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Review

Neural regulation of drug resistance in cancer treatment

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ABSTRACT

The treatment of cancer has made great progress. However, drug resistance remains problematic. Multiple physiologic processes of tumor development can be dominated by central and sympathetic nervous systems. The interactions between the nervous system, immune system, and tumor occur consistently and dynamically. Recent evidence suggests that nerves and neural signals are intimately involved in the development of resistance to cancer therapies. In this review, we will provide an overview of the recent progress in this rapidly growing area and discuss the potential new strategies for targeting the neural signaling pathway to improve the effectiveness of chemotherapies, targeted therapies, and immunotherapies.

1. Introduction

The treatment of cancer has undergone major advances, yielding significant improvements in survival over the past decades due to an increasingly profound understanding of the underlying biological processes and molecular mechanisms of cancer development and progression. Various treatment strategies, including chemotherapy, newer immunotherapy, and targeted therapy, have been proposed and modified to increase effectiveness and precision. Though many successful approaches for cancer treatment have been developed, primary or secondary resistance to all of the therapies occurs sooner or later. Unfortunately, mechanistic links between various anti-cancer therapies and resistance emergence have not been fully identified. Clarifying the mechanisms of primary and adaptive resistance will hold potential for innovative drug development and improving the outcome of cancer patients.

Principal mechanisms for chemotherapy resistance are mainly associated with the expression of various proteins and enzymes, which can reduce drug transport/activation and increase drug degradation/inactivation, and dysfunction of cell cycle proteins (such as p53). Multiple potential mechanisms of intrinsic (de novo) and acquired or adaptive resistance to targeted therapy have been proposed, including the activation of compensatory survival signaling pathways in cancer cells, the induction of new mutations that empower cancer cells with drug resistance phenotype, and the selection and expansion of rare pre-existing subclones of resistant cells, etc. Multifarious mechanisms of targeted therapy resistance can be coalesced into pathway reactivation, pathway bypass, and pathway indifference [1]. Resistance to cancer immunotherapy may be related to various factors, which affect any links in the chain of “the cancer-immunity cycle” [2], such as cancer antigen presentation, priming and activation of immune cells, trafficking and infiltration of T cells into tumors, and recognition and killing of cancer cells by T cells [3–5].

A growing body of research indicates that multiple physiologic processes of tumor development can be dominated by central and sympathetic nervous systems (SNS). Solid tumors are innervated by sympathetic nerve fibers, which play critical roles in modulating biological behaviors and drug response of tumor cells by increasing their release of neurotransmitters. On the other hand, tumor cells can produce neurotrophic growth factors [such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF)], which stimulate the growth of sympathetic and sensory nerves and direct nerves to their correct targets (Fig. 1) [6–14].

As early as more than 60 years ago, Cohen et al. firstly demonstrated experimentally that nerve growth-stimulating factors released by tumors stimulated outgrowth of nerve fibers from sympathetic ganglia in vitro [15]. A landmark study by Magnon et al. found that the sympathetic and parasympathetic nerve fibers in the normal prostate tissues

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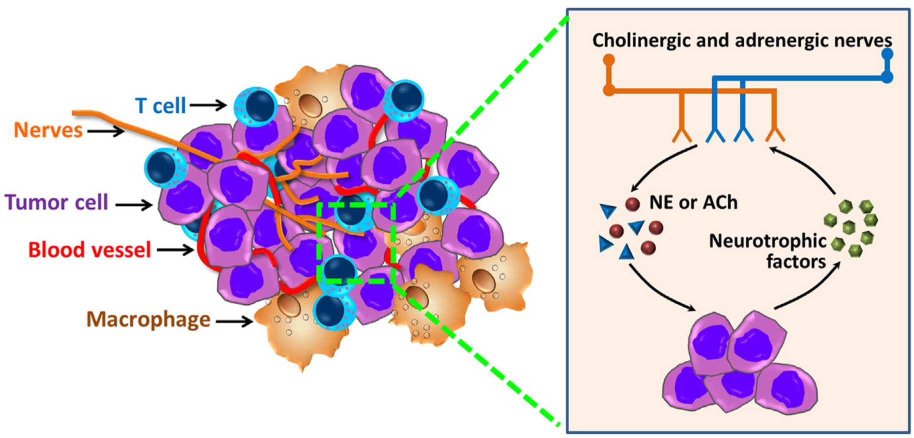

Fig. 1. A vicious cycle between innervation and tumor growth. Nervous systems modulate biological behaviors of tumor cells by release of neurotransmitters. Neurotrophic growth factors produced by tumor cells stimulate abnormal innervation in tumor tissues.

infiltrated into the prostate cancer tissues and promoted cancer dissemination [16]. Pundavela et al. also indicated that nerve infiltration in breast tumors driven by the production of NGF in tumor cells correlated with tumor aggressiveness [17]. The densities and distribution of nerve fibers in tumor tissues were associated with advanced stage and poor clinical outcome in the patients with ovarian cancer and prostate adenocarcinoma [16,18]. In gastric mucosa, cholinergic stimulation of the gastric epithelium induced the NGF expression and overexpressed NGF within gastric epithelium, in turn, expanded enteric nerves. The nerve-epithelial interaction controlled by a feed-forward acetylcholine (Ach)-NGF axis promoted abnormal innervations and carcinogenesis in gastric cancer [19,20]. In pancreatic ductal adenocarcinoma catecholamines promoted the cancer development, NGF secretion, and pancreatic nerve density in a β2-AR-dependent mechanism [21]. The early tumor development could be prevented by chemical or surgical sympathectomy or by genetic deletion of β2- and β3-adrenergic receptors (ARs). The findings implicate that the nervous system may be a master controller in cancer progression and metastasis [11,13,22,23].

Recent studies suggest that nerves and neural signals, as the key components of tumor microenvironment and host macroenvironment, manipulate therapy resistance of cancer [8–10,13,24]. In this review, we provide an overview of the recent progress in this rapidly growing area and discuss the potential new strategies for targeting the neural signaling pathway and rationally designed combination therapies in cancer treatment.

2. Chemotherapy resistance

Chemotherapy has become a generally accepted and widely applied therapeutic modality for many types of cancers. However, emergence of intrinsic or acquired chemotherapeutic resistance constitutes a major barrier to progress in managing cancer. Among cancer patients, emotional distress and psychiatric syndromes are prevalent. The psychosocial stress can be sustained over months or even years, leading to prolonged secretion of neuroendocrine hormones and neurotransmitters (epinephrine, norepinephrine, and cortisol) [25]. Recent studies suggest that poor response to chemotherapeutics may be attributed to abnormal functional activities of the nervous and neuroendocrine systems.

2.1. Catecholamine and adrenergic signaling

Several lines of evidence indicate a close relationship between adrenergic signaling and p53 pathway, by which most of the cytotoxic anti-cancer drugs in current use induce apoptosis of cancer cells. Hara et al. reported that the activation of β2-AR by stress-related catecholamines promoted Gs-protein-dependent activation of protein kinase A and recruitment of β-arrestin, which facilitates AKT-mediated activation of mouse double minute 2 homolog (MDM2) and subsequent degradation of p53 by MDM2 [26]. The effects of catecholamines could be abrogated in β-arrestin1-knockout mice, in which the p53 levels were preserved in the thymus that responds prominently to acute or chronic stress. The study by us demonstrated that catecholamines inhibited doxorubicin-induced p53 acetylation and transcription-activation activities by up-regulating the expression of Sirt1, a regulator of p53 acetylation, in cervical cancer cells, resulting in chemoresistance. Knockdown of the Sirt1 expression by the specific siRNA could block the effects of β2-AR agonist. Notably, β2-AR was overexpressed in cervical cancer tissues. The findings suggest that the p53-dependent, chemotherapeutics-induced cytotoxicity in cervical cancer cells may be compromised by catecholamines-induced up-regulation of the Sirt1 expression through activating the β2-AR signaling [27].

Accumulating evidences suggest that aberrant activation of the adrenergic signaling affect sensitivity to cytotoxic chemotherapeutics by modulating the expression of other anti-apoptotic genes and inhibiting cellular apoptosis. Eng et al. found that low temperature-induced stress could elicit a sympathetic cold stress response, which activated pro-survival pathways by increasing the level of noradrenaline and activating β-AR, driving therapeutic resistance to cisplatin and paclitaxel in the murine models of pancreatic tumor. The activation of the adrenergic signaling influenced the levels of several anti-apoptotic molecules, such as MCL-1, BCL2, and BCL-XL [28]. Another study showed that catecholamines remarkably impaired paclitaxel- and cisplatin-triggered apoptosis in ovarian cancer cells, mainly through activating the β2-AR-cAMP-PLC-PKC-CREB signaling [29].

A recent study showed that catecholamines promoted the NGF secretion and pancreatic nerve density. Pancreatic NGF overexpression accelerated the development of pancreatic ductal adenocarcinoma in mice, suggesting that catecholamines drive a β2-AR-neurotrophin feedforward loop, increase sympathetic innervation, and consequently promote tumor progression. Blockade of the β2-AR and NGF pathways improved therapeutic efficacy of gemcitabine in mice. Moreover, the treatment with nonselective β-blocker increased overall survival (OS) in the patients with pancreatic ductal adenocarcinoma [21].

2.2. Cortisol

Stress-induced dysregulation of neuroendocrine system also activate the production of cortisol from the adrenal cortex. Our previous study found that cortisol induced the expression of HPV oncogenic E6 protein in cervical cancer cells. Increased expression of the E6 protein inhibited p53-mediated up-regulation of miR-145, which could augment p53-

dependent apoptosis induced by chemotherapeutics. Overexpression of miR-145 enhanced sensitivity of cervical cancer cells to mitomycin and reversed the chemoresistance induced by glucocorticoids. Our data revealed a direct role of glucocorticoids in the development of a chemoresistance phenotype in cervical cancer cells by modulating the p53-miR-145 pathway via induction of HPV oncogenic E6 protein [30]. Feng et al. also demonstrated that chronic restraint stress resulted in the elevation of the glucocorticoid level and reduction of the p53 expression in mice. Glucocorticoid transcriptionally activated SGK1, a ubiquitously expressed serine-threonine kinase, which promoted the phosphorylation of MDM2 on Ser166/186 and thus resulted in MDM2-dependent p53 degradation, implicating that the glucocorticoid-induced SGK1 mediates the inhibitory effect of glucocorticoids on p53 through enhancing MDM2 activity. [31]. These data indicate that the hypersecretion of glucocorticoids under chronic stress may confer resistance of tumor cells to chemotherapeutic drugs.

2.3. Acetylcholine (ACh) and other neural signals

An interesting finding is that the spontaneous gastric tumors frequently arise in the lesser curvature of the stomach, an area with the highest density of vagus nerve terminals in mice. It was reported that vagotomy reduced the secretion of gastric acid and recurrence of gastric cancer in the previous studies [32,33]. The recent study further demonstrated that denervation attenuates tumorigenesis in mouse models of gastric cancer. Vagotomy or botulinum toxin type A, which can inhibit the exocytosis of neurotransmitters and block nerve activities, also enhanced the therapeutic effects of systemic chemotherapy and prolonged survival. Mechanism analysis revealed that vagal innervation contributed to gastric tumorigenesis via M3 receptor-mediated Wnt signaling. Treatment of the mice with the specific M3 receptor antagonist darifenacin in combination with chemotherapy also reduced tumor growth. Furthermore, tumor stage correlated with neural density and activated Wnt signaling in gastric cancer patients [19].

A recent study by Takahashi et al. demonstrated that TRPA1, a neuronal redox-sensing Ca^{2+}-influx channel, which functions as a major stress sensor in nociceptive neurons, was overexpressed in diverse cancer types. High level of TRPA1 mediated Ca2 + −dependent anti-apoptotic pathways and protected cancer cells against chemotherapeutics. It seems that cancer cells are capable of counteracting chemotherapy-associated oxidative stress by transmitting pain signal. Notably, TRAP1 inhibitors, which are currently under clinical evaluation for pain therapy, enhanced chemosensitivity in xenograft models [34].

Taken together, overexcitability of neuroendocrine system under physiological and pathological statues may influence the proliferation and survival of malignant cells and interfere with the efficacy of chemotherapy by multiple mechanisms.

3. Targeted drug resistance

Growing evidence reveals that the β-AR-mediated signal can trigger a wide variety of signal pathways involving in the survival and proliferation of cancer cells, resulting in the activation of oncogenic and signal proteins, such as epithelial growth factor receptor (EGFR) family, signal transducers and activators of transcription (STAT) protein family, and mitogen-activated protein kinase (MAPK) family. Crosstalk between growth factor receptors and neuroreceptors stimulated by neurotransmitters may activate a complex intracellular signaling network and promote the proliferation of cancer cells, resulting in the failure of targeted therapeutics.

3.1. Adrenergic signaling and EGFR targeted therapies

The EGFR family members (EGFR and Her2) are attractive targets for cancer therapy. It has been known that ligand-independent EGFR transactivation occurs in diverse cell types. The molecular mechanisms of the EGFR transactivation involve the activation of the ADAM (a disintegrin and metalloprotease) family by the β-AR agonists, the shedding of the transmembrane EGFR ligands by ADAM, and subsequent binding of the ligands to EGFR, ultimately leading to the activation of the EGFR downstream pathways [35]. EGFR can also directly form a complex with β1-AR or β2-AR in response to the stimulation of catecholamines, transmiting signals to its downstream pathways, such as MAPK or phosphoinositide 3-kinase (PI3K)/Akt pathway [36–40]. These studies reveal that the crosstalk between β-ARs and EGFR family may influence the essential survival signal and sensitivity of cancer cells to the EGFR targeted therapies.

EGFR tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib are effective therapies for non-small cell lung cancer (NSCLC) patients and have shown higher objective response rates and progression-free survival (PFS) in the patients with NSCLC, compared to cytotoxic therapy [41]. However, aberrant activation of the adrenergic signaling enables NSCLC cells to acquire resistance to erlotinib in vitro and in vivo. The study by Nilsson et al. demonstrated that crosstalk between β2-AR-mediated signal induced by stress hormones and mutant EGFR signal resulted in the expression of interleukin-6 (IL-6) and EGFR inhibitor resistance, which can be abrogated by β-blockers or IL-6 inhibition. Clinical data further confirmed that high circulating concentration of IL-6 correlated with a poor PFS and OS in the patients treated with EGFR inhibitors, whereas circulating IL-6 concentration was lower in the patients receiving β-blockers, suggesting that NSCLC patients treated with EGFR inhibitors may benefit from β-blocker use [42]. Monoamine oxidase A (a catecholamine neurotransmitter degrading enzyme) could suppress the effects of norepinephrine/epinephrine, synergize with EGFR inhibitors or AR antagonists, and abrogate norepinephrine-induced malignant phenotypes of hepatocellular carcinoma (HCC) [43]. It has also been reported that the activation of the β2-AR signaling confers resistance to sorafenib, a small inhibitor of several tyrosine protein kinases and Raf family kinases in HCC [44].

The Her2-targeting antibody trastuzumab is currently used as the first-line therapy for Her2-positive breast cancer and gastric cancer [45,46]. However, trastuzumab resistance is a major clinical problem in the treatment of Her2-overexpressing cancers [47]. Crosstalk of the Her2 network and other signaling pathways can trigger a stronger or more sustained biological response. Our previous study revealed a positive feedback loop comprised by β2-AR and Her2 in human breast cancer cells. Her2-mediated ERK signaling induced the up-regulation of the β2-AR expression by promoting catecholamine release, whereas the activation of the β2-AR signaling promoted the Her2 expression. Moreover, the β2-AR level positively correlated with the Her2 status in clinical breast tumor samples [48]. Our recent study found that the expression of β2-AR negatively correlated with trastuzumab response in the patients with Her2-overexpressing breast cancer. Catecholamine stimulation resulted in the deficiency of phosphatase and tensin homolog, which is closely linked to trastuzumab resistance, and activation of PI3K and Akt, a major determinant of trastuzumab resistance. Simultaneously, catecholamines induced the activation of mammalian target of rapamycin (mTOR), a downstream effector of PI3K. Thus, the anti-proliferative effect of trastuzumab was potently antagonized by catecholamines through activating a trastuzumab resistance-dependent PI3K/Akt/mTOR signaling pathway. Our retrospective study also demonstrated that concurrent treatment of β-blocker and trastuzumab significantly improved PFS and OS in the patients with metastatic breast cancer, implicating the possibility for combination therapy with trastuzumab plus β-blocker in Her2-overexpressing breast cancer [49]. In gastric cancer models, we found that the activation of β2-AR by catecholamines resulted in “targeting failure” of trastuzumab [50]. Mechanistically, the activation of the adrenergic signaling up-regulated the expression of MUC4, which interferes with the recognition and physical binding of trastuzumab to Her2 molecules [51,52]. The potent anti-tumor effects of Her2 targeted therapy are due to its ability to attenuate multiple oncogenic signaling pathways. Therefore, with the interference of the β2-AR signaling the emergence of resistance to Her2 targeted drugs is inevitable.

3.2. Neurotrophic factors and their receptors

Recent studies demonstrated that both Ach and catecholamines could induce the expression of NGF in tumor and non-tumor cells. The feed-forward Ach/catecholamine-NGF axis enhanced abnormal innervations in tumor tissues and manipulated the bio-behaviors of tumor cells [19,21]. Overexpression of the NGF receptor (TrkA, P75NTR or CD271) was found in various solid tumors. Targeting NGF/TrkA via selective small-molecule-inhibitors or antibodies has gained enormous attention in the drug discovery for cancer treatment [53]. More recently, an interesting study by Zhou et al. found that p53 could bind to the NGFR gene promoter and induce its expression in cancer cells. Conversely, NGFR inactivated p53 by directly binding to its central DNA-binding domain and by enhancing its MDM2-mediated ubiquitination and proteolysis, suggesting that cancer cells may hijack the anti-p53 activity of NGFR toward their growth advantage [54]. Activation of NGFR (CD271) induced a more invasive and metastatic phenotype of tumor cells [55]. The gold nanocluster-assisted delivery of the NGF siRNA effectively inhibited the tumor progression in the pancreatic tumor model [56]. Other neurotrophic factors are also intimately involved in the development of cancer. For example, BDNF supports the survival and stemness of glioblastoma stem cells [57]. Artemin, which has a critical role in sympathetic innervation, secreted by newly identified 'Ter-cells' promoted HCC growth [58]. Neurotrophic factors and their receptors as potential therapeutic targets may evoke great interest in the coming decade.

4. Immunotherapy resistance

Improving the functions of immune system to destroy tumors by using immunotherapy has long been recognized as an important approach to anti-cancer treatment. With a number of recent clinical successes of T cell checkpoint inhibitors, immunotherapy has become a promising treatment strategy for several cancers [59,60]. However, only a fraction of patients developed durable responses. Resistance to cancer immunotherapy appears to be a common occurrence [61–64]. So far, the exploration of the mechanisms for immunotherapy resistance has been focused on the genotypic features of cancer patients (such as genomic and transcriptomic features) and cancer-associated immune evasion, etc. [65–77]. Recently, the investigation on the communication between the immune and nervous systems has shed new light on the understanding of the neural signaling-mediated immunotherapy resistance [78,79].

4.1. Inhibition of T cell activation and trafficking by adrenergic signaling

Tumor immunotherapy aims to stimulate the immune system via a variety of reagents to enhance the immune response. Activation of CD8+ cytotoxic T cells has been regarded as an important anti-tumor mechanism of the immune system. Emerging evidence suggests that SNS modulates CD4+ and CD8+ T cell responses [80,81]. Norepinephrine or the β2-AR specific agonists (such as albuterol and salmeterol) significantly suppressed the secretion of IFN-γ and TNF-α and cytolytic capacity in both human and murine CD8+ T cells in response to viral infection. The anti-viral CD8+ T cell responses could be enhanced by administration of a β2-adrenergic antagonist. Ablation of the mouse peripheral SNS by 6-hydroxydopamine increased primary CD8+ T cell responses to viral and cellular antigens. The findings revealed a critical role of the β2-AR-mediated signaling in CD8+ T cell function and adaptive T cell responses to infection. T regulatory (Treg) cells suppress the proliferation and release of cytokines in several subsets of immune cells and anti-tumor CD8+ T cell responses, whereas the activation of the adrenergic signaling triggered by cold stress or surgical stress induced Treg cells [82–84]. In addition, the activation of the adrenergic signaling sequesters antigen-primed T cells in lymph nodes and prevents their migration to the sites, where they exert immunosurveillance functions [85,86]. Other neural signals may also be involved in the regulation of T cells trafficking. A recent study showed that intracranial tumors induced sequestration of T cells in bone marrow and suggested that some signals from brain triggered the dysfunction of T cell trafficking through unrevealed mechanism [87]. These findings suggest that the neural signaling may affect anti-tumor immunity and cancer immunotherapy.

4.2. Resistance to immune checkpoint inhibitor induced by adrenergic signaling activation

The modulation of checkpoints is a very successful anti-cancer strategy and opens promising prospects for cancer therapies. The programmed death receptor-1 (PD-1)/programmed death-ligand 1 (PD-L1) and cytotoxic T lymphocyte-associated antigen 4 (CTLA4) are increasingly recognized as powerful targets for enhancing the cytotoxic T cell functions. PD-1/PD-L1 blockade therapy by the antibodies against PD-1 (pembrolizumab and nivolumab) has achieved unprecedented clinical success in cancer treatment. However, a significant proportion of the patients treated with anti-PD1 antibodies have failed to respond [88,89]. The underlying mechanisms are not explored extensively. The recent studies implicate that the β-AR signaling has a detrimental effect on immune checkpoint blockade. Bucsek et al. reported that CD8+ T cell frequency and functional orientation within the tumor microenvironment were regulated by the β2-AR-mediated signaling. Blockade of the β-adrenergic signaling by propranolol (a sympatholytic nonselective β-blocker) greatly augmented the anti-tumor efficacy of the anti-PD-1 antibody in tumor-bearing mice, with increased intratumoral frequency of effector CD8+ T cells and significantly increased efficacy of the anti-PD-1 checkpoint blockade. The ratio of effector CD8+ T cells to Tregs, which is a favorable prognostic indicator in a variety of cancer types [90], was evidently increased in the mice treated with propranolol [91]. The study highlights the potential of the adrenergic stress and β-AR signaling to inhibit the functions of effector CD8+ T cells and to undermine checkpoint inhibitor therapy.

Nissen et al. also indicated that elevated β-AR signaling inhibited CD8+ T cell responses to immune modulating antibodies, including the anti-PD-1 and anti-4-1BB antibodies. Chronic treatment with the nonselective β-agonist isoprenaline significantly suppressed the proliferation, IFNγ production, and cytolytic killing capacity of antigen-specific CD8+ T cells and impaired the efficacy of CD8+ T cell targeting immunotherapies [92]. A recent study by Kokolus et al. showed that Propranolol (pan β-blocker) and β2-selective blocker (ICI 118,551) enhanced the control of murine melanoma growth by the anti-PD-1 antibody/IL-2 therapy. Their retrospective clinical data demonstrated that taking pan β-blockers exhibited a better survival benefit in metastatic melanoma patients that received IL-2, anti-PD-1 and/or anti-CTLA-4 therapies, compared to either those taking no β-blocker or β1-selective blockers [93]. The studies demonstrate that the inhibitory effects of the β-adrenergic signaling on immunotherapy occur mainly through direct suppression of CD8+ T cell activation.

4.3. The effects of adrenergic signaling on other immunotherapies

Allogeneic hematopoietic cell transplantation is considered as a type of immunotherapy for the patients with hematological malignancies, in despite of possibly inducing graft-versus-host disease (GVHD). T cells are the principal effector cells mediating the graft-versus-tumor (GVT) effect, directly killing tumor cells or indirectly contributing to tumor lysis through the secretion of cytokines [94]. Recent studies demonstrated that activation of adrenergic signaling inhibited GVHD [95] and that the pretreatment of host mice with the β2-AR blocker (ICI118,551) critically enhanced the GVT effect of donor CD8+ T cells. β2-AR deficiency in host mice resulted in enhanced antigen presentation by CD11c + cells, enhanced CD8+ T cell priming, activation, and expansion, improved tumor killing, and increased memory CD8+ T cells as well. These findings demonstrate an important role of the β2-AR signaling in suppressing immune cell function and GVT activity [96].

Immune stimulation by cytokines or other biological response modifiers is a common approach in tumor immunotherapy. Perioperative use of recombinant IL-2 and IFN-γ has been explored in early phase clinical trials. Interleukin-12 (IL-12) has emerged as one of the most potent agents for anti-tumor immunotherapy. Unfortunately, clinical trials showed limited success [97]. Further development of the nonspecific cytokine therapy has been hindered by tolerability of such treatment regimens. The study by Levi et al. showed that the β-adrenergic agonist or behavioral stress significantly impaired IL-12-induced NK cell activation and tumor clearance [98]. Psychological stress also affected immune-stimulatory effects of CpG—C, a synthetic biological response modifier, on NK cell activation and disrupted the efficacy of immunostimulatory treatment through induction of catecholamines and glucocorticoids [99].

Neural regulation of immune response is an interesting and rapidly developed field [78,79,100–104]. Increasing evidence reveals that the SNS signaling modulates several critical steps of "the cancer-immunity cycle" [2], including T cell priming and activation, trafficking and infiltration of T cells into tumor tissues, and killing of tumor cells by effector cells (Fig. 2). A recent study suggests that the nerve signals may be hijacked by the pathogen to induce immune evasion [105,106]. Given the existence of the "vicious cycles" constituted by tumor cells and nerve systems [13,19,21], it is reasonably conceivable that tumor cells may also operate the neural signaling to promote tumor immune evasion and to inhibit the anti-tumor immune response.

5. Conclusion

In recent decades, tremendous progress has been made in the treatment of cancer, including cancer targeted therapy and immunotherapy. A compelling challenge is the occurrence of resistance, which affects up to 60–70% of patients treated. Relatively little is known about the resistance mechanisms, especially the mechanisms associated with cancer immunotherapy and targeted therapy [1].

Targeted therapy targets critical molecules in cancer cells. These molecules associate with the malignant phenotypes or survival signaling of cancer cells. However, cancer cells display the impressive heterogeneity. Besides, the phenotypic alterations of cancer cells consistently occur during treatment, resulting in the emergence of drug resistant subpopulation. Additionally, the survival signals of cancer cells can also change in response to the stress of a targeted therapy. Once an important survival signaling is suppressed, a compensatory signaling pathway will be switched on eventually to support the growth of tumor cells under drug pressure. As a matter of fact, the resistance to certain therapeutics develops quickly [107–109].

Cancer immunotherapy is to boost the immune system by targeting the molecules on immune cells in order to destroy cancer cells. These molecules act as a brake or accelerator in anti-cancer immune response. Each of the molecules has a complex mechanism of action, whereas many of these molecules compete with each other in the same signaling pathway. Moreover, immune cells are highly versatile and plastic cells that are able to adapt quickly to a variety of unanticipated situations. It is difficult to coordinate appropriate immune responses by manipulating a single brake or accelerator molecule because of the overwhelming complexity and diversity of immune cell responses [110,111]. In addition, conventional anti-cancer therapies have both direct and indirect effects on the immune system, inevitably resulting in resistance to immunotherapy [112]. So far, the response rates for immunotherapies are still limited. On the other hand, the adverse effects, mostly due to autoimmune reactions, cannot be ignored [113].

Central and SNS govern functional activities of many organs, including the organs of the immune system. Development and progression of tumor as an integrated organ can also be dominated by nervous systems as well [13]. Nerve fibers branch profusely into both immune and tumor tissues. The signaling of neurotransmitters from sympathetic nerve fibers can modulate biological behaviors of both tumor and non-tumor cells by binding to related receptors on these cells, critically influencing the efficacy of cancer treatment. Targeting the specific neural circuits to modulate tumor-immune communication will serve the purpose of killing two birds with one stone to reinvigorate anti-tumor immune functions and to eliminate malignant cells (Fig. 3).

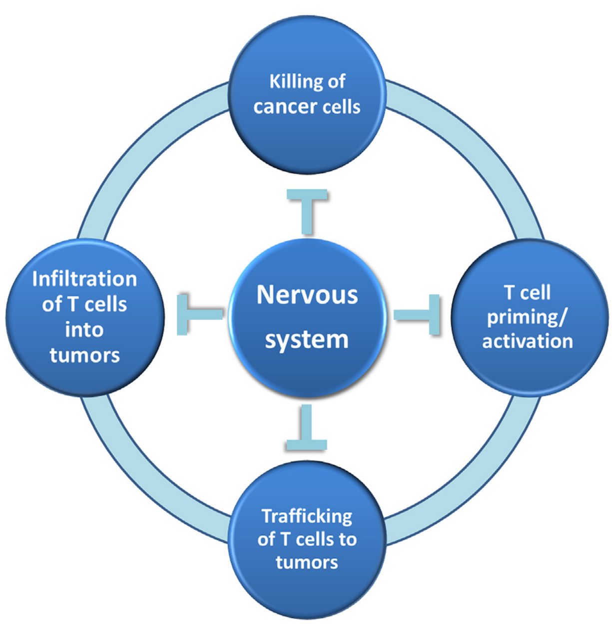

Fig. 2. Manipulation of the cancer-immunity cycle by nervous systems. Aberrant neural signaling inhibits T cell priming and activation, trafficking and infiltration of T cells into tumor tissues, and killing of tumor cells by effector cells.

6. Remaining questions

The neural regulation of drug resistance in cancer treatment is one of the most rapidly emerging transdisciplinary fields, in which there are several important challenges. Firstly, we have a little insight into how tumors affect the activities of central and peripheral nervous systems. Two recent studies revealed that tumors induced anorexia and sleep abnormalities by influencing the activities of calcitonin gene-related peptide (CGRP) neurons in the parabrachial nucleus and hypocretin/orexin neurons within lateral-hypothalamic area [114,115]. Functional and anatomical carification of the mechanisms underlying the behavior manipulation by tumors is important for improving the quality of life and therapeutic efficacy for cancer patients. Secondly, the excitement and success of cancer targeted therapy and immunotherapy, at present, has set the stage for new combination therapy in the field of cancer treatment [88]. Combination of targeted therapy or immunotherapy with intervention of neural signals (such as the adrenergic signaling by using β-blockers) will likely be a potential therapeutic strategy to avoid drug resistance and to lower the risk of adverse effects, though the combination therapies still need to be systematically assessed in prospective clinical trials. In addition, the dose range and treatment schedule for β-blockers in the combination therapies have yet to be further determined. Thirdly, other neural signals that are involved in inducing therapeutic resistance remain to be characterized. Translating the dialog between the nervous system, immune system, and cancer will be interesting and challenging, which will be valuable to expand our

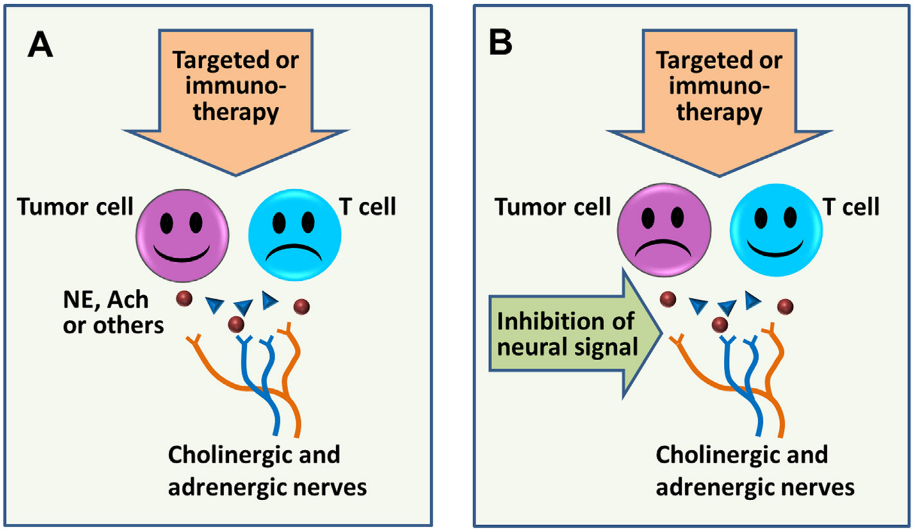

Fig. 3. Targeting the specific neural circuits to modulate tumor-immune communication. A, Nervous systems manipulate biological behaviors of both tumor and non-tumor cells by releasing neuro-transmitters and critically influence the efficacy of cancer treatment. B, Blockade of the neural signaling invigorates anti-tumor immune functions and suppresses the growth of tumor cells.

understanding of cancer treatment and rehabilitation, to overcome therapeutic resistance, and to develop novel therapeutic strategies.

Conflict of interest statement

The authors declare no competing interests.

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