KiSS1 as a downstream target of the canonical TGFβ/Smad2 pathway in TNBC and is somehow necessary for TGFβ-induced cancer cell invasion. There is some *in vivo* evidence also consistent with the aforementioned results. Cho et al.[175] concluded that KISS1R haploinsufficiency delays breast tumor initiation, progression, and metastasis through its downstream RhoA signaling pathway. Plentiful clinical data also support the premetastatic role of KP and KISS1R. Compared with normal healthy breast tissue, TNBC tumor biopsies tend to display higher KiSS1/KiSS1R mRNA and protein expression[176].

Other peptides also participate in cancer metastasis. Neuromedin U, a secretory neuropeptide, is regarded to be involved in anoikis resistance in breast cancer, which is important for the survival of circulating tumor cells[177]. Another research also confirmed Neuromedin U could promote cancer migration and invasion *via* ERK1/2 kinase activation[178]. NPY is a well-studied neuropeptide contributing to various steps of tumor progression and several studies confirm its role in invasion and metastasis. In Ewing sarcoma, NPY participates in tumor-hypoxia-induced bone metastasis *via* overactivation of the RhoA pathway and cytokinesis failure[179]. Blocking Y5R with related antagonists will prevent bone metastasis[179]. NPY system is also associated with metastasis in prostate cancer. A transcriptomic study, which focused on the expression of NPY in prostate cancer development, demonstrated that lower NPY expression was associated with more aggressive grade, higher genomic risk, and shorter metastases-free survival[180]. Expression of the NPY system was upregulated in pre-invasive prostate intraepithelial neoplasia, primary prostate cancer, and metastases[70]. What's more, this system was increased in the perineural invasion (PNI) and extraprostatic extension area[70]. But the exact molecular mechanism of how the NPY system influences prostate cancer metastasis remains to be explored. SP could also act on NK1R and induce increased expression of MMP-2 in pancreatic cancer cells, which is reflexed as enhancement of cancer migration and PNI[181]. Other research also demonstrated SP signaling could induce epithelial−mesenchymal transition in head and neck cancer, which is considered the early stage of the metastatic cascade[182]. More importantly, clinical studies hint at the relationship between serum levels of SP and the occurrence of metastasis but more efforts are needed to confirm the causality[183]. Recently, ground-breaking research led by Tavazoie clarified a novel prometastatic mechanism mediated by the SP/NK1R axis[184]. Researchers found the presence of a high NK1R-expressing cancer cell population in breast cancer, unexpectedly, the overactivated SP signaling led to apoptosis. Single-stranded RNAs leaked from dying cells in turn acted on the neighboring tumoral Toll-like receptor 7 and finally promoted cancer metastasis.

4.5. *Cancer immunology*

The nervous and immune systems present the body with two interfaces to perceive, integrate, and respond to environmental insults or internal injuries. In the previous section, we have discussed in detail how neuropeptides go about regulating various functions of immune cells. If scenarios are envisioned in more complex and specific situations, for example, how intertumoral peptidergic neurons go about influencing tumor immunity might provide us with a more direct understanding.

The nociceptive signaling pathway is an important mechanism for neurostimulation-mediated modulation of the tumor immune microenvironment. Nociceptive stimulation can activate the peripheral nervous system to release many neuropeptides, such as CGRP and SP[185]. While in physiological condition, peptidergic nerves innervated immune organs and lymphoid tissues[186]. Nervous ends release CGRP, SP, and some other peptides, which could be recognized by surface receptors on immune cells, regulating aspects of T cell differentiation in the thymus and contributing to compartmental immune responses[186]. CGRP has complex effects on the immune system. It may exert a negative regulatory role on innate immune responses, thereby limiting tissue damage caused by inflammation[187,188]. However, it can also play a pro-inflammatory role, for example, by promoting T cell

homing or facilitating the migration of eosinophils to inflammatory sites through β-integrin activation[187,188]. The release of CGRP by neurons can also regulate the cytokine release from macrophages or dendritic cells, thus impacting antigen presentation[189]. Oral cancer is innervated by the sensory nerve, with CGRP as the primary neurotransmitter, which regulates tumor-related immune responses through its interaction with RAMP1. Researchers also observed increased RAMP1 expression and tumor-infiltrating lymphocytes[190]. Animal experiments have shown that in the CRGP knockout mouse model of oral cancer, higher infiltration of $CD4^+$ and $CD8^+$ T lymphocytes, as well as natural killer cells and smaller tumor volumes, can be observed[191]. Similar results have also been demonstrated in melanoma. Research has indicated that nociceptive neurons are capable of detecting secretory leukocyte protease inhibitors (SLPI) released by melanoma. SLPI, in turn, triggers the release of CGRP, which acts on $CD8^+$-positive T cells. As a result, these T cells increase their expression of injury immune checkpoint receptor proteins, leading to T-cell exhaustion. Blocking the CGRP receptor RAMP1 with drugs or genetically deleting the transient receptor potential vanilloid 1 (a sensory neuron ion channel) can decrease sensory signaling within the TME, reduce T cell exhaustion, inhibit tumor growth, and prolong overall survival[192].

Tachykinins can promote the increase of pro-inflammatory cytokines such as IL-6 and IL-8 in the circulatory system. SP is widely studied in the immunological field and has been verified to take part in immune cell migration, immune cell proliferation, and immune cell activation[94,102,193]. In essence, the reason why the tachykinin family has an important impact on immunity is that they can influence the function of hematopoietic stem cells. Broadly speaking, they can stimulate the activity of hematopoietic stem cells and promote hematopoiesis[194].

SP and NK1R signaling promotes the survival of activated T cells and also stimulates macrophages to release pro-inflammatory cytokines. Natural killer cells express NK1R, where SP binds to enhance cytotoxicity[195]. T cells could synthesize SP and express the NK1R during inflammation and infection. SP/NK1R promotes T-cell proliferation in an autocrine way[196].

The immune checkpoint molecules are considered the main mechanism for tumors to escape from immune surveillance. PD-1/PD-L1 or Fas/Fas-L are classical ICPs that are abundantly studied. Taking PD-1 and PD-L1 as an example, when PD-L1 binds to PD-1 expressed on immune cells, it can lead to depletion of T cells and thus affect the body's anti-tumor effects. This binding triggers an immune inhibitory signal that suppresses the activation and function of T cells, limiting their ability to attack tumor cells. This immune evasion mechanism enables tumors to evade attacks from the body's immune system, increasing their survival and spreading ability. Researchers confirm that immune checkpoint molecules such as PD-L1 are expressed in neurons infiltrating into tumors. In addition, a trend toward higher infiltration of $FOXP3^+$ regulatory T cells in areas harboring a higher density of $PD\text{-}L1^+$ nerve fibers was observed. Another study also found that acetylcholine could downregulate the expression of PD-1 on T-cells. So, the role in which neuropeptides take part in the related process deserves studied.

4.6. *Other cancer hallmarks*

Several studies also confirm neuropeptides and their receptor take part in the acquisition of other cancer hallmarks, especially metabolic reprogramming, and bidirectional regulation between microbiomes and tumors. However, the current evidence is still insufficient and needs to be explored in greater depth.

5. Neuropeptides influence cancer comorbidities

Thanks to a change in attitude, we no longer think of tumors as a disease that affects a single system. Understanding how tumors interact with distant organs will be crucial for advances in the prevention and more effective treatment of human cancers[197]. In addition to the tumor itself, patients also suffer from tumor comorbidities, and it's also an important part of antitumor therapy. Considering the universality of neuropeptides and their receptors expressed between organs and tumors, cancer-induced aberrant levels of neuropeptidergic signals may contribute to these comorbidities. Modulation of aberrant neuropeptide signaling may have multiple benefits for patients (Fig. 4).

5.1. *Neurological dysfunctions*

In our previous fragmentary description, neuropeptides in tumors can be released in an autocrine or paracrine manner by tumor cells as well as by other TME cellular components. The disruption of neuropeptide-releasing balance leads to dysfunctions of plentiful neural circuits, reflected in cancer-induced stress, depression, and other negative emotions. Some neuropeptides also can impair the BBB. For example, SP could change the expression of tight junction proteins ZO-1 and claudin-5 in brain microvascular endothelial cells[198,199]. Bradykinin and angiotensin have also been proven to disrupt the BBB under several circumstances[200]. Destruction of the BBB allows more direct communication between the brain and circulatory system so neuropeptides could bypass the BBB and infiltrate the brain parenchyma. What's more, under the context of tumor-bearing organisms, many potent substances will be released to penetrate and disrupt BBB during cancer progression, which facilitates the transportation of tumor-derived neuropeptides to the brain parenchyma.

Of all the neuropeptides, SP was considered to be the most related to emotion regulation, as the limbic system, which includes the hypothalamus, amygdala, and hippocampus, over-expresses NK1Rs. Tumor-derived SP could travel to the brain *via* systemic circulation. After combination with SP, NK1R expressed on nerves increased the activity of the corresponding encephalic region[201]. In addition to the direct effects of SP, it can indirectly affect mood by modulating the HPA axis, which plays a dominant role in stress regulation[202]. SP could regulate cortisol secretion *via* the hypothalamus and adrenal gland. The intracerebroventricular injection of SP could decrease the adrenocorticotropic hormone levels in rat models[203]. Blocking NK1R signaling with aprepitant has been proposed as an antidepressant therapy, but its effectiveness has been questioned[204,205]. However, it is a promising direction and, given the broad regulatory role of NK1R in tumors, it would also be beneficial for patients to conduct trials of the antidepressant efficacy of aprepitant in tumor patients. Other neuropeptides also contribute to these blue moods. The cerebrospinal fluid (CSF) level of NPY was significantly decreased in depressive disorder while antidepressant treatment could recover the concentration[206]. On the other hand, the administration of NPYR agonists or genetic upregulation of NPY could also exert antidepressant effects[207]. Considering NPYR has primarily a pro-tumor effect, improving the mood of patients with cancer through NPYR could do more harm than good.

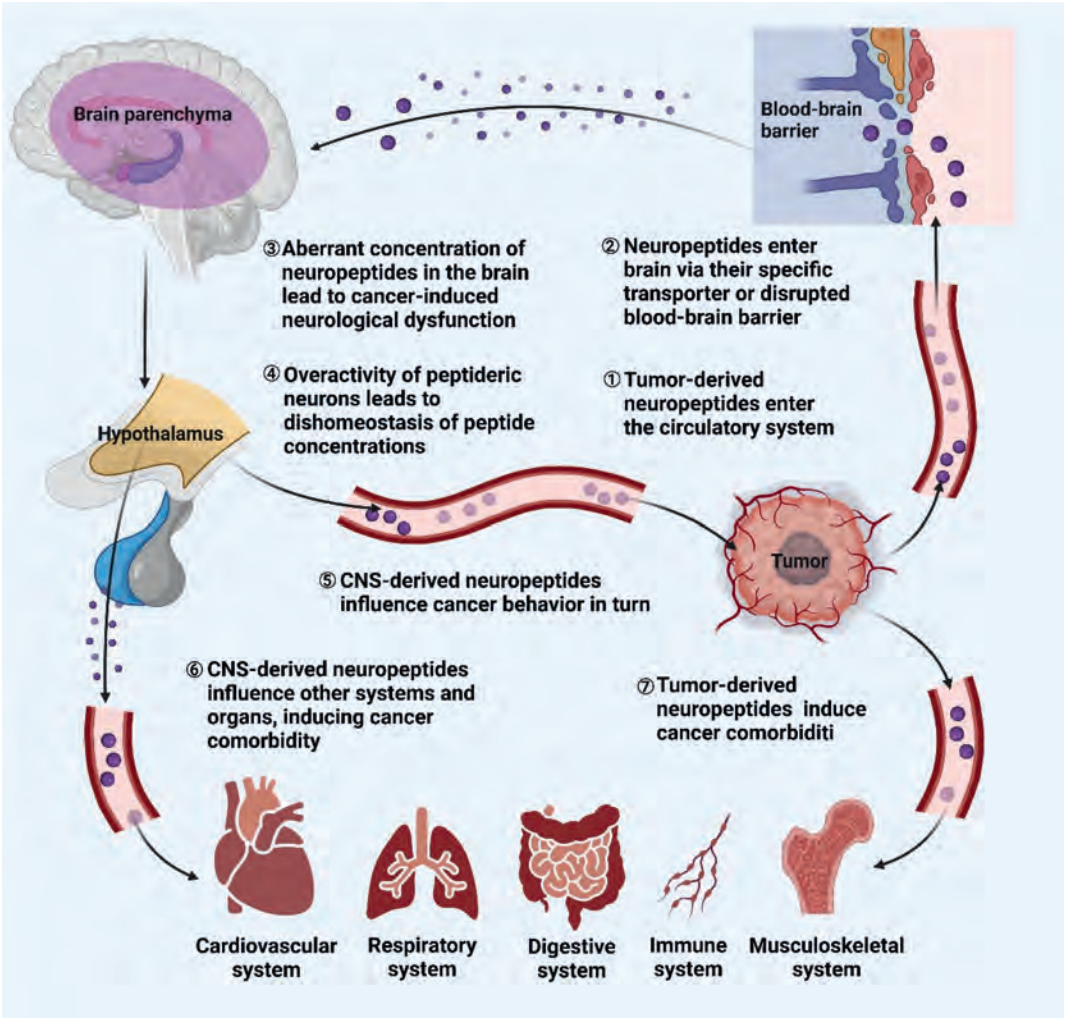

Figure 4 Neuropeptides contribute to cancer comorbidities. Serving as neurotransmitters, neuromodulators, and hormones, neuropeptides exert great effects on the regulation of the whole body. Under the tumor-bearing content, the abnormal concentrations of neuropeptides contribute to cancer comorbidities, especially neural cognition dysfunctions. Tumor-derived neuropeptides enter the systemic circulation and enter brain parenchyma simply *via* specific transporters or disrupted blood−brain barrier. The aberrant concentration of neuropeptides leads to neurological dysfunctions and neuroendocrine abnormalities. Abnormalities in the body's neuropeptide levels, whether of tumor or neurological origin, influence multiple organs and participate in tumor comorbidities, such as cardiac failure, vasospasm, impaired digestion, weakened bones, fractures, and others.

5.2. Cancer anorexia-cachexia

Cancer anorexia-cachexia is observed in 80% of patients with advanced cancer, especially in gastrointestinal tumors. Our previous work has discussed in detail the pathogenic mechanisms of various cytokines and other particles under the context of inter-organ communication[208]. Considering that one of the major mechanisms contributing to cachexia is anorexia, which is precisely regulated by neural activity, neuropeptides play an important role.

In the previous section, we have discussed in detail how neuropeptides affect food intake. NPY, acting in the hypothalamus, could activate feeding behavior by stimulating the complex sequence of behaviors from food seeking to food ingestion[209]. In the anorexia tumor-bearing rats, the concentration of NPY was drastically decreased[210]. However, the administration of NPY to the corresponding encephalic region did not reverse the situation, indicating anorexia also decreases the expression of NPY receptors[211]. Immunocytochemical visualization and semi-quantitative image analysis in another study also support this result[212]. Among all anorexigenic peptides, α-MSH has the most potent effect on tonic inhibition of feeding and body-weight gain, primarily *via* type 4 melanocortin receptor (MC4-R) to exert its functions[213]. Researchers didn't confirm the upregulation of α-MSH in anorectic rats with cancer. As we know, the activity of NPY neurons itself has an inhibitory effect on the function of α-MSH, which can exert a more dominant function when the balance between the two is disturbed[214]. Encouragingly, the MC4-R antagonist attenuated anorexia in a mouse model and may represent a breakthrough in clinical treatment[215]. Other peptides could also influence the formerly discussed mechanism. For example, leptin exerts a direct regulatory function on the activation of NPY neurons and POMC neurons, which coexpress leptin receptors[216,217]. Abnormal secretion of leptin inevitably alters its complex regulation, leaving the organism in a more disorganized state. At present, it seems we lack some clinical evidence to

demonstrate the important role of NPY, as well as other neuropeptides, in cancer anorexia.

Cachexia is characterized by adipose rearrangement, muscle wasting, and metabolic disorders[215]. Researchers currently believe that the development of cachexia is primarily associated with the overproduction of inflammatory factors such as interleukin-1 beta (IL-1b), interleukin-6 (IL-6), leukemia inhibitory factor (LIF), and tumor necrosis factor-alpha (TNF-α)[218,219]. There is no direct evidence that neuropeptides are involved in the pathogenesis of cachexia, but they may influence the disease progression *via* the nerve−immunology axis.

5.3. Cardio-oncology diseases

In patients with a neuroendocrine neoplasm, it was common for them to suffer from carcinoid syndrome (CS). The symptoms of carcinoid syndrome, including diarrhea, difficulty in breathing, skin flush, facial lesions, and tachycardia, are caused by overexpression of serotonin and other vasoactive substances, such as tachykinin, and kallikrein[220]. In these patients, there is a high incidence of heart disease, termed carcinoid heart disease (CHD), mainly associated with uncontrolled fibroblast growth and fibrogenesis. The valvular lesions produced by high circulating serotonin levels are similar to those of ergot-alkaloid derivatives or fenfluramine. The role of serotonin in the development of CHD is supported by markedly elevated levels (2- to 4-fold above normal) of circulating serotonin in those with the disease. Additionally, urinary 5-hydroxyindole acetic acid (5-HIAA), the major metabolite of serotonin, is also elevated in patients with CHD compared to carcinoid patients without cardiac involvement. A high level of circulating serotonin is associated with increased transforming growth factor-β latency-associated peptide and latent binding protein in the tissue of an involved heart valve, both of which promote fibrosis. Serotonin receptors are present on heart valves and participate in collagen synthesis in valvular interstitial cells. In experimental animal studies, long-term serotonin administration can produce morphologic and echocardiographic valvular alterations similar to those in human CHD.

Vasospasm is another cardiovascular-related acute event leading to mortality in cancer patients and this kind of comorbidity is mainly induced by anti-cancer therapy[221]. ET-1, NPY, and other neuropeptides that exert potent vasoconstrictive functions are regarded as early biomarkers for cerebral vasospasm[222,223]. Their roles and clinical implications under tumor-bearing context deserve exploration.

5.4. Cancer pain

Pain may be the first symptom felt by cancer patients. It is also very common that approximately 45% of all patients with advanced cancer experience pain of moderate to severe intensity[224]. Cancer pain could further be divided into cancer-induced bone pain, chemotherapy-induced neuropathic pain, and others, which share different pathologic mechanisms.

SP plays a predominant role in transmitting the pain impulse, and other neuropeptides such as VIP, CGRP, and CCK also participate in the process[225−227]. Noxious stimulation of peripheral tissues leads to the release or generation of multiple factors including prostates, lipids, and ions. These factors can activate several classes of receptors and channels expressed by peptidergic nociceptors. If the factors excite nociceptors and generate action potentials, SP and CGRP are also released from the central projections of nociceptors in superficial laminae of the spinal cord dorsal horn, where neuropeptides activate receptors on spinal neurons to transmit painful stimuli centrally[228]. As we discussed in the former context, SP signaling not only participates in pain impulses but also promotes cancer proliferation *via* the regulation of immune cells. Recent research also confirms the mediated functions of NPY in chronic pain. Intrathecal injections of NPY modulate nociceptive stimulus, leading to analgesia in chronic models, but the exact mechanism remains exploration[229]. Exploring whether interfering with related neuropeptide signaling could help alleviate cancer pain might be a good direction for research.

Pain relief treatment is a must to enhance the quality of a patient's survival. When we talk about this issue, the use of opioids is an inescapable topic. They remain the main therapy for severe malignant pain, working at PNS or CNS, through blockade of presynaptic release of neurotransmitters from primary afferent terminals to trigger postsynaptic hyperpolarization of interneurons in the dorsal horn, as well as involving top-down opioidergic controls from superior centers[230,231]. Exogenous and endogenous opioids exert analgesic effects by acting on MORs expressed in glutamatergic and GABAergic neurons, respectively[232]. However, abuse of opioids leads to another enormous problem: opioid use disorder (OUD). Patients with OUD present with structural changes in many organs as well as loss of function, with the most serious clinical outcome being death. People with OUD have impaired executive function, impaired decision-making, impaired verbal working memory, and impaired cognitive impulsivity and cognitive flexibility[233]. More importantly, overstimulation of MOR in the medulla results in respiratory depression, leading to hypoxic brain injury[234]. Opioids also cause vasodilation and hypotension, directly or indirectly associated with some cerebrovascular disease[235]. Opioid treatment is associated with cancer recurrence in several types of cancer and opioids also contribute to cancer progression[236−238]. In our previous discussion, many experiments demonstrated that long-term activation of MOR favors tumor survival. How to rationalize the use of opioids is a perennial issue. Recently, researchers also developed a hybrid peptide based on opioid and neurotensin[239]. This kind of hybrid peptide offered long-lasting antinociceptive activity and has a propensity to delay tolerance development, which may be a promising direction.

5.5. Cancer-related sleep disorder

Patients with cancer frequently suffer from sleep disorders, including insomnia, circadian misalignment, hypersomnia, somnolence syndrome, and nightmares, with a high prevalence experienced by patients with breast cancer[240]. These problems are associated with a drastic reduction in the patient's quality of life and increased mortality. Accumulating evidence links aberrant levels of neuropeptides and abnormal movement of peptidergic nerves to the influence of the processes.

The lateral hypothalamus contains numerous neural populations that receive, integrate, and fire to influence systemic physiology and behavior. Recent studies confirm nerves that release orexin-A and -B (H/O nerves) are important in stabilizing wakefulness[241,242]. HO neurons are sensitive to signals arriving from the periphery including other neuropeptides such as leptin, and ghrelin, basic nutrients such as glucose, and dietary amino acids, and changes in physicochemical information such as pH and CO_2[243]. Two key efferent outputs from HO neurons drive changes in peripheral physiology relevant to cancer. One is

through the engagement of the HPA to elicit the secretion of glucocorticoids. Additionally, HO neurons innervate multiple autonomic output nuclei in the brainstem and can signal *via* the sympathetic nervous system to alter the whole-body energy balance.

MCH neurons are co-mingled among HO neurons, which counters the function of HO neurons[244]. MCH neurons are active during rapid eye movement (REM) sleep, while they are silent during wakefulness[245]. Few studies have examined the relationship between the abnormal activity of MCH neurons under tumor-bearing context and sleep disorders.

5.6. Other comorbidities

Neuropeptides also participate in other cancer comorbidities such as bone weakness and fracture. The intimate relationship between NPY and bone metabolism has been confirmed. For example, NPY inhibits osteogenesis *via* the restraint of runt-related transcription factor 2[246]. But paradoxically, other studies confirm NPY could promote bone formation and fracture repair. At a low dose, NPY stimulates BMSC osteogenic differentiation[247]. Clinical observation found that in patients with fractures, NPY levels tend to increase[248].

Neuropeptides also participate in influencing metabolic syndrome, which is occasionally accompanied by tumorigenesis. It is a disease marked by obesity, high blood pressure, and insulin resistance[249]. Recent research demonstrated neuropeptides played an important role in metabolic syndrome[250]. The NPY system plays a core role in the energy steady-state regulation system. As we formerly discussed, NPY and POMC neurons could regulate the feeding process. Recent studies also confirmed they participated in the subsequent coordination of the conversion, storage, and utilization of carbohydrates and lipids[251]. More importantly, the NPY system is intimately associated with insulin resistance. Researchers found that inhibition of the hypothalamic NPY signaling would increase the secretion of insulin, suggesting the inhibitory role of NPY in the process[252]. On the other hand, peripheral insulin also exerted an inhibitory effect on central NPY activation[253]. It is thought-provoking that under the insulin resistance situation, the standing increase in insulin finally led to the upregulation of NPY levels in the hypothalamus, indicating the resistance of hypothalamic NPY to feedback regulation of insulin elevation[249]. Several studies also pointed out that NPY is a strong vasoconstrictor and coordinates with norepinephrine to exert a positive time-changing effect on the heart, which is associated with hypertension[254].

However, there is no direct evidence that NPY is associated with tumor-metabolism syndrome. Given that neuropeptide systems are implicated in various symptoms of the metabolic syndrome, it is worth exploring their effects in the context of cancer.

6. Intervention strategy of neuropeptide system in cancers

Neuropeptides are increasingly being developed for use as therapeutic agents in the treatment of many diseases, in particular cancer[255]. The anticancer effects of neuropeptides could be the direct result of the binding of their paired receptors, or they may be conjugated to a chemotherapy drug or radionuclide and used to target the agent to cancer cells (Fig. 5). Considering the specificity of tumor cells in expressing neuropeptide receptors, neuropeptide-based delivery systems have a promising future. However, to become an ideal delivery system, there remain some flaws that need to be overcome. Neuropeptides and their analogs are easily degraded by proteases and have some difficulty being absorbed into the bloodstream, hindering their clinical implication. To solve these problems and enhance the efficiency and selectivity of therapeutic delivery, great achievements have been made. Peptide cyclization, peptide-loaded nanoparticles, the conjugation of peptide drugs to natural or synthetic polymers, and manipulation of the amino acid sequence have been implicated in the half-life of peptide drugs and improved peptide drug delivery[256–259]. What's more, the aberrant expression mode of neuropeptides and their corresponding receptors could also point to cancer initiation and progression with great possibility of serving as cancer biomarkers (Fig. 5). In the subsequent sections, we summarize the current status of some of the directions in which neuropeptides are being used in oncology therapy, as well as future perspectives, highlighting some of the dilemmas they currently face.

6.1. Agonist/antagonist-based cancer therapy

Considering the specific expression models of neuropeptide receptors in various cancers, targeting these receptors is wise. Solid evidence has proven the agonists/antagonists present on the market have the great potential to constrain cancer progression (Table 2[260–267]). As we foresaid, there remain some neuropeptides exerting anti-tumor effects. Using agonists towards their corresponding receptors would be a potential strategy to inhibit cancer progression distinctly and safely. However, their therapeutic potential may be limited due to short plasma high-life[16]. Many neuropeptide analogs are designed to overcome this defect. Taking SST as an example, SST analogs have been a mainstay of therapy in functioning neuroendocrine tumors, in which hypertension is very occasional. Carcinoid syndrome is termed a phenomenon that tumor secretion of various neuropeptides and neurotransmitters such as histamine[268,269]. Following the current guidelines, SST analogs are thought of as the first-line therapy for the reduction of carcinoid syndrome[270]. What's more, SST analogs could also exert antiproliferative effects and inhibit tumor growth *via* its corresponding receptor somatostatin receptor 2 (SSTR2), such as gastrointestinal tumors, breast tumors, small cellular lung carcinoma (SCLC), and others[271–277]. But limited clinical trials prove their effectiveness. In a random clinical study, 130 patients with SCLC and positive SSTRs received chemotherapy or chemotherapy plus lanreotide; significantly better results regarding median time to progression and median survival were observed in the experimental arm[278]. Another clinical trial illustrated that a combination of docetaxel and pasireotide, a kind of somatostatin analog, showed potent clinical efficacy within metastatic castrate-resistant prostate cancer[279]. More importantly, somatostatin shows a desirable role in the management of postoperative complications. In the PREFIPS randomized clinical trial, researchers found that somatostatin was as effective as octreotide in preventing postoperative pancreatic fistula[280]. Another prospective, single-blind, placebo-controlled clinical trial demonstrated postoperative somatostatin could reduce the duration of surgical drainage and corresponding complications in gastric cancer patients who received D2 radical gastrectomy[281].

Considering that most neuropeptide receptors have tumor-promoting effects, neuropeptide receptor antagonists may have better prospects for application. For example, Pascetta et al.[282] confirmed using NPYR antagonists could reduce MAPK signaling, cell proliferation, cell migration, and spheroid growth and invasion. However, among all the antagonists, the NK1R

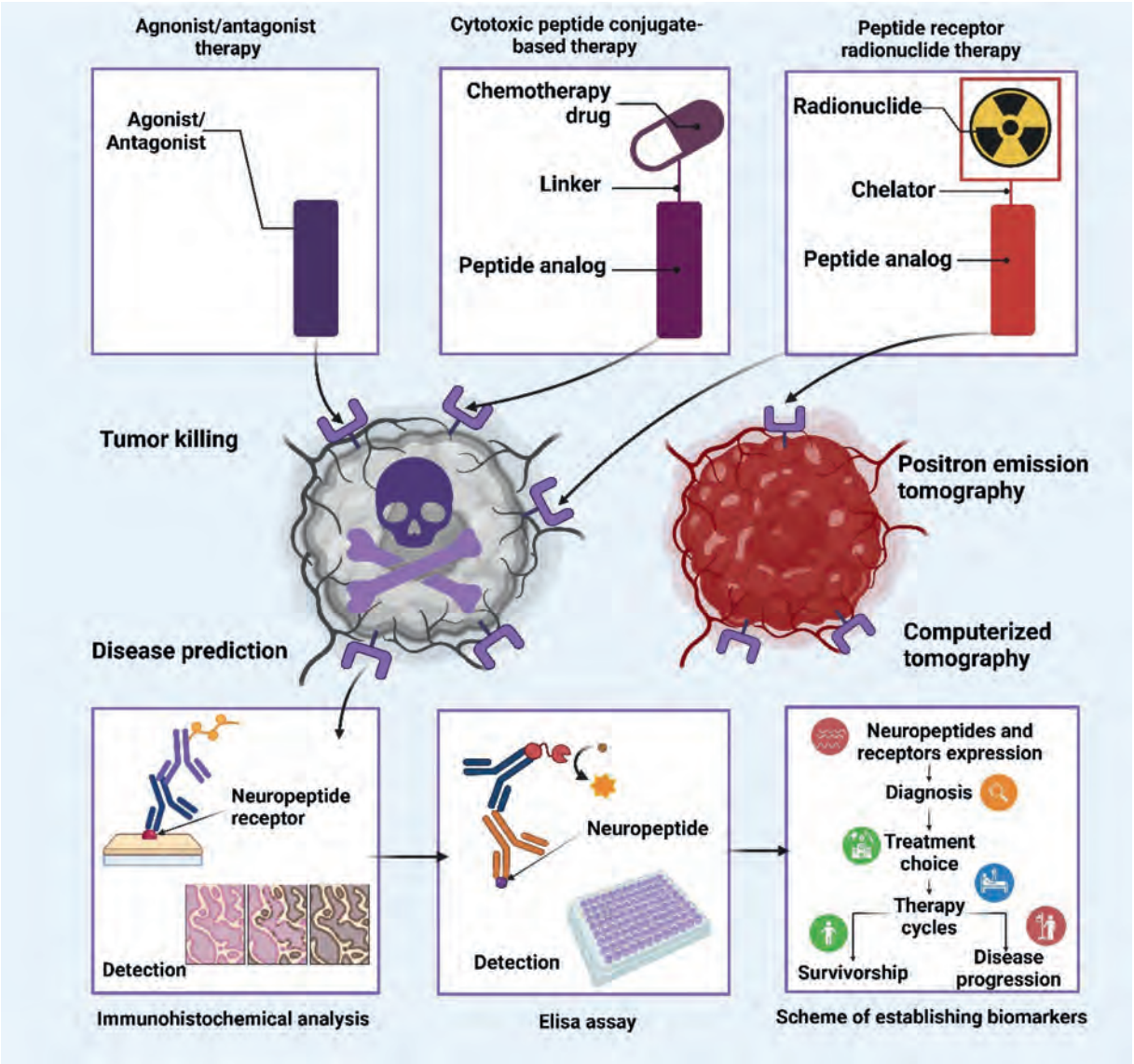

Figure 5 Neuropeptide system may be an ideal target for cancer therapy. Neuropeptide receptors, whose presence on cancer cells differs from their normal counterparts, may be ideal antitumor targets. Current targeting modalities for neuropeptides can be categorized into three types: agonists/antagonist-based cancer therapy, cytotoxic peptide conjugate-based cancer therapy, and peptide-receptor radionuclide therapy. These treatment modalities play an important role in tumor killing as well as tumor imaging. In addition, neuropeptides can be used as cancer biomarkers to determine tumorigenesis, and the severity of their condition, or to inform the choice of treatment. This figure was created using BioRender (https://biorender.com/).

antagonist, aprepitant is well studied. Researchers found Aprepitant could promote apoptosis and exert a broad-spectrum antitumor effect[261]. In cancer cells, aprepitant promotes G2/M-phase cell cycle arrest and also induces apoptosis by increasing reactive oxygen species in mitochondria[283]. However, there is not enough clinical evidence on the anti-tumor effectiveness of aprepitant as a monotherapy. Co-administration of chemotherapy drugs and aprepitant exerts a more effective antitumor action than the administration of chemotherapy drugs alone[284]. It's reported that aprepitant could increase the sensitivity of tumor cells to doxorubicin[285]. Aprepitant could also reduce the side effects induced by chemotherapy drugs. For example, aprepitant could relieve the cardiotoxicity caused by doxorubicin[285]. Co-administration of cisplatin and aprepitant would reduce hepatotoxicity and nephrotoxicity induced by the cisplatin[286]. Several clinical experiments demonstrated aprepitant also had a potential effect on the prevention of chemotherapy-induced nausea and vomiting, which was originally designed to reduce those symptoms[287,288]. Additionally, aprepitant has a high tolerance and safety. The normal cells will not be influenced after administration of a high dose of aprepitant. The IC_{50} for normal cells such as lymphocytes and fibroblasts is higher than the IC_{50} for cancer cells[289,290]. But there remain some faults to overcome. For example, aprepitant can easily cross the BBB, which may affect the central nervous system[142].

It seems that we have completed great achievement to administrate the potential effects of neuropeptide analogs on cancer therapy from pre-clinical perspectives. Another issue worth considering is how we can translate these research findings into clinical implications. To achieve this goal, high-throughput screening based on multi-omics may be a potential method. For

Table 2 Antitumor effect of neuropeptide antagonist/agonist.

Neuropeptide antagonist/ agonist	Target site	Functions	Ref.
Aprepitant	NK1R	Direct antitumor effects, and prevention of chemotherapy-induced nausea and vomiting	264,265
Rolapitant	NK1R	Direct antitumor effects, chemosensitization, and prevention of chemotherapy-induced nausea and vomiting	266
Paltusotine	SSTR2	Direct antitumor effects	267
Octreotide	SSTR2	No direct antitumor effects, and prolonged survival	264
Rimegepant	CALCRL	Direct antitumor effects	269
Alvimopan	MOR	Promotion of faster recovery after surgery	270
Meclinertant	NTSR1	Direct antitumor effects	271

example, Genome-wide pan-GPCR cell libraries are a kind of novel strategy that provides a powerful platform for GPCR ligand screening and facilitates the study of GPCR mechanisms and drug safety evaluation[291].

6.2. *Cytotoxic peptide conjugate-based cancer therapy*

Conventional chemotherapeutic drug treatment may be constrained in its application due to the following: multidrug resistance, toxicity to normal cells, lack of tumor selectivity, and other plights[292]. Targeted delivery of chemotherapeutic drugs could somehow handle these questions. Nowadays, peptide-drug conjugates (PDCs) have been improved, providing small molecular weight, intensive penetration ability, increased circulation stability, low immunogenicity, and simple design, making them advantageous compared to other designs[293,294]. Treatment strategies are further polarized into two main directions: cell-penetrating peptides (CPPs) and tumor-targeting peptides (TTPs). The former tend to penetrate the cell membrane *via* endocytosis- or receptor-mediated uptake pathways. CPPs usually transport insoluble small molecule drugs, proteins, and nucleic acids directly into cells in a non-invasive manner and without disturbing the membrane integrity, have very good tolerability, and do not evoke immunogenicity. While TTPs bind to receptors overexpressed on the tumor cells with high specificity and affinity but poor membrane permeability[295].

Due to the heterogeneous expression of their corresponding receptors, neuropeptides unsurprisingly serve as important carriers in the design of TTP. For example, Moody et al.[296] designed a kind of PDC, VIP-ellipticine conjugates, and confirmed its antitumor role in lung cancer cells *via* $VPAC_1$. They text the increased cytotoxicity of this conjugate in breast cancer cells, and received ideal results[297]. However, NPY-based TTPs are the most widely studied. Kufka et al.[298] have developed NPY-Tubugi-1 conjugates and confirmed their antitumor role in Y1R-overexpressing cell lines, such as HT-29, Colo 320, and PC-3. Ahrens et al.[299] developed a cleavable cytolysin-NPY conjugate and they subsequently proved this conjugate enables a receptor-specific delivery as well as a potent intracellular drug-release with high cytotoxic activity. Another research also connected methotrexate (MTX) to NPY analog and MTX-NPY conjugates showed higher potency than MTX on MTX-resistant cells[300]. BBS-based TTPs show great success in treating small cell lung cancer, due to the overexpression of BBS receptors in over 85% of SCLCs[301,302]. Paclitaxel (PTX), a classical and efficient chemotherapeutic drug was crosslinked with BBS, exerting better antitumor function than unmodified PTX[303]. More importantly, Tao and his team developed a PTX-loaded human serum albumin nanoparticle modified with SP as the targeting ligand[304]. And this delivery system of PTX achieved active glioblastoma multiforme targeting effect and remarkable anti-tumor efficacy. Researchers also combined doxorubicin and BBS analogs to get another PDC[305]. Doxil-BN-AA1 enhanced its anti-tumor effect compared with non-modified pegylated liposomal doxorubicin[306].

6.3. *Peptide-receptor radionuclide therapy*

Peptide receptor radionuclide therapy (PPRT) is a type of targeted radionuclide therapy based on peptides labeled with radionuclides that selectively target cancer cells[307]. Due to the presence of high levels of receptors in tumors and their ability to form ligand−receptor complexes, radiopharmaceuticals can be internalized and accumulate inside tumors more accurately[16]. Depending on the connected radionuclide and the type of emitted radiation, PPRT can be used for tumor killing or tumor imaging. For example, lutetium-177 (^{177}Lu) or yttrium-90 (^{90}Y) would release beta-particles causing DNA single-strand breaks and leading to cell death[308,309]. Despite the direct effect of beta-particles on target cells, neighboring cells will also be influenced using the cross-fire effect and bystander effect, indirectly enhancing the therapeutic effect[310,311]. Gallium-68 (^{68}Ga), copper-64 (^{64}Cu), and fluorine-18 (^{18}F) could release positrons for positron emission tomography (PET) imaging. And γ-emitters such as indium-111 (^{111}In) or technetium-99 (^{99}Tc) could be used in single photon emission computed tomography (SPECT)[312]. These radionuclides could be chelated within multifarious chelators such as DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,20-tetra-acetic acid), DTPA (diethylenetriamine penta-acetic acid), and NODAGA (1,4,7-triazacyclononane,1-glutaric acid-4,7-acetic acid)[313]. The chelators could be further tagged to peptides like octreotide, gastrin, cholecystokinin, neuropeptide Y, and others.

In the previous section, we mentioned that NET overexpresses SSTR at high levels and logically SSA based PPRT shows great potential in the treatment. Many relevant clinical trials are underway or have been concluded to demonstrate their effectiveness (Table 3). A phase III randomized controlled trial NETTER-1 demonstrated that the combination of ^{177}Lu-DOTA-TATE and best supportive care (including Octreotide 30 mg) exceeded the monthly administration of octreotide 60 mg alone in 229 patients affected with NETs[314]. ^{177}Lu-DOTATATE even showed more well-tolerated and safer than high-dose octreotide[315]. In 2018, the FDA subsequently approved using ^{177}Lu-DOTATATE to treat NET patients with SSTR expression[316]. ^{177}Lu-DOTATATE could also be implicated in radioiodine-refractory differentiated thyroid cancer (RrDTC) but its therapeutic response is heterogeneous[317]. A recent systematic review shows that ^{68}Ga-DOTA-SSTR PET studies may revolutionize the routine neuro-oncology practice with the improvement of diagnostic accuracy and patient eligibility for radionuclide therapies[318].

NPY could also serve as an ideal delivered peptide. ^{111}In-pb12 and ^{nat}Tb-pb12 showed high binding affinity to Y1R on MCF-

Table 3 Summary of recent RCTs on PRRTs.

Study name	NCT number	Study design	Population	Arm1	Arm2	Outcomes
NETTER-2	NCT0397288	A phase 3 multi-center, randomized, open-label study	Patients with Grade 2 and Grade 3 advanced GEP-NET	Lutathera and long-acting octreotide	High dose long-acting octreotide	Progression free survival, objective response rate, time to decline total health status; duration of response, rate of adverse events, time to death
NeoLuPaNET	NCT04385992	A prospective phase II single-arm trial	Resectable PanNETs,	^{177}Lu-dotatate	NA	Postoperative morbidity, postoperative mortality
COMPETE	NCT03049189	A prospective, randomized, controlled, open-label, multicenter phase 3 study	Patients with inoperable, progressive, somatostatin receptor-positive (SSTR^{+}), neuroendocrine tumors of gastroenteric or pancreatic origin (GEP-NET).	^{177}Lu- edotreotide	Everolimus	Progression-free survival, overall survival
ALPHAMEDIX02	NCT05153772	A phase 2 open label multicenter, single-arm study	Patients with positive somatostatin positive neuroendocrine tumors with no prior history of peptide receptor radionuclide therapy (PRRT naïve)	^{212}Pb-dotamtate (AlphaMedix)	NA	Objective response rate by response evaluation criteria in solid tumors, number of patients with treatment-related adverse events, median progression free survival; overall survival, time to tumor progression
	NCT03773133	A multicenter, open-label phase 1/2 study	Patients with locally advanced or metastatic cancers expressing sstr2 as identified by Satoreotide trizoxetan positron emission tomography (PET/CT) scans.	^{177}Lu-OPS201,68Ga-OPS202	NA	Maximum tolerated cumulative activity, objective response rate over the two treatment cycle
	NCT04318561	A prospective, randomized, double-blinded study	Patients with histologically confirmed metastatic, well-differentiated neuroendocrine tumors	^{68}Ga-dotate	^{68}Ga DOTA-LM3 ^{68}Ga-dotate	Blood pressure, heart rate, pulse oximetry, electrocardiogram QT interval, incidence of adverse effect, C_{max} (maximum concentration achieved in units of Bq/mL), T_{max} (time to achieve C_{max}), Standard uptake value (SUV), Lesion numbers
ETCTN 10388	NCT04234568	A multicenter randomized phase 2 trial	Patients with well differentiated somatostatin receptor-positive neuroendocrine tumor	^{177}Lu-dotatate	Triapine + ^{177}Lu-dotatate	Overall response rate, median progression free survival, plasma deoxyribonucleosides, circulating DNA and plasma hPG80
LEVEL	NCT05918302	A randomized, open-label, phase 3 international trial	Patients with progressive, advanced, and well/moderately differentiated NETs of lung (typical/atypical) or thymic origin.	^{177}Lu- edotreotide	Everolimus	Progression free survival, overall response rate, duration of response, overall survival, safety, and quality of life
COMPOSE	NCT04919226	A prospective, randomized, controlled, open-label, multicenter study	Patients with well-differentiated aggressive grade 2 and grade 3, somatostatin receptor-positive, neuroendocrine tumors of gastroenteric or pancreatic origin.	^{177}Lu-edotreotide	Capecitabine+ temozolomide	Progression free survival, objective response rate, overall survival, duration of response, disease control rate, duration of disease control

7 cells and their specific uptake has also been confirmed in the xenograft model[319]. ^{68}Ga-DOTA-BVD15 have shown great potential to be used in PET imaging[320]. And BBS analogs labeled with ^{111}In, ^{64}Cu, ^{99m}Tc, ^{68}Ga, and ^{18}F were also texted in imaging studies[321]. ^{99m}Tc-BB$^{2-14}$ visualized prostate cancer in patients[322]. When using ^{99m}Tc-RGD-BB, tumors were visualized in 6/6 breast cancer patients[323]. It remains to be determined if the imaging of GRPR will be useful in the early detection of breast and/or prostate cancer. However, there is a lack of validated large-scale clinical trials to demonstrate their potential for clinical implication.

6.4. Cancer biomarkers

The early detection of cancer can reduce cancer mortality and save lives to a great extent. Thus, a great deal of effort has been devoted to the exploration of new technologies to detect early signs of the disease. Cancer biomarkers cover a broad range of biochemical entities, such as nucleic acids, proteins, sugars, small metabolites, and cytogenetic and cytokinetic parameters, as well as entire tumor cells found in the fluid.

Given the stability of neuropeptides in the blood and their differential expression indicative of tumor progression, plasma neuropeptide concentrations may serve as an ideal biomarker. For example, neuroblastoma is frequently connected with elevated plasma levels of NPY, which are also associated with poor clinical outcomes[324]. What's more, SP was observed to be increased in ovarian tumors indicating worsened outcomes[325]. Another example is that calcitonin gene-related peptide is undetectable in the plasma of healthy individuals while it's drastically increased in patients with medullary thyroid cancer[326]. It is also interesting to note that before and after radiotherapy for prostate cancer, the levels of neuropeptides such as VIP and CGRP in the bloodstream change and increase significantly[327].

Compared to neuropeptides, neuropeptide receptors may be able to provide more and more accurate information about a patient's condition, associated with polymorphism of the receptor and differential expression between normal and neoplastic tissues. Taking NPY receptors as an important pattern, back in the 21st century, Reubi used autoradiography to identify the expression of NPY receptors in breast carcinoma and they found that Y1 receptors are significantly overexpressed in 85% of primary carcinomas and 100% of lymph node metastases[328]. However, normal breast tissue dominantly expresses Y2 receptors, indicating the expression shift from Y2 to Y1 when cells undergo neoplastic transformation[328]. More importantly, cumulative evidence suggests that different NPY receptors may mediate different functions, which in turn generalizes to the following rule: (1) NPY receptors are mainly expressed in specific endocrine tumors, epithelial malignancies, and embryonal tumors; (2) tumor cells express predominantly Y1 and/or Y2 subtypes; (3) Y1 receptors are mainly involved in the modulation of cancer cell proliferation, whereas Y2 receptor activation appears to promote angiogenesis; and (4) Y5 receptors regulate cell proliferation, chemotactic migration, invasion, and contribute to chemoresistance[16]. Other neuropeptide receptors may serve as negative predictors. For example, according to various clinical data, a decrease in KISS1R expression is associated with poorer prognosis in cancer patients, and the downregulation of its ligand-KP is linked to recurrent cancer invasion and shorter survival[168,329].

Perhaps continuing to focus on the expression of a single neuropeptide/receptor as a tumor marker is no longer sufficient for the status quo. What we should be thinking about is how to develop more commercially available high-throughput assays for better pre-cancer diagnosis and prediction of tumor patients by combined neuropeptide/neuropeptide receptor expression levels.

7. Conclusions

Studies on the influence of the neuropeptide system in cancer initiation and progression have grown by leaps and bounds. Plenty of neuropeptides and their corresponding receptors are found in a variety of cancers and their TMEs. Some characters of them could be summarized but we often receive inconsistent findings. Neuropeptides exert distinct actions that vary from cell to cell and cancer to cancer, probably associated with different downstream signaling cascades. These signaling cascades lead to totally different "fates" of cancer cells, reflecting on cancer hallmarks. More importantly, there may be mutations in key regulatory proteins and their corresponding genes in the signaling pathway, which in turn may lead to the accumulation of signals. Take Kirsten rat sarcoma (KRAS), the most common mutated gene in colorectal cancer as an example. Once the mutations occur, the hydrolysis of GTP is interrupted and nucleotide exchange is subsequently enhanced, which further leads to the accumulation of activated KRAS protein. Staining activation of KRAS signaling finally promotes cancer progression[330]. Researchers also found Gαq mutations are associated with worse prognosis in uveal melanoma patients. More importantly. VGF, a kind of neuropeptide precursor, is upregulated by the aberrant Gαq/MAPK/CREB axis. VGF further binds to TGFBR2 and finally promotes endothelial−mesenchymal transition and cancer metastasis[331]. Another important reason leading to the paradoxical roles of certain neuropeptides across different tumor types is associated with the homo-oligomerization of neuropeptide receptors, all of which are GPCRs[332]. GPCRs can interact with each other to form homomers and heteromers, attaining unique expression, ligand binding, intracellular signaling trafficking, and exerting more sophisticated effects[333]. For example, MOR and DOR combine and form heteromers, which are coupled with distinct signaling pathways. MOR−DOR heteromers are associated with alterations in the induction of tolerance in response to morphine and other opioids[334]. It's also observed that chronic morphine administration would increase the abundance of MOR-DOR heteromers, indicating the compensatory role of oligomerization in the regulation of neuropeptide signaling[335]. However, oligomerization of various types of GPCRs in tumor cells has rarely been discussed, and this may also be a direction for future research. The different secretomes of different tumors likewise influence the balance of neuropeptide signaling, which is also a long-ignored reason. More importantly, different results may be obtained by using different experimental models. The experiment led by Tavazoie is the best illustration. It seems that overactivation of SP signaling leads to the death of tumor cells, but the contents released by these dying cells, such as single-stranded RNAs, subsequently promote the proliferation and metastasis of the remaining ones[184]. Alternatively, certain neuropeptides may have more pronounced effects on immune cells or other cellular components compared to tumor cells, and these indirect impacts are also frequently overlooked by us.

Current cancer research on peptides is focused on three aspects: structure, localization, and function[16]. On a molecular level, studies on the structure of neuropeptides and corresponding receptors provide the solid fundament for further related studies. An exploration of localization could be demonstrated as a search

for novel neuropeptide receptors discrepant expressed in certain tumors. As for functions, there are two directions to spare. First, exploration of the functions of neuropeptides and receptors under physiological conditions needs to be enhanced, which is basic for related research in a tumor-bearing context. Second, the functions of neuropeptides and receptors in cancer progression need to be well-summarized. It is also wise to rethink the probabilities for them as a potential therapeutic target.

Previous studies on neuropeptides in tumors have been largely limited to techniques such as immunohistochemistry, providing only a glimpse of the complex neuropeptide system. Different neuropeptide systems have different effects on different tumors, and these conclusions are often contradictory, deeply troubling researchers. How to distinguish the contradictory functions of neuropeptides in TME and precisely target subsets with desired functionality remains a huge challenge. To achieve this, we need to plant a more precise landscape. Single-cell transcriptomics and other omics point the way out of this dilemma. We can build a clear spectrum of the expression situation of neuropeptides and their receptors in TME with advanced techniques. Hökfelt's group[336] have created a detailed landscape of the human prefrontal cortex and presented an overview of the peptidergic systems in 17 subregions of hPFC based on RNA sequencing and RNAscope. Their works contribute to great improvement in the study of neuropeptides and somehow indicate the future directions. We need plenty of landscapes for plenty of kinds of cancers. We confirmedly believe that the combination of various bioanalytical, bioinformatics, and molecular neuropharmacological tools will drive neuropeptide research to new frontiers with likely benefits toward cancer therapy.

Acknowledgments

This work was financially supported by the High-Level Talent Introduction Funds from the First Hospital of Lanzhou University (China). We apologize to colleagues whose important work could not be cited due to space constraints.

Author contributions

Zikai Dong: Writing − original draft, Visualization, Conceptualization. Yongfei Wang: Writing − original draft. Weilin Jin: Writing − review & editing, Supervision, Funding acquisition, Conceptualization.

Conflicts of interest

The authors declare that they have no competing interests.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015;**65**:87−108.
2. Le TT, Oudin MJ. Understanding and modeling nerve-cancer interactions. *Dis Model Mech* 2023;**16**:dmm049729.
3. Olar A, He D, Florentin D, Ding Y, Ayala G. Biologic correlates and significance of axonogenesis in prostate cancer. *Hum Pathol* 2014;**45**:1358−64.
4. Rowe CW, Dill T, Griffin N, Jobling P, Faulkner S, Paul JW, et al. Innervation of papillary thyroid cancer and its association with extrathyroidal invasion. *Sci Rep* 2020;**10**:1539.
5. Li J, Ma Q, Liu H, Guo K, Li F, Li W, et al. Relationship between neural alteration and perineural invasion in pancreatic cancer patients with hyperglycemia. *PLoS One* 2011;**6**:e17385.
6. Pundavela J, Roselli S, Faulkner S, Attia J, Scott RJ, Thorne RF, et al. Nerve fibers infiltrate the tumor microenvironment and are associated with nerve growth factor production and lymph node invasion in breast cancer. *Mol Oncol* 2015;**9**:1626−35.
7. Borniger JC. Cancer neuroscience at the brain-body interface. *Genes Dev* 2024;**38**:787−92.
8. Retamales-Ortega R, Oróstica L, Vera C, Cuevas P, Hernández A, Hurtado I, et al. Role of nerve growth factor (NGF) and miRNAs in epithelial ovarian cancer. *Int J Mol Sci* 2017;**18**:507.
9. Khosla R, Banik A, Kaushal S, Battu P, Gupta D, Anand A. Is brain-derived neurotrophic factor: a common link between neurodegenerative disorders and cancer?. *Curr Alzheimer Res* 2019;**16**:344−52.
10. Kanwore K, Kanwore K, Guo X, Xia Y, Zhou H, Zhang L, et al. Testosterone upregulates glial cell line-derived neurotrophic factor (GDNF) and promotes neuroinflammation to enhance glioma cell survival and proliferation. *Inflamm Regen* 2023;**43**:49.
11. Nasarre P, Potiron V, Drabkin H, Roche J. Guidance molecules in lung cancer. *Cell Adhes Migr* 2010;**4**:130−45.
12. Jiang S, Hu L, Wang X, Li J, Zhang Z. Neurotransmitters: emerging targets in cancer. *Oncogene* 2020;**39**:503−15.
13. Körner M, Waser B, Reubi JC. Neuropeptide Y receptors in renal cell carcinomas and nephroblastomas. *Int J Cancer* 2005;**115**:734−41.
14. Körner M, Waser B, Reubi JC. Neuropeptide Y receptor expression in human primary ovarian neoplasms. *Lab Invest* 2004;**84**:71−80.
15. Ashraf S, Crowe R, Loizidou MC, Turmaine M, Taylor I, Burnstock G. The absence of autonomic perivascular nerves in human colorectal liver metastases. *Br J Cancer* 1996;**73**:349−59.
16. Wu Y, Berisha A, Borniger JC. Neuropeptides in cancer: friend and foe?. *Adv Biol(Weinh)* 2022;**6**:2200111.
17. Zhang X, Li L, Hu W, Hu M, Tao Y, Hu H, et al. Neurokinin-1 receptor promotes non-small cell lung cancer progression through transactivation of EGFR. *Cell Death Dis* 2022;**13**:41.
18. Hökfelt T, Bartfai T, Bloom F. Neuropeptides: opportunities for drug discovery. *Lancet Neurol* 2003;**2**:463−72.
19. Gozes I, Brenneman DE, Geppetti P, Kastin AJ, Mains RE, Moody TW, et al. Neuropeptides: brain messengers of many faces. *Trends Neurosci* 2001;**24**:687−90.
20. Bertagna X. Proopiomelanocortin-derived peptides. *Endocrinol Metab Clin North Am* 1994;**23**:467−85.
21. Böhm M, Grässel S. Role of proopiomelanocortin-derived peptides and their receptors in the osteoarticular system: from basic to translational research. *Endocr Rev* 2012;**33**:623−51.
22. Harno E, Gali Ramamoorthy T, Coll AP, White A. POMC: the physiological power of hormone processing. *Physiol Rev* 2018;**98**:2381−430.
23. Vincent SR, Johansson O, Hökfelt T, Meyerson B, Sachs C, Elde RP, et al. Neuropeptide coexistence in human cortical neurones. *Nature* 1982;**298**:65−7.
24. Wang Y, Wang M, Yin S, Jang R, Wang J, Xue Z, et al. NeuroPep: a comprehensive resource of neuropeptides. *Database J Biol Databases Curation* 2015;**2015**:bav038.
25. Bakos J, Zatkova M, Bacova Z, Ostatnikova D. The role of hypothalamic neuropeptides in neurogenesis and neuritogenesis. *Neural Plast* 2016;**2016**:3276383.
26. Hökfelt T, Broberger C, Xu ZQ, Sergeyev V, Ubink R, Diez M. Neuropeptides—an overview. *Neuropharmacology* 2000;**39**:1337−56.
27. Zhang M, Chen T, Lu X, Lan X, Chen Z, Lu S. G protein-coupled receptors (GPCRs): advances in structures, mechanisms, and drug discovery. *Signal Transduct Target Ther* 2024;**9**:1−43.
28. Hu G, Mai T, Chen C. Visualizing the GPCR network: classification and evolution. *Sci Rep* 2017;**7**:15495.
29. Pal K, Melcher K, Xu H. Structure and mechanism for recognition of peptide hormones by Class B G-protein-coupled receptors. *Acta Pharmacol Sin* 2012;**33**:300−11.

30. Pin JP, Galvez T, Prézeau L. Evolution, structure, and activation mechanism of family 3/C G-protein-coupled receptors. *Pharmacol Ther* 2003;**98**:325−54.
31. Chun L, Zhang W, Liu J. Structure and ligand recognition of class C GPCRs. *Acta Pharmacol Sin* 2012;**33**:312−23.
32. Kozielewicz P, Turku A, Schulte G. Molecular pharmacology of class F receptor activation. *Mol Pharmacol* 2020;**97**:62−71.
33. Neves SR, Ram PT, Iyengar R. G protein pathways. *Science* 2002; **296**:1636−9.
34. MacDonald JF, Kotecha SA, Lu W, Jackson MF. Convergence of PKC-dependent kinase signal cascades on NMDA receptors. *Curr Drug Targets* 2001;**2**:299−312.
35. Cole SW, Sood AK. Molecular pathways: beta-adrenergic signaling in cancer. *Clin Cancer Res* 2012;**18**:1201−6.
36. de Rooij J, Zwartkruis FJ, Verheijen MH, Cool RH, Nijman SM, Wittinghofer A, et al. Epac is a Rap1 guanine-nucleotide-exchange factor directly activated by cyclic AMP. *Nature* 1998;**396**:474−7.
37. Taskén K, Skålhegg BS, Taskén KA, Solberg R, Knutsen HK, Levy FO, et al. Structure, function, and regulation of human cAMP-dependent protein kinases. *Adv Second Messenger Phosphoprotein Res* 1997;**31**:191−204.
38. Langendorf CG, O'Brien MT, Ngoei KRW, McAloon LM, Dhagat U, Hoque A, et al. CaMKK2 is inactivated by cAMP−PKA signaling and 14-3-3 adaptor proteins. *J Biol Chem* 2020;**295**:16239−50.
39. Rehfuss RP, Walton KM, Loriaux MM, Goodman RH. The cAMP-regulated enhancer-binding protein ATF-1 activates transcription in response to cAMP-dependent protein kinase A. *J Biol Chem* 1991; **266**:18431−4.
40. Ullah R, Yin Q, Snell AH, Wan L. RAF−MEK−ERK pathway in cancer evolution and treatment. *Semin Cancer Biol* 2022;**85**:123−54.
41. Whitehead IP, Zohn IE, Der CJ. Rho GTPase-dependent transformation by G protein-coupled receptors. *Oncogene* 2001;**20**: 1547−55.
42. Yamamoto M, Marui N, Sakai T, Morii N, Kozaki S, Ikai K, et al. ADP-ribosylation of the rhoA gene product by botulinum C3 exoenzyme causes Swiss 3T3 cells to accumulate in the G1 phase of the cell cycle. *Oncogene* 1993;**8**:1449−55.
43. Baranwal S, Alahari SK. Rho GTPase effector functions in tumor cell invasion and metastasis. *Curr Drug Targets* 2011;**12**:1194−201.
44. Ramos EJB, Meguid MM, Campos ACL, Coelho JCU. Neuropeptide Y, α-melanocyte−stimulating hormone, and monoamines in food intake regulation. *Nutrition* 2005;**21**:269−79.
45. Zhang L, Hernandez-Sanchez D, Herzog H. Regulation of feeding-related behaviors by arcuate neuropeptide Y neurons. *Endocrinology* 2019;**160**:1411−20.
46. van den Pol AN, Yao Y, Fu L, Foo K, Huang H, Coppari R, et al. Neuromedin B and gastrin-releasing peptide excite arcuate nucleus neuropeptide Y neurons in a novel transgenic mouse expressing strong Renilla green fluorescent protein in NPY neurons. *J Neurosci* 2009;**29**:4622−39.
47. Holzer P, Reichmann F, Farzi A. Neuropeptide Y, peptide YY and pancreatic polypeptide in the gut−brain axis. *Neuropeptides* 2012;**46**: 261−74.
48. Fujimiya M, Inui A. Peptidergic regulation of gastrointestinal motility in rodents. *Peptides* 2000;**21**:1565−82.
49. Diaz Heijtz R, Wang S, Anuar F, Qian Y, Björkholm B, Samuelsson A, et al. Normal gut microbiota modulates brain development and behavior. *Proc Natl Acad Sci U S A* 2011;**108**: 3047−52.
50. Dyzma M, Boudjeltia KZ, Faraut B, Kerkhofs M. Neuropeptide Y and sleep. *Sleep Med Rev* 2010;**14**:161−5.
51. Manfredi-Lozano M, Leysen V, Adamo M, Paiva I, Rovera R, Pignat JM, et al. GnRH replacement rescues cognition in Down syndrome. *Science* 2022;**377**:eabq4515.
52. Shi Z, Bonillas AC, Wong J, Padilla SL, Brooks VL. Neuropeptide Y suppresses thermogenic and cardiovascular sympathetic nerve activity *via* Y1 receptors in the paraventricular nucleus and dorsomedial hypothalamus. *J Neuroendocrinol* 2021;**33**:e13006.
53. Pinho-Ribeiro FA, Verri WA, Chiu IM. Nociceptor sensory neuron-immune interactions in pain and inflammation. *Trends Immunol* 2017;**38**:5−19.
54. Gressens P, Paindaveine B, Hill JM, Evrard P, Brenneman DE. Vasoactive intestinal peptide shortens both G1 and S phases of neural cell cycle in whole postimplantation cultured mouse embryos. *Eur J Neurosci* 1998;**10**:1734−42.
55. Millar BC, Schlüter KD, Zhou X, McDermott BJ, Piper HM. Neuropeptide Y stimulates hypertrophy of adult ventricular cardiomyocytes. *Am J Physiol* 1994;**266**:C1271−7.
56. Dockray GJ. Restraining the trophic effects of gastrin. *Peptides* 2016; **82**:128−9.
57. Martínez-Herrero S, Martínez A. Adrenomedullin: not just another gastrointestinal peptide. *Biomolecules* 2022;**12**:156.
58. Keleg S, Kayed H, Jiang X, Penzel R, Giese T, Büchler MW, et al. Adrenomedullin is induced by hypoxia and enhances pancreatic cancer cell invasion. *Int J Cancer* 2007;**121**:21−32.
59. Letizia C, Tamburrano G, Alo P, Paoloni A, Caliumi C, Marinoni E, et al. Adrenomedullin, a new peptide, in patients with insulinoma. *Eur J Endocrinol* 2001;**144**:517−20.
60. Censi S, Manso J, Mian C. Other markers of medullary thyroid cancer, not only calcitonin. *Eur J Endocrinol* 2023;**188**:lvac009.
61. Warrington JI, Richards GO, Wang N. The role of the calcitonin peptide family in prostate cancer and bone metastasis. *Curr Mol Biol Rep* 2017;**3**:197−203.
62. Lin S, Li Y, Sun X, Chen Q, Huang S, Lin S, et al. Update on the role of neuropeptide Y and other related factors in breast cancer and osteoporosis. *Front Endocrinol* 2021;**12**:705499.
63. Kim SK, Kwon GY, Shin SW, Choe BK. Expression of neuropeptide Y by glutamatergic stimulation in rat C6 glioma cells. *Neurochem Int* 2000;**36**:19−26.
64. Sánchez ML, Rodríguez FD, Coveñas R. Neuropeptide Y peptide family and cancer: antitumor therapeutic strategies. *Int J Mol Sci* 2023;**24**:9962.
65. Körner M, Reubi JC. NPY receptors in human cancer: a review of current knowledge. *Peptides* 2007;**28**:419−25.
66. Janssens K, Vanhoutte G, Lybaert W, Demey W, Decaestecker J, Hendrickx K, et al. NPY methylated ctDNA is a promising biomarker for treatment response monitoring in metastatic colorectal cancer. *Clin Cancer Res Off J Am Assoc Cancer Res* 2023;**29**: 1741−50.
67. Tilan J, Kitlinska J. Neuropeptide Y (NPY) in tumor growth and progression: lessons learned from pediatric oncology. *Neuropeptides* 2016;**55**:55−66.
68. Li Y, Chen S, Li Z. Plasma neuropeptide Y (NPY) levels in patients with gastric and colorectal carcinomas. *Chin J Oncol* 1998;**20**: 213−5.
69. Kristensen G, Røder MA, Berg KD, Elversang J, Iglesias-Gato D, Moreira J, et al. Predictive value of combined analysis of pro-NPY and ERG in localized prostate cancer. *APMIS Acta Pathol Microbiol Immunol Scand* 2018;**126**:804−13.
70. Sigorski D, Wesołowski W, Gruszecka A, Gulczyński J, Zieliński P, Misiukiewicz S, et al. Neuropeptide Y and its receptors in prostate cancer: associations with cancer invasiveness and perineural spread. *J Cancer Res Clin Oncol* 2023;**149**:5803−22.
71. Waldmann J, Fendrich V, Reichert M, Hecker A, Bartsch DK, Padberg W, et al. Expression of neuropeptide Y and its receptors Y1 and Y2 in pancreatic intraepithelial neoplasia and invasive pancreatic cancer in a transgenic mouse model and human samples of pancreatic cancer. *J Surg Res* 2018;**223**:230−6.
72. Zhou Q, Zhang Z, Long S, Li W, Wang B, Liang N. Opioids in cancer: the κ-opioid receptor. *Mol Med Rep* 2022;**25**:44 (Review).
73. Zhang H, Zhou D, Gu J, Qu M, Guo K, Chen W, et al. Targeting the mu-opioid receptor for cancer treatment. *Curr Oncol Rep* 2021;**23**: 111.
74. Belltall A, Mazzinari G, Diaz-Cambronero O, Eroles P, Argente Navarro MP. Antagonists of the mu-opioid receptor in the cancer patient: fact or fiction?. *Curr Oncol Rep* 2022;**24**:1337−49.

75. Singleton PA, Moss J, Karp DD, Atkins JT, Janku F. The mu opioid receptor: a new target for cancer therapy?. *Cancer* 2015;**121**:2681−8.
76. Momen Razmgah M, Ghahremanloo A, Javid H, AlAlikhan A, Afshari AR, Hashemy SI. The effect of substance P and its specific antagonist (aprepitant) on the expression of MMP-2, MMP-9, VEGF, and VEGFR in ovarian cancer cells. *Mol Biol Rep* 2022;**49**:9307−14.
77. Ebrahimi S, Javid H, Alaei A, Hashemy SI. New insight into the role of substance P/neurokinin-1 receptor system in breast cancer progression and its crosstalk with microRNAs. *Clin Genet* 2020;**98**: 322−30.
78. Muñoz M, Coveñas R. Involvement of substance P and the NK-1 receptor in pancreatic cancer. *World J Gastroenterol* 2014;**20**: 2321−34.
79. Iwamura M, Egawa S, Uchida T, Koshiba K, Cockett AT, Gershagen S. Suppression of the growth and invasiveness of human prostate cancer cells *in vitro* by neuropeptide antagonist substance P analogues. *Urol Oncol* 1998;**4**:24−8.
80. Kunikowska J, Morgenstern A, Pełka K, Bruchertseifer F, Królicki L. Targeted alpha therapy for glioblastoma. *Front Med* 2022;**9**:1085245.
81. Batlle E, Clevers H. Cancer stem cells revisited. *Nat Med* 2017;**23**: 1124−34.
82. Najafi M, Mortezaee K, Majidpoor J. Cancer stem cell (CSC) resistance drivers. *Life Sci* 2019;**234**:116781.
83. Peng J, Chen H, Zhang B. Nerve-stem cell crosstalk in skin regeneration and diseases. *Trends Mol Med* 2022;**28**:583−95.
84. Kitamura K, Kangawa K, Kawamoto M, Ichiki Y, Nakamura S, Matsuo H, et al. Adrenomedullin: a novel hypotensive peptide isolated from human pheochromocytoma. *Biochem Biophys Res Commun* 1993;**192**:553−60.
85. Larrue C, Guiraud N, Mouchel PL, Dubois M, Farge T, Gotanègre M, et al. Adrenomedullin−CALCRL axis controls relapse-initiating drug tolerant acute myeloid leukemia cells. *Nat Commun* 2021;**12**:422.
86. Angenendt L, Bormann E, Pabst C, Alla V, Görlich D, Braun L, et al. The neuropeptide receptor calcitonin receptor-like (CALCRL) is a potential therapeutic target in acute myeloid leukemia. *Leukemia* 2019;**33**:2830−41.
87. Simonetti G, Angeli D, Petracci E, Fonzi E, Vedovato S, Sperotto A, et al. Adrenomedullin expression characterizes leukemia stem cells and associates with an inflammatory signature in acute myeloid leukemia. *Front Oncol* 2021;**11**:684396.
88. Coffman L, Mooney C, Lim J, Bai S, Silva I, Gong Y, et al. Endothelin receptor-A is required for the recruitment of antitumor T cells and modulates chemotherapy induction of cancer stem cells. *Cancer Biol Ther* 2013;**14**:184−92.
89. Pérez-Moreno P, Indo S, Niechi I, Huerta H, Cabello P, Jara L, et al. Endothelin-converting enzyme-1c promotes stem cell traits and aggressiveness in colorectal cancer cells. *Mol Oncol* 2020;**14**:347−62.
90. Herroon MK, Rajagurubandara E, Hardaway AL, Powell K, Turchick A, Feldmann D, et al. Bone marrow adipocytes promote tumor growth in bone *via* FABP4-dependent mechanisms. *Oncotarget* 2013;**4**:2108−23.
91. Tang K, Liu J, Jovanovic L, An J, Hill MM, Vela I, et al. Adipocytes promote prostate cancer stem cell self-renewal through amplification of the cholecystokinin autocrine loop. *Oncotarget* 2015;**7**:4939−48.
92. Mashaghi A, Marmalidou A, Tehrani M, Grace PM, Pothoulakis C, Dana R. Neuropeptide substance P and the immune response. *Cell Mol Life Sci CMLS* 2016;**73**:4249−64.
93. Lee S, Pi S, Kim S, Min K, Lee H, Chang H, et al. Substance P regulates macrophage inflammatory protein 3alpha/chemokine C−C ligand 20 (CCL20) with heme oxygenase-1 in human periodontal ligament cells. *Clin Exp Immunol* 2007;**150**:567−75.
94. Guo C, Lai J, Luo H, Douglas S, Ho W. Substance P up-regulates macrophage inflammatory protein-1beta expression in human T lymphocytes. *J Neuroimmunol* 2002;**131**:160−7.
95. Castellani ML, Vecchiet J, Salini V, Conti P, Theoharides TC, Caraffa A, et al. Stimulation of CCL2 (MCP-1) and CCL2 mRNA by substance P in LAD2 human mast cells. *Transl Res J Lab Clin Med* 2009;**154**:27−33.
96. Tran MT, Lausch RN, Oakes JE. Substance P differentially stimulates IL-8 synthesis in human corneal epithelial cells. *Investig Ophthalmol Vis Sci* 2000;**41**:3871−7.
97. Mathers AR, Tckacheva OA, Janelsins BM, Shufesky WJ, Morelli AE, Larregina AT. *In vivo* signaling through the neurokinin 1 receptor favors transgene expression by Langerhans cells and promotes the generation of Th1- and Tc1-biased immune responses. *J Immunol Baltim Md* 1950 2007;**178**:7006−17.
98. Takashima A. Harnessing DCs by substance P. *Blood* 2013;**121**: 2815−6.
99. Janelsins BM, Sumpter TL, Tkacheva OA, Rojas-Canales DM, Erdos G, Mathers AR, et al. Neurokinin-1 receptor agonists bias therapeutic dendritic cells to induce type 1 immunity by licensing host dendritic cells to produce IL-12. *Blood* 2013;**121**:2923−33.
100. Rameshwar P, Gascón P. Substance P (SP) mediates production of stem cell factor and interleukin-1 in bone marrow stroma: potential autoregulatory role for these cytokines in SP receptor expression and induction. *Blood* 1995;**86**:482−90.
101. Mei G, Xia L, Zhou J, Zhang Y, Tuo Y, Fu S, et al. Neuropeptide SP activates the WNT signal transduction pathway and enhances the proliferation of bone marrow stromal stem cells. *Cell Biol Int* 2013; **37**:1225−32.
102. Calvo CF, Chavanel G, Senik A. Substance P enhances IL-2 expression in activated human T cells. *J Immunol Baltim Md* 1950 1992;**148**:3498−504.
103. Lambrecht BN, Germonpré PR, Everaert EG, Carro-Muino I, De Veerman M, de Felipe C, et al. Endogenously produced substance P contributes to lymphocyte proliferation induced by dendritic cells and direct TCR ligation. *Eur J Immunol* 1999;**29**:3815−25.
104. Fu W, Qin B, Zhou A, Yu Q, Huang Q, Liang Z. Regulation of NK92-MI cell cytotoxicity by substance P. *Scand J Immunol* 2011; **74**:107−13.
105. Serra MC, Bazzoni F, Della Bianca V, Greskowiak M, Rossi F. Activation of human neutrophils by substance P. Effect on oxidative metabolism, exocytosis, cytosolic Ca^{2+} concentration and inositol phosphate formation. *J Immunol Baltim Md* 1950 1988;**141**: 2118−24.
106. Wozniak A, McLennan G, Betts WH, Murphy GA, Scicchitano R. Activation of human neutrophils by substance P: effect on FMLP-stimulated oxidative and arachidonic acid metabolism and on antibody-dependent cell-mediated cytotoxicity. *Immunology* 1989; **68**:359−64.
107. Hartung HP, Toyka KV. Activation of macrophages by substance P: induction of oxidative burst and thromboxane release. *Eur J Pharmacol* 1983;**89**:301−5.
108. Murris-Espin M, Pinelli E, Pipy B, Leophonte P, Didier A. Substance P and alveolar macrophages: effects on oxidative metabolism and eicosanoid production. *Allergy* 1995;**50**:334−9.
109. Tancowny BP, Karpov V, Schleimer RP, Kulka M. Substance P primes lipoteichoic acid- and Pam3CysSerLys4-mediated activation of human mast cells by up-regulating Toll-like receptor 2. *Immunology* 2010;**131**:220−30.
110. Ansel JC, Kaynard AH, Armstrong CA, Olerud J, Bunnett N, Payan D. Skin-nervous system interactions. *J Invest Dermatol* 1996; **106**:198−204.
111. Eglezos A, Andrews PV, Boyd RL, Helme RD. Effects of capsaicin treatment on immunoglobulin secretion in the rat: further evidence for involvement of tachykinin-containing afferent nerves. *J Neuroimmunol* 1990;**26**:131−8.
112. Maghni K, Michoud MC, Alles M, Rubin A, Govindaraju V, Meloche C, et al. Airway smooth muscle cells express functional neurokinin-1 receptors and the nerve-derived preprotachykinin-a gene: regulation by passive sensitization. *Am J Respir Cell Mol Biol* 2003;**28**:103−10.
113. Ziche M, Morbidelli L, Pacini M, Geppetti P, Alessandri G, Maggi CA. Substance P stimulates neovascularization *in vivo* and proliferation of cultured endothelial cells. *Microvasc Res* 1990;**40**: 264−78.

114. Jimeno R, Gomariz RP, Gutiérrez-Cañas I, Martínez C, Juarranz Y, Leceta J. New insights into the role of VIP on the ratio of T-cell subsets during the development of autoimmune diabetes. *Immunol Cell Biol* 2010;**88**:734−45.
115. Sharma V, Delgado M, Ganea D. VIP protects Th2 cells by down-regulating granzyme B expression. *Ann N Y Acad Sci* 2006;**1070**: 540−4.
116. Hou Y, Sun L, LaFleur MW, Huang L, Lambden C, Thakore PI, et al. Neuropeptide signalling orchestrates T cell differentiation. *Nature* 2024;**635**:444−52.
117. Bagnato A, Rosanò L. The endothelin axis in cancer. *Int J Biochem Cell Biol* 2008;**40**:1443−51.
118. Brewster LM, Garcia VP, Levy MV, Stockelman KA, Goulding A, DeSouza NM, et al. Endothelin-1-induced endothelial microvesicles impair endothelial cell function. *J Appl Physiol Bethesda Md* 1985 2020;**128**:1497−505.
119. Wan Y, Xue R, Wang Y, Zhang Q, Huang S, Wu W, et al. The effect of neuropeptide Y on brown-like adipocyte's differentiation and activation. *Peptides* 2015;**63**:126−33.
120. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. *Nature* 1994;**372**:425−32.
121. Scott MM, Lachey JL, Sternson SM, Lee CE, Elias CF, Friedman JM, et al. Leptin targets in the mouse brain. *J Comp Neurol* 2009;**514**:518−32.
122. Zierath JR, Frevert EU, Ryder JW, Berggren PO, Kahn BB. Evidence against a direct effect of leptin on glucose transport in skeletal muscle and adipocytes. *Diabetes* 1998;**47**:1−4.
123. William WN, Ceddia RB, Curi R. Leptin controls the fate of fatty acids in isolated rat white adipocytes. *J Endocrinol* 2002;**175**: 735−44.
124. Lee M, Fried SK. Integration of hormonal and nutrient signals that regulate leptin synthesis and secretion. *Am J Physiol Endocrinol Metab* 2009;**296**:E1230−8.
125. Jones SM, Kazlauskas A. Growth factor-dependent signaling and cell cycle progression. *FEBS Lett* 2001;**490**:110−6.
126. Aaronson SA. Growth factors and cancer. *Science* 1991;**254**: 1146−53.
127. Cuttitta F, Carney DN, Mulshine J, Moody TW, Fedorko J, Fischler A, et al. Bombesin-like peptides can function as autocrine growth factors in human small-cell lung cancer. *Nature* 1985;**316**: 823−6.
128. Castellone MD, Laukkanen MO, Teramoto H, Bellelli R, Alì G, Fontanini G, et al. Cross talk between the bombesin neuropeptide receptor and Sonic hedgehog pathways in small cell lung carcinoma. *Oncogene* 2015;**34**:1679−87.
129. Lee L, Ramos-Alvarez I, Moody TW, Mantey SA, Jensen RT. Neuropeptide bombesin receptor activation stimulates growth of lung cancer cells through HER3 with a MAPK-dependent mechanism. *Biochim Biophys Acta Mol Cell Res* 2020;**1867**:118625.
130. Garcia-Recio S, Fuster G, Fernandez-Nogueira P, Pastor-Arroyo EM, Park SY, Mayordomo C, et al. Substance P autocrine signaling contributes to persistent HER2 activation that drives malignant progression and drug resistance in breast cancer. *Cancer Res* 2013;**73**: 6424−34.
131. Preston SR, Miller GV, Primrose JN. Bombesin-like peptides and cancer. *Crit Rev Oncol Hematol* 1996;**23**:225−38.
132. Körner M, Reubi JC. Neuropeptide Y receptors in primary human brain tumors: overexpression in high-grade tumors. *J Neuropathol Exp Neurol* 2008;**67**:741−9.
133. DeMorrow S, Onori P, Venter J, Invernizzi P, Frampton G, White M, et al. Neuropeptide Y inhibits cholangiocarcinoma cell growth and invasion. *Am J Physiol Cell Physiol* 2011;**300**:C1078−89.
134. Pyronnet S, Bousquet C, Najib S, Azar R, Laklai H, Susini C. Antitumor effects of somatostatin. *Mol Cell Endocrinol* 2008;**286**: 230−7.
135. Voisin T, El Firar A, Rouyer-Fessard C, Gratio V, Laburthe M. A hallmark of immunoreceptor, the tyrosine-based inhibitory motif ITIM, is present in the G protein-coupled receptor OX1R for orexins and drives apoptosis: a novel mechanism. *FASEB J Off Publ Fed Am Soc Exp Biol* 2008;**22**:1993−2002.
136. El Firar A, Voisin T, Rouyer-Fessard C, Ostuni MA, Couvineau A, Laburthe M. Discovery of a functional immunoreceptor tyrosine-based switch motif in a 7-transmembrane-spanning receptor: role in the orexin receptor OX1R-driven apoptosis. *FASEB J Off Publ Fed Am Soc Exp Biol* 2009;**23**:4069−80.
137. Rouet-Benzineb P, Rouyer-Fessard C, Jarry A, Avondo V, Pouzet C, Yanagisawa M, et al. Orexins acting at native OX_1 receptor in colon cancer and neuroblastoma cells or at recombinant OX_1 receptor suppress cell growth by inducing apoptosis. *J Biol Chem* 2004;**279**: 45875−86.
138. Suo L, Chang X, Zhao Y. The orexin-A-regulated Akt/mTOR pathway promotes cell proliferation through inhibiting apoptosis in pancreatic cancer cells. *Front Endocrinol* 2018;**9**:647.
139. Zhang S, Liu N, Ma M, Huang H, Handley M, Bai X, et al. Methionine enkephalin (MENK) suppresses lung cancer by regulating the Bcl-2/Bax/caspase-3 signaling pathway and enhancing natural killer cell-driven tumor immunity. *Int Immunopharmacol* 2021;**98**:107837.
140. Qu N, Wang R, Meng Y, Liu N, Zhai J, Shan F. Methionine enkephalin inhibited cervical carcinoma *via* apoptosis promotion and reduction of myeloid derived suppressor cell infiltrated in tumor. *Int Immunopharmacol* 2022;**110**:108933.
141. Muñoz M, Coveñas R. Involvement of substance P and the NK-1 receptor in cancer progression. *Peptides* 2013;**48**:1−9.
142. Muñoz M, Coveñas R. The neurokinin-1 receptor antagonist aprepitant: an intelligent bullet against cancer?. *Cancers* 2020;**12**:2682.
143. Javid H, Afshari AR, Zahedi Avval F, Asadi J, Hashemy SI. Aprepitant promotes caspase-dependent apoptotic cell death and G2/M arrest through PI3K/Akt/NF-κB axis in cancer stem-like esophageal squamous cell carcinoma spheres. *Biomed Res Int* 2021;**2021**: 8808214.
144. Zhou J, Geng K, Ping F, Gao Y, Liu L, Feng B. Cross-talk between 5-hydroxytryptamine and substance P in the melanogensis and apoptosis of B16F10 melanoma cells. *Eur J Pharmacol* 2016;**775**: 106−12.
145. Hashizume H, Baluk P, Morikawa S, McLean JW, Thurston G, Roberge S, et al. Openings between defective endothelial cells explain tumor vessel leakiness. *Am J Pathol* 2000;**156**:1363−80.
146. Hennig IM, Laissue JA, Horisberger U, Reubi JC. Substance-P receptors in human primary neoplasms: tumoral and vascular localization. *Int J Cancer* 1995;**61**:786−92.
147. Chamary VL, Robson T, Loizidou M, Boulos PB, Burnstock G. Progressive loss of perivascular nerves adjacent to colorectal cancer. *Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol* 2000; **26**:588−93.
148. Pal S, Wu J, Murray JK, Gellman SH, Wozniak MA, Keely PJ, et al. An antiangiogenic neurokinin-B/thromboxane A2 regulatory axis. *J Cell Biol* 2006;**174**:1047−58.
149. Wang T, Chen S, Wang S, Shi L, Wang C, Zhang J, et al. Targeting neurokinin-3 receptor: a novel anti-angiogenesis strategy for cancer treatment. *Oncotarget* 2017;**8**:40713−23.
150. Mentlein R, Dahms P, Grandt D, Krüger R. Proteolytic processing of neuropeptide Y and peptide YY by dipeptidyl peptidase IV. *Regul Pept* 1993;**49**:133−44.
151. Robich MP, Matyal R, Chu LM, Feng J, Xu SH, Laham RJ, et al. Effects of neuropeptide Y on collateral development in a swine model of chronic myocardial ischemia. *J Mol Cell Cardiol* 2010;**49**: 1022−30.
152. Pons J, Kitlinska J, Ji H, Lee E, Zukowska Z. Mitogenic actions of neuropeptide Y in vascular smooth muscle cells: synergetic interactions with the beta-adrenergic system. *Can J Physiol Pharmacol* 2003;**81**:177−85.
153. Zukowska-Grojec Z, Pruszczyk P, Colton C, Yao J, Shen GH, Myers AK, et al. Mitogenic effect of neuropeptide Y in rat vascular smooth muscle cells. *Peptides* 1993;**14**:263−8.

154. Saraf R, Mahmood F, Amir R, Matyal R. Neuropeptide Y is an angiogenic factor in cardiovascular regeneration. *Eur J Pharmacol* 2016;**776**:64−70.
155. Zukowska Z, Grant DS, Lee EW. Neuropeptide Y: a novel mechanism for ischemic angiogenesis. *Trends Cardiovasc Med* 2003;**13**: 86−92.
156. Harrison M, Zinovkin D, Pranjol MZI. Endothelin-1 and its role in cancer and potential therapeutic opportunities. *Biomedicines* 2024; **12**:511.
157. Fares J, Fares MY, Khachfe HH, Salhab HA, Fares Y. Molecular principles of metastasis: a hallmark of cancer revisited. *Signal Transduct Target Ther* 2020;**5**:1−17.
158. Folkman J. Angiogenesis. *Annu Rev Med* 2006;**57**:1−18.
159. Leenders WPJ, Küsters B, de Waal RMW. Vessel co-option: how tumors obtain blood supply in the absence of sprouting angiogenesis. *Endothel J Endothel Cell Res* 2002;**9**:83−7.
160. Eccles SA, Welch DR. Metastasis: recent discoveries and novel treatment strategies. *Lancet* 2007;**369**:1742−57.
161. Ly T, Harihar S, Welch DR. KISS1 in metastatic cancer research and treatment: potential and paradoxes. *Cancer Metastasis Rev* 2020;**39**: 739−54.
162. Bari R, Zhang Y, Zhang F, Wang N, Stipp CS, Zheng J, et al. Transmembrane interactions are needed for KAI1/CD82-mediated suppression of cancer invasion and metastasis. *Am J Pathol* 2009; **174**:647−60.
163. Kotani M, Detheux M, Vandenbogaerde A, Communi D, Vanderwinden JM, Le Poul E, et al. The metastasis suppressor gene KiSS-1 encodes kisspeptins, the natural ligands of the orphan G protein-coupled receptor GPR54. *J Biol Chem* 2001;**276**:34631−6.
164. Masui T, Doi R, Mori T, Toyoda E, Koizumi M, Kami K, et al. Metastin and its variant forms suppress migration of pancreatic cancer cells. *Biochem Biophys Res Commun* 2004;**315**:85−92.
165. Zhao X, Lu L, Pokhriyal N, Ma H, Duan L, Lin S, et al. Overexpression of RhoA induces preneoplastic transformation of primary mammary epithelial cells. *Cancer Res* 2009;**69**:483−91.
166. Lee JH, Miele ME, Hicks DJ, Phillips KK, Trent JM, Weissman BE, et al. KiSS-1, a novel human malignant melanoma metastasis-suppressor gene. *J Natl Cancer Inst* 1996;**88**:1731−7.
167. Jabeen S, Qureshi MZ, Javed Z, Iqbal MJ, Ismail M, Farooqi AA. Kisspeptin mediated signaling in cancer. *Curr Top Med Chem* 2016; **16**:2471−6.
168. Ciaramella V, Della Corte CM, Ciardiello F, Morgillo F. Kisspeptin and cancer: molecular interaction, biological functions, and future perspectives. *Front Endocrinol* 2018;**9**:115.
169. Guzman S, Brackstone M, Radovick S, Babwah AV, Bhattacharya MM. KISS1/KISS1R in cancer: friend or foe?. *Front Endocrinol* 2018;**9**:437.
170. Shengbing Z, Feng LJ, Bin W, Lingyun G, Aimin H. Expression of KiSS-1 gene and its role in invasion and metastasis of human hepatocellular carcinoma. *Anat Rec Hoboken NJ* 2007 2009;**292**:1128−34.
171. Cvetkovic D, Dragan M, Leith SJ, Mir ZM, Leong HS, Pampillo M, et al. KISS1R induces invasiveness of estrogen receptor-negative human mammary epithelial and breast cancer cells. *Endocrinology* 2013;**154**:1999−2014.
172. Goertzen CG, Dragan M, Turley E, Babwah AV, Bhattacharya M. KISS1R signaling promotes invadopodia formation in human breast cancer cell *via* β-arrestin2/ERK. *Cell Signal* 2016;**28**:165−76.
173. Zajac M, Law J, Cvetkovic DD, Pampillo M, McColl L, Pape C, et al. GPR54 (KISS1R) transactivates EGFR to promote breast cancer cell invasiveness. *PLoS One* 2011;**6**:e21599.
174. KiSS1 gene as a novel mediator of TGFβ-mediated cell invasion in triple negative breast cancer. *Cell Signal* 2018;**42**:1−10.
175. Cho S, Wang Y, Rodriguez M, Tan K, Zhang W, Luo J, et al. Haploinsufficiency in the prometastasis Kiss1 receptor Gpr54 delays breast tumor initiation, progression and lung metastasis. *Cancer Res* 2011;**71**:6535−46.
176. Blake A, Dragan M, Tirona RG, Hardy DB, Brackstone M, Tuck AB, et al. G protein-coupled KISS1 receptor is overexpressed in triple negative breast cancer and promotes drug resistance. *Sci Rep* 2017;**7**: 46525.
177. Rani S, Corcoran C, Shiels L, Germano S, Breslin S, Madden S, et al. Neuromedin U: a candidate biomarker and therapeutic target to predict and overcome resistance to HER-tyrosine kinase inhibitors. *Cancer Res* 2014;**74**:3821−33.
178. Przygodzka P, Sochacka E, Soboska K, Pacholczyk M, Papiewska-Pająk I, Przygodzki T, et al. Neuromedin U induces an invasive phenotype in CRC cells expressing the NMUR2 receptor. *J Exp Clin Cancer Res CR* 2021;**40**:283.
179. Lu C, Mahajan A, Hong S, Galli S, Zhu S, Tilan JU, et al. Hypoxia-activated neuropeptide Y/Y5 receptor/RhoA pathway triggers chromosomal instability and bone metastasis in Ewing sarcoma. *Nat Commun* 2022;**13**:2323.
180. Alshalalfa M, Nguyen PL, Beltran H, Chen W, Davicioni E, Zhao S, et al. Transcriptomic and clinical characterization of neuropeptide Y expression in localized and metastatic prostate cancer: identification of novel prostate cancer subtype with clinical implications. *Eur Urol Oncol* 2019;**2**:405−12.
181. Li X, Ma G, Ma Q, Li W, Liu J, Han L, et al. Neurotransmitter substance P mediates pancreatic cancer perineural invasion *via* NK-1R in cancer cells. *Mol Cancer Res MCR* 2013;**11**:294−302.
182. Singh S, Kumaravel S, Dhole S, Roy S, Pavan V, Chakraborty S. Neuropeptide substance P enhances inflammation-mediated tumor signaling pathways and migration and proliferation of head and neck cancers. *Indian J Surg Oncol* 2021;**12**:93−102.
183. Kuol N, Stojanovska L, Apostolopoulos V, Nurgali K. Role of the nervous system in cancer metastasis. *J Exp Clin Cancer Res CR* 2018; **37**:5.
184. Padmanaban V, Keller I, Seltzer ES, Ostendorf BN, Kerner Z, Tavazoie SF. Neuronal substance P drives metastasis through an extracellular RNA−TLR7 axis. *Nature* 2024;**633**:207−15.
185. Baral P, Udit S, Chiu IM. Pain and immunity: implications for host defence. *Nat Rev Immunol* 2019;**19**:433−47.
186. Goetzl EJ, Xia M, Ingram DA, Kishiyama JL, Kaltreider B, Byrd PK, et al. Neuropeptide signaling of lymphocytes in immunological responses. *Int Arch Allergy Immunol* 2009;**107**:202−4.
187. Springer J, Geppetti P, Fischer A, Groneberg DA. Calcitonin gene-related peptide as inflammatory mediator. *Pulm Pharmacol Ther* 2003;**16**:121−30.
188. Holzmann B. Antiinflammatory activities of CGRP modulating innate immune responses in health and disease. *Curr Protein Pept Sci* 2013;**14**:268−74.
189. Duan J, Zhou Y, Zhou A, Guan X, Liu T, Yang H, et al. Calcitonin gene-related peptide exerts anti-inflammatory property through regulating murine macrophages polarization *in vitro*. *Mol Immunol* 2017;**91**:105−13.
190. Tsuru S, Ito Y, Matsuda H, Hosono K, Inoue T, Nakamoto S, et al. RAMP1 signaling in immune cells regulates inflammation-associated lymphangiogenesis. *Lab Investig J Tech Methods Pathol* 2020;**100**: 738−50.
191. McIlvried LA, Atherton MA, Horan NL, Goch TN, Scheff NN. Sensory neurotransmitter calcitonin gene-related peptide modulates tumor growth and lymphocyte infiltration in oral squamous cell carcinoma. *Adv Biol* 2022;**6**:e2200019.
192. Balood M, Ahmadi M, Eichwald T, Ahmadi A, Majdoubi A, Roversi K, et al. Nociceptor neurons affect cancer immunosurveillance. *Nature* 2022;**611**:405−12.
193. Blum AM, Metwali A, Crawford C, Li J, Qadir K, Elliott DE, et al. Interleukin 12 and antigen independently induce substance P receptor expression in T cells in murine schistosomiasis mansoni. *FASEB J Off Publ Fed Am Soc Exp Biol* 2001;**15**:950−7.
194. Murthy RG, Reddy BY, Ruggiero JE, Rameshwar P. Tachykinins and hematopoietic stem cell functions: implications in clinical disorders and tissue regeneration. *Front Biosci J Virtual Libr* 2007;**12**:4779−87.
195. Lang K, Drell TL, Niggemann B, Zänker KS, Entschladen F. Neurotransmitters regulate the migration and cytotoxicity in natural killer cells. *Immunol Lett* 2003;**90**:165−72.

196. Wang X, Douglas SD, Peng J, Zhou D, Wan Q, Ho W. An *in vitro* model of morphine withdrawal manifests the enhancing effect on human immunodeficiency virus infection of human T lymphocytes through the induction of substance P. *Am J Pathol* 2006;**169**: 1663−70.
197. Swanton C, Bernard E, Abbosh C, André F, Auwerx J, Balmain A, et al. Embracing cancer complexity: hallmarks of systemic disease. *Cell* 2024;**187**:1589−616.
198. Gao X, Bayraktutan U. Substance P reversibly compromises the integrity and function of blood−brain barrier. *Peptides* 2023;**167**: 171048.
199. Ko JA, Murata S, Nishida T. Up-regulation of the tight-junction protein ZO-1 by substance P and IGF-1 in A431 cells. *Cell Biochem Funct* 2009;**27**:388−94.
200. Banks WA, Kastin AJ. Review: interactions between the blood-brain barrier and endogenous peptides: emerging clinical implications. *Am J Med Sci* 1988;**295**:459−65.
201. Ebner K, Singewald N. The role of substance P in stress and anxiety responses. *Amino Acids* 2006;**31**:251−72.
202. Iftikhar K, Siddiq A, Baig SG, Zehra S. Substance P: a neuropeptide involved in the psychopathology of anxiety disorders. *Neuropeptides* 2020;**79**:101993.
203. Chowdrey HS, Jessop DS, Lightman SL. Substance P stimulates arginine vasopressin and inhibits adrenocorticotropin release *in vivo* in the rat. *Neuroendocrinology* 1990;**52**:90−3.
204. Keller M, Montgomery S, Ball W, Morrison M, Snavely D, Liu G, et al. Lack of efficacy of the substance P (neurokinin1 receptor) antagonist aprepitant in the treatment of major depressive disorder. *Biol Psychiatry* 2006;**59**:216−23.
205. Kramer MS, Winokur A, Kelsey J, Preskorn SH, Rothschild AJ, Snavely D, et al. Demonstration of the efficacy and safety of a novel substance P (NK1) receptor antagonist in major depression. *Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol* 2004; **29**:385−92.
206. Hou C, Jia F, Liu Y, Li L. CSF serotonin, 5-hydroxyindolacetic acid and neuropeptide Y levels in severe major depressive disorder. *Brain Res* 2006;**1095**:154−8.
207. Thorsell A, Michalkiewicz M, Dumont Y, Quirion R, Caberlotto L, Rimondini R, et al. Behavioral insensitivity to restraint stress, absent fear suppression of behavior and impaired spatial learning in transgenic rats with hippocampal neuropeptide Y overexpression. *Proc Natl Acad Sci U S A* 2000;**97**:12852−7.
208. Wang Y, An Z, Lin D, Jin W. Targeting cancer cachexia: molecular mechanisms and clinical study. *MedComm* 2022;**3**:e164.
209. Woods SC, Figlewicz DP, Madden L, Porte D, Sipols AJ, Seeley RJ. NPY and food intake: discrepancies in the model. *Regul Pept* 1998; **75**−**76**:403−8.
210. Chance WT, Balasubramaniam A, Thompson H, Mohapatra B, Ramo J, Fischer JE. Assessment of feeding response of tumor-bearing rats to hypothalamic injection and infusion of neuropeptide Y. *Peptides* 1996;**17**:797−801.
211. Laviano A, Meguid MM, Rossi-Fanelli F. Cancer anorexia: clinical implications, pathogenesis, and therapeutic strategies. *Lancet Oncol* 2003;**4**:686−94.
212. Ramos EJ, Suzuki S, Marks D, Inui A, Asakawa A, Meguid MM. Cancer anorexia-cachexia syndrome: cytokines and neuropeptides. *Curr Opin Clin Nutr Metab Care* 2004;**7**:427−34.
213. Wu Q, Chen J, Hua T, Cai J. Alpha-melanocyte-stimulating hormone-mediated appetite regulation in the central nervous system. *Neuroendocrinology* 2023;**113**:885−904.
214. Wisse BE, Frayo RS, Schwartz MW, Cummings DE. Reversal of cancer anorexia by blockade of central melanocortin receptors in rats. *Endocrinology* 2001;**142**:3292−301.
215. Marks DL, Ling N, Cone RD. Role of the central melanocortin system in cachexia. *Cancer Res* 2001;**61**:1432−8.
216. Elias CF, Lee C, Kelly J, Aschkenasi C, Ahima RS, Couceyro PR, et al. Leptin activates hypothalamic CART neurons projecting to the spinal cord. *Neuron* 1998;**21**:1375−85.
217. Hahn TM, Breininger JF, Baskin DG, Schwartz MW. Coexpression of Agrp and NPY in fasting-activated hypothalamic neurons. *Nat Neurosci* 1998;**1**:271−2.
218. Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. *N Engl J Med* 1990;**323**:236−41.
219. Anker SD, Ponikowski PP, Clark AL, Leyva F, Rauchhaus M, Kemp M, et al. Cytokines and neurohormones relating to body composition alterations in the wasting syndrome of chronic heart failure. *Eur Heart J* 1999;**20**:683−93.
220. Lundin L, Norheim I, Landelius J, Oberg K, Theodorsson-Norheim E. Carcinoid heart disease: relationship of circulating vasoactive substances to ultrasound-detectable cardiac abnormalities. *Circulation* 1988;**77**:264−9.
221. Herrmann J. Vascular toxic effects of cancer therapies. *Nat Rev Cardiol* 2020;**17**:503−22.
222. Cosentino F, Katusić ZS. Does endothelin-1 play a role in the pathogenesis of cerebral vasospasm?. *Stroke* 1994;**25**:904−8.
223. Schebesch KM, Brawanski A, Bele S, Schödel P, Herbst A, Bründl E, et al. Neuropeptide Y—an early biomarker for cerebral vasospasm after aneurysmal subarachnoid hemorrhage. *Neurol Res* 2013;**35**: 1038−43.
224. Everdingen MHJ van den B, Hochstenbach LMJ, Joosten EAJ, Tjan-Heijnen VCG, Janssen DJA. Update on prevalence of pain in patients with cancer: systematic review and meta-analysis. *J Pain Symptom Manage* 2016;**51**:1070−90.e9.
225. Harrison S, Geppetti P. Substance p. *Int J Biochem Cell Biol* 2001;**33**: 555−76.
226. McDougall JJ, Watkins L, Li Z. Vasoactive intestinal peptide (VIP) is a modulator of joint pain in a rat model of osteoarthritis. *Pain* 2006; **123**:98−105.
227. Bernard A, Danigo A, Bourthoumieu S, Mroué M, Desmoulière A, Sturtz F, et al. The cholecystokinin type 2 receptor, a pharmacological target for pain management. *Pharm Basel Switz* 2021;**14**: 1185.
228. Steinhoff MS, von Mentzer B, Geppetti P, Pothoulakis C, Bunnett NW. Tachykinins and their receptors: contributions to physiological control and the mechanisms of disease. *Physiol Rev* 2014;**94**:265−301.
229. Diaz-delCastillo M, Woldbye DPD, Heegaard AM. Neuropeptide Y and its involvement in chronic pain. *Neuroscience* 2018;**387**:162−9.
230. Glaum SR, Miller RJ, Hammond DL. Inhibitory actions of delta 1-, delta 2-, and mu-opioid receptor agonists on excitatory transmission in lamina II neurons of adult rat spinal cord. *J Neurosci Off J Soc Neurosci* 1994;**14**:4965−71.
231. Trafton JA, Abbadie C, Marek K, Basbaum AI. Postsynaptic signaling *via* the [mu]-opioid receptor: responses of dorsal horn neurons to exogenous opioids and noxious stimulation. *J Neurosci Off J Soc Neurosci* 2000;**20**:8578−84.
232. Zhang X, Dou Y, Yuan L, Li Q, Zhu Y, Wang M, et al. Different neuronal populations mediate inflammatory pain analgesia by exogenous and endogenous opioids. *Elife* 2020;**9**:e55289.
233. Herlinger K, Lingford-Hughes A. Opioid use disorder and the brain: a clinical perspective. *Addict Abingdon Engl* 2022;**117**:495−505.
234. White JM, Irvine RJ. Mechanisms of fatal opioid overdose. *Addict Abingdon Engl* 1999;**94**:961−72.
235. Chen A, Ashburn MA. Cardiac effects of opioid therapy. *Pain Med Malden Mass* 2015;**16**(Suppl 1):S27−31.
236. Sessler DI, Pei L, Huang Y, Fleischmann E, Marhofer P, Kurz A, et al. Recurrence of breast cancer after regional or general anaesthesia: a randomised controlled trial. *Lancet Lond Engl* 2019;**394**: 1807−15.
237. Juneja R. Opioids and cancer recurrence. *Curr Opin Support Palliat Care* 2014;**8**:91−101.
238. Bhoir S, Uhelski M, Guerra-Londono JJ, Cata JP. The role of opioid receptors in cancer. *Adv Biol* 2023;**7**:e2300102.
239. Frączek K, Ferraiolo M, Hermans E, Bujalska-Zadrozny M, Kasarello K, Erdei A, et al. Novel opioid-neurotensin-based hybrid

peptide with spinal long-lasting antinociceptive activity and a propensity to delay tolerance development. *Acta Pharm Sin B* 2020;**10**: 1440−52.
240. Walker WH, Borniger JC. Molecular mechanisms of cancer-induced sleep disruption. *Int J Mol Sci* 2019;**20**:2780.
241. Sakurai T, Amemiya A, Ishii M, Matsuzaki I, Chemelli RM, Tanaka H, et al. Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. *Cell* 1998;**92**:573−85.
242. de Lecea L, Kilduff TS, Peyron C, Gao X, Foye PE, Danielson PE, et al. The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. *Proc Natl Acad Sci U S A* 1998;**95**:322−7.
243. de Lecea L. Twenty-three years of hypocretins: the "Rosetta Stone" of sleep/arousal circuits. *Front Neurol Neurosci* 2021;**45**:1−10.
244. Bittencourt JC, Presse F, Arias C, Peto C, Vaughan J, Nahon JL, et al. The melanin-concentrating hormone system of the rat brain: an immuno- and hybridization histochemical characterization. *J Comp Neurol* 1992;**319**:218−45.
245. Verret L, Goutagny R, Fort P, Cagnon L, Salvert D, Léger L, et al. A role of melanin-concentrating hormone producing neurons in the central regulation of paradoxical sleep. *BMC Neurosci* 2003;**4**:19.
246. Zhang Y, Chen C, Liu Y, Rao S, Tan Y, Qian Y, et al. Neuronal induction of bone−fat imbalance through osteocyte neuropeptide Y. *Adv Sci* 2021;**8**:e2100808.
247. Liu S, Jin D, Wu J, Xu Z, Fu S, Mei G, et al. Neuropeptide Y stimulates osteoblastic differentiation and VEGF expression of bone marrow mesenchymal stem cells related to canonical Wnt signaling activating *in vitro*. *Neuropeptides* 2016;**56**:105−13.
248. Gu X, Zhang X, Hu B, Zi Y, Li M. Neuropeptide Y accelerates postfracture bone healing by promoting osteogenesis of mesenchymal stem cells. *Neuropeptides* 2016;**60**:61−6.
249. Huang Y, Lin X, Lin S. Neuropeptide Y and metabolism syndrome: an update on perspectives of clinical therapeutic intervention strategies. *Front Cell Dev Biol* 2021;**9**:695623.
250. Rasmusson AM, Schnurr PP, Zukowska Z, Scioli E, Forman DE. Adaptation to extreme stress: post-traumatic stress disorder, neuropeptide Y and metabolic syndrome. *Exp Biol Med Maywood NJ* 2010;**235**:1150−62.
251. Varela L, Horvath TL. Leptin and insulin pathways in POMC and AgRP neurons that modulate energy balance and glucose homeostasis. *EMBO Rep* 2012;**13**:1079−86.
252. Könner AC, Brüning JC. Selective insulin and leptin resistance in metabolic disorders. *Cell Metab* 2012;**16**:144−52.
253. Gelling RW, Morton GJ, Morrison CD, Niswender KD, Myers MG, Rhodes CJ, et al. Insulin action in the brain contributes to glucose lowering during insulin treatment of diabetes. *Cell Metab* 2006;**3**: 67−73.
254. Morris MJ, Cox HS, Lambert GW, Kaye DM, Jennings GL, Meredith IT, et al. Region-specific neuropeptide Y overflows at rest and during sympathetic activation in humans. *Hypertens Dallas Tex 1979* 1997;**29**:137−43.
255. Li CM, Haratipour P, Lingeman RG, Perry JJP, Gu L, Hickey RJ, et al. Novel peptide therapeutic approaches for cancer treatment. *Cells* 2021;**10**:2908.
256. Werle M, Bernkop-Schnürch A. Strategies to improve plasma half life time of peptide and protein drugs. *Amino Acids* 2006;**30**:351−67.
257. Guo R, Zhang X, Ji L, Wei Z, Duan Z, Qiao Z, et al. Recent progress of therapeutic peptide based nanomaterials: from synthesis and self-assembly to cancer treatment. *Biomater Sci* 2020;**8**:6175−89.
258. Patel A, Patel M, Yang X, Mitra AK. Recent advances in protein and Peptide drug delivery: a special emphasis on polymeric nanoparticles. *Protein Pept Lett* 2014;**21**:1102−20.
259. Roxin Á, Zheng G. Flexible or fixed: a comparative review of linear and cyclic cancer-targeting peptides. *Future Med Chem* 2012;**4**: 1601−18.
260. Cao X, Yang Y, Zhou W, Wang Y, Wang X, Ge X, et al. Aprepitant inhibits the development and metastasis of gallbladder cancer *via* ROS and MAPK activation. *BMC Cancer* 2023;**23**:471.
261. Muñoz M, Coveñas R. The Neurokinin-1 receptor antagonist aprepitant: an intelligent bullet against cancer?. *Cancers* 2020;**12**:2682.
262. Du T, Gu Q, Zhang Y, Gan Y, Liang R, Yang W, et al. Rolapitant treats lung cancer by targeting deubiquitinase OTUD3. *Cell Commun Signal CCS* 2024;**22**:195.
263. Zhao J, Fu H, Yu J, Hong W, Tian X, Qi J, et al. Prospect of acromegaly therapy: molecular mechanism of clinical drugs octreotide and paltusotine. *Nat Commun* 2023;**14**:962.
264. Cascinu S, Catalano V, Giordani P, Baldelli AM, Agostinelli R, Catalano G. Gastrointestinal cancer refractory to chemotherapy: a role for octreotide?. *Chemotherapy* 2001;**47**(Suppl 2):127−33.
265. Jiang L, Zhou Y, Tang S, Yang D, Zhang Y, Zhang J, et al. Nociceptive adenosine A2A receptor on trigeminal nerves orchestrates CGRP release to regulate the progression of oral squamous cell carcinoma. *Int J Oral Sci* 2024;**16**:46.
266. Clyne M. Bladder cancer: faster recovery after radical cystectomy with alvimopan. *Nat Rev Urol* 2014;**11**:186.
267. Takahashi K, Ehata S, Miyauchi K, Morishita Y, Miyazawa K, Miyazono K. Neurotensin receptor 1 signaling promotes pancreatic cancer progression. *Mol Oncol* 2021;**15**:151−66.
268. Thorson A, Biorck G, Bjorkman G, Waldenstrom J. Malignant carcinoid of the small intestine with metastases to the liver, valvular disease of the right side of the heart (pulmonary stenosis and tricuspid regurgitation without septal defects), peripheral vasomotor symptoms, bronchoconstriction, and an unusual type of cyanosis; a clinical and pathologic syndrome. *Am Heart J* 1954;**47**:795−817.
269. Pernow B, Waldenstrom J. Paroxysmal flushing and other symptoms caused by 5-hydroxytryptamine and histamine in patients with malignant tumours. *Lancet Lond Engl* 1954;**267**:951.
270. Pavel M, O'Toole D, Costa F, Capdevila J, Gross D, Kianmanesh R, et al. ENETS consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. *Neuroendocrinology* 2016;**103**:172−85.
271. Watt HL, Kharmate GD, Kumar U. Somatostatin receptors 1 and 5 heterodimerize with epidermal growth factor receptor: agonist-dependent modulation of the downstream MAPK signalling pathway in breast cancer cells. *Cell Signal* 2009;**21**:428−39.
272. Qian ZR, Li T, Ter-Minassian M, Yang J, Chan JA, Brais LK, et al. Association between somatostatin receptor expression and clinical outcomes in neuroendocrine tumors. *Pancreas* 2016;**45**:1386−93.
273. Coopmans EC, van Meyel SWF, Pieterman KJ, van Ipenburg JA, Hofland LJ, Donga E, et al. Excellent response to pasireotide therapy in an aggressive and dopamine-resistant prolactinoma. *Eur J Endocrinol* 2019;**181**:K21−7.
274. Gomes-Porras M, Cárdenas-Salas J, Álvarez-Escolá C. Somatostatin analogs in clinical practice: a review. *Int J Mol Sci* 2020;**21**:1682.
275. Beck-Peccoz P, Brucker-Davis F, Persani L, Smallridge RC, Weintraub BD. Thyrotropin-secreting pituitary tumors. *Endocr Rev* 1996;**17**:610−38.
276. Miller GM, Alexander JM, Bikkal HA, Katznelson L, Zervas NT, Klibanski A. Somatostatin receptor subtype gene expression in pituitary adenomas. *J Clin Endocrinol Metab* 1995;**80**:1386−92.
277. Katznelson L, Laws ER, Melmed S, Molitch ME, Murad MH, Utz A, et al. Acromegaly: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2014;**99**:3933−51.
278. Zarogoulidis K, Eleftheriadou E, Kontakiotis T, Gerasimou G, Zarogoulidis P, Sapardanis I, et al. Long acting somatostatin analogues in combination to antineoplastic agents in the treatment of small cell lung cancer patients. *Lung Cancer Amst Neth* 2012;**76**:84−8.
279. Thakur MK, Heilbrun L, Dobson K, Boerner J, Stark K, Li J, et al. Phase I trial of the combination of docetaxel, prednisone, and pasireotide in metastatic castrate-resistant prostate cancer. *Clin Genitourin Cancer* 2018;**16**:e695−703.
280. Gaujoux S, Regimbeau JM, Piessen G, Truant S, Foissac F, Barbier L, et al. Somatostatin *versus* octreotide for prevention of postoperative pancreatic fistula: the PREFIPS randomized clinical trial: a FRENCH 007-ACHBT study. *Ann Surg* 2024;**280**:179−87.

281. Song W, Chen J, Zhang X, Xu J, He Y, Cai S, et al. Effect of somatostatin in advanced gastric cancer after D2 radical gastrectomy. *World J Gastroenterol* 2014;**20**:14927−33.
282. Pascetta SA, Kirsh SM, Cameron M, Uniacke J. Pharmacological inhibition of neuropeptide Y receptors Y1 and Y5 reduces hypoxic breast cancer migration, proliferation, and signaling. *BMC Cancer* 2023;**23**:494.
283. Ge C, Huang H, Huang F, Yang T, Zhang T, Wu H, et al. Neurokinin-1 receptor is an effective target for treating leukemia by inducing oxidative stress through mitochondrial calcium overload. *Proc Natl Acad Sci U S A* 2019;**116**:19635−45.
284. Bashash D, Safaroghli-Azar A, Bayati S, Razani E, Pourbagheri-Sigaroodi A, Gharehbaghian A, et al. Neurokinin-1 receptor (NK1R) inhibition sensitizes APL cells to anti-tumor effect of arsenic trioxide *via* restriction of NF-κB axis: shedding new light on resistance to aaprepitant. *Int J Biochem Cell Biol* 2018;**103**:105−14.
285. Robinson P, Kasembeli M, Bharadwaj U, Engineer N, Eckols KT, Tweardy DJ. Substance P receptor signaling mediates doxorubicin-induced cardiomyocyte apoptosis and triple-negative breast cancer chemoresistance. *Biomed Res Int* 2016;**2016**:1959270.
286. Un H, Ugan RA, Kose D, Bayir Y, Cadirci E, Selli J, et al. A novel effect of aprepitant: protection for cisplatin-induced nephrotoxicity and hepatotoxicity. *Eur J Pharmacol* 2020;**880**:173168.
287. Zelek L, Navari R, Aapro M, Scotté F. Single-dose NEPA *versus* an aprepitant regimen for prevention of chemotherapy-induced nausea and vomiting in patients receiving moderately emetogenic chemotherapy. *Cancer Med* 2023;**12**:15769−76.
288. Liu G, Jin Y, Jiang Y, Zhao J, Jiang C, Zhang Z, et al. A comparison of the efficacy of 5 mg olanzapine and aprepitant in the prevention of multiple-day cisplatin chemotherapy-induced nausea and vomiting. *Int J Clin Pract* 2022;**2022**:5954379.
289. Muñoz M, González-Ortega A, Salinas-Martín MV, Carranza A, Garcia-Recio S, Almendro V, et al. The neurokinin-1 receptor antagonist aprepitant is a promising candidate for the treatment of breast cancer. *Int J Oncol* 2014;**45**:1658−72.
290. Muñoz M, Rosso M. The NK-1 receptor antagonist aprepitant as a broad spectrum antitumor drug. *Invest New Drugs* 2010;**28**:187−93.
291. Yang H, Wang Y, Liu W, He T, Liao J, Qian Z, et al. Genome-wide pan-GPCR cell libraries accelerate drug discovery. *Acta Pharm Sin B* 2024;**14**:4296−311.
292. Marin JJG, Romero MR, Blazquez AG, Herraez E, Keck E, Briz O. Importance and limitations of chemotherapy among the available treatments for gastrointestinal tumours. *Anticancer Agents Med Chem* 2009;**9**:162−84.
293. Gong L, Zhao H, Liu Y, Wu H, Liu C, Chang S, et al. Research advances in peptide−drug conjugates. *Acta Pharm Sin B* 2023;**13**:3659−77.
294. Mckertish CM, Kayser V. Advances and limitations of antibody drug conjugates for cancer. *Biomedicines* 2021;**9**:872.
295. Ahrens VM, Bellmann-Sickert K, Beck-Sickinger AG. Peptides and peptide conjugates: therapeutics on the upward path. *Future Med Chem* 2012;**4**:1567−86.
296. Moody TW, Czerwinski G, Tarasova NI, Moody DL, Michejda CJ. The development of VIP−ellipticine conjugates. *Regul Pept* 2004;**123**:187−92.
297. Moody TW, Czerwinski G, Tarasova NI, Michejda CJ. VIP-ellipticine derivatives inhibit the growth of breast cancer cells. *Life Sci* 2002;**71**:1005−14.
298. Kufka R, Rennert R, Kaluđerović GN, Weber L, Richter W, Wessjohann LA. Synthesis of a tubugi-1-toxin conjugate by a modulizable disulfide linker system with a neuropeptide Y analogue showing selectivity for hY1R-overexpressing tumor cells. *Beilstein J Org Chem* 2019;**15**:96−105.
299. Ahrens VM, Kostelnik KB, Rennert R, Böhme D, Kalkhof S, Kosel D, et al. A cleavable cytolysin−neuropeptide Y bioconjugate enables specific drug delivery and demonstrates intracellular mode of action. *J Control Release* 2015;**209**:170−8.
300. Böhme D, Krieghoff J, Beck-Sickinger AG. Double methotrexate-modified neuropeptide Y analogues express increased toxicity and overcome drug resistance in breast cancer cells. *J Med Chem* 2016;**59**:3409−17.
301. Carney DN, Cuttitta F, Moody TW, Minna JD. Selective stimulation of small cell lung cancer clonal growth by bombesin and gastrin-releasing peptide. *Cancer Res* 1987;**47**:821−5.
302. Zhang Y, Holland E, Dinh A, Au D, Sun L. Bombesin−drug conjugates in targeted therapy for small cell lung cancer. *Am J Cancer Res* 2022;**12**:927−37.
303. Safavy A, Raisch KP, Matusiak D, Bhatnagar S, Helson L. Single-drug multiligand conjugates: synthesis and preliminary cytotoxicity evaluation of a paclitaxel-dipeptide "scorpion" molecule. *Bioconjug Chem* 2006;**17**:565−70.
304. Ruan C, Liu L, Lu Y, Zhang Y, He X, Chen X, et al. Substance P-modified human serum albumin nanoparticles loaded with paclitaxel for targeted therapy of glioma. *Acta Pharm Sin B* 2018;**8**:85−96.
305. Chen H, Lin R, Schiltz RL, Chakravarti D, Nash A, Nagy L, et al. Nuclear receptor coactivator ACTR is a novel histone acetyltransferase and forms a multimeric activation complex with P/CAF and CBP/p300. *Cell* 1997;**90**:569−80.
306. Accardo A, Mannucci S, Nicolato E, Vurro F, Diaferia C, Bontempi P, et al. Easy formulation of liposomal doxorubicin modified with a bombesin peptide analogue for selective targeting of GRP receptors overexpressed by cancer cells. *Drug Deliv Transl Res* 2019;**9**:215−26.
307. Merola E, Grana CM. Peptide receptor radionuclide therapy (PRRT): innovations and improvements. *Cancers* 2023;**15**:2975.
308. Filippi L, Evangelista L, Schillaci O. Integrated use of ^{90}Y-labeled microspheres and immune checkpoint inhibitors in hepatic tumors: current status and future directions. *Expert Rev Gastroenterol Hepatol* 2023;**17**:531−8.
309. Morgan KA, Rudd SE, Noor A, Donnelly PS. Theranostic nuclear medicine with gallium-68, lutetium-177, copper-64/67, actinium-225, and lead-212/203 radionuclides. *Chem Rev* 2023;**123**:12004−35.
310. Prise KM, O'Sullivan JM. Radiation-induced bystander signalling in cancer therapy. *Nat Rev Cancer* 2009;**9**:351−60.
311. Murray D, McEwan AJ. Radiobiology of systemic radiation therapy. *Cancer Biother Radiopharm* 2007;**22**:1−23.
312. Kelkar SS, Reineke TM. Theranostics: combining imaging and therapy. *Bioconjug Chem* 2011;**22**:1879−903.
313. Gubbi S, Koch CA, Klubo-Gwiezdzinska J. Peptide receptor radionuclide therapy in thyroid cancer. *Front Endocrinol* 2022;**13**:896287.
314. Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, et al. Phase 3 trial of ^{177}Lu-dotatate for midgut neuroendocrine tumors. *N Engl J Med* 2017;**376**:125−35.
315. Strosberg J, Wolin E, Chasen B, Kulke M, Bushnell D, Caplin M, et al. Health-related quality of life in patients with progressive midgut neuroendocrine tumors treated with ^{177}Lu-dotatate in the Phase III NETTER-1 trial. *J Clin Oncol Off J Am Soc Clin Oncol* 2018;**36**:2578−84.
316. Das S, Al-Toubah T, El-Haddad G, Strosberg J. ^{177}Lu-DOTATATE for the treatment of gastroenteropancreatic neuroendocrine tumors. *Expert Rev Gastroenterol Hepatol* 2019;**13**:1023−31.
317. Roll W, Riemann B, Schäfers M, Stegger L, Vrachimis A. ^{177}Lu-DOTATATE therapy in radioiodine-refractory differentiated thyroid cancer: a single center experience. *Clin Nucl Med* 2018;**43**:e346−51.
318. Palmisciano P, Watanabe G, Conching A, Ogasawara C, Ferini G, Bin-Alamer O, et al. The role of [^{68}Ga]Ga-DOTA-SSTR PET radiotracers in brain tumors: a systematic review of the literature and ongoing clinical trials. *Cancers* 2022;**14**:2925.
319. Chastel A, Worm DJ, Alves ID, Vimont D, Petrel M, Fernandez S, et al. Design, synthesis, and biological evaluation of a multifunctional neuropeptide-Y conjugate for selective nuclear delivery of radiolanthanides. *EJNMMI Res* 2020;**10**:16.
320. Zhang C, Pan J, Lin K, Dude I, Lau J, Zeisler J, et al. Targeting the neuropeptide Y1 receptor for cancer imaging by positron emission

tomography using novel truncated peptides. *Mol Pharm* 2016;**13**: 3657−64.
321. Moody TW, Ramos-Alvarez I, Jensen RT. Neuropeptide G protein-coupled receptors as oncotargets. *Front Endocrinol* 2018;**9**:345.
322. De Vincentis G, Remediani S, Varvarigou AD, Di Santo G, Iori F, Laurenti C, et al. Role of ^{99m}Tc-bombesin scan in diagnosis and staging of prostate cancer. *Cancer Biother Radiopharm* 2004;**19**:81−4.
323. Chen Q, Ma Q, Chen M, Chen B, Wen Q, Jia B, et al. An exploratory study on ^{99m}Tc-RGD-BBN peptide scintimammography in the assessment of breast malignant lesions compared to ^{99m}Tc-3P4-RGD2. *PLoS One* 2015;**10**:e0123401.
324. Chlenski A, Liu S, Cohn SL. The regulation of angiogenesis in neuroblastoma. *Cancer Lett* 2003;**197**:47−52.
325. Skrabanek P, Dervan P, Cannon D, Powell D. Substance P in ovarian carcinoid. *J Clin Pathol* 1980;**33**:160−2.
326. Rubinstein C, Fletcher DR, Shulkes A, Hardy KJ. Elevated plasma calcitonin gene-related peptide and the symptoms associated with medullary thyroid cancer. *Aust N Z J Surg* 1992;**62**:892−6.
327. Forsgren S, Landström F, Kjörell U, Henriksson R, Franzén L. Analysis of VIP and CGRP plasma levels after radiotherapy for treatment of metastasis from prostatic carcinoma. *Ann N Y Acad Sci* 2000;**921**:279−83.
328. Reubi JC, Gugger M, Waser B, Schaer JC. Y_1-mediated effect of neuropeptide Y in cancer: breast carcinomas as targets. *Cancer Res* 2001;**61**:4636−41.
329. Dhar DK, Naora H, Kubota H, Maruyama R, Yoshimura H, Tonomoto Y, et al. Downregulation of KiSS-1 expression is responsible for tumor invasion and worse prognosis in gastric carcinoma. *Int J Cancer* 2004;**111**:868−72.
330. Zhu G, Pei L, Xia H, Tang Q, Bi F. Role of oncogenic KRAS in the prognosis, diagnosis and treatment of colorectal cancer. *Mol Cancer* 2021;**20**:143.
331. Ouyang S, Shi S, Ding W, Ge Y, Su Y, Mo J, et al. Neuropeptide precursor VGF promotes liver metastatic colonization of Gαq mutant uveal melanoma by facilitating tumor microenvironment *via* paracrine loops. *Adv Sci Weinh Baden* 2024:e2407967.
332. Milligan G, Ward RJ, Marsango S. GPCR homo-oligomerization. *Curr Opin Cell Biol* 2019;**57**:40−7.
333. Dale NC, Johnstone EKM, Pfleger KDG. GPCR heteromers: an overview of their classification, function and physiological relevance. *Front Endocrinol* 2022;**13**:931573.
334. Costantino CM, Gomes I, Stockton SD, Lim MP, Devi LA. Opioid receptor heteromers in analgesia. *Expert Rev Mol Med* 2012; **14**:e9.
335. Gupta A, Mulder J, Gomes I, Rozenfeld R, Bushlin I, Ong E, et al. Increased abundance of opioid receptor heteromers after chronic morphine administration. *Sci Signal* 2010;**3**:ra54.
336. Zhong W, Barde S, Mitsios N, Adori C, Oksvold P, Feilitzen K von, et al. The neuropeptide landscape of human prefrontal cortex. *Proc Natl Acad Sci U S A* 2022;**119**:e2123146119.