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Original Article

Neuroregulation in Esophageal Cancer: Unveiling the Role of Neural Pathways in Tumor Progression and Therapy Optimization

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Abstract

Esophageal cancer (EC) remains a highly lethal malignancy with limited therapeutic success and poor survival rates despite advances in surgical and systemic treatments. Recent insights into the intricate interplay between the nervous system and tumor biology have revealed the critical role of neural pathways in shaping the tumor microenvironment (TME). These interactions influence tumor progression, metastasis, and resistance to therapy, positioning neural regulation as a promising yet underexplored area in EC research. Neurotransmitter agents and neurotrophic factors actively modulate key processes, including angiogenesis, immune evasion, and cellular plasticity, while also contributing to therapeutic resistance. Additionally, identifying tumor biomarkers related to neural activity offers new possibilities for early detection and personalized treatment strategies. This review synthesizes current evidence on the contributions of nervous system physiological phenomena to EC, exploring the mechanisms by which neural signaling interacts with immune modulation and TME. By examining the dual roles of neural regulation in promoting tumor aggressiveness and mediating therapeutic outcomes, the review highlights the potential for targeting these pathways to improve clinical management. Furthermore, gaps in the current literature, such as the variability of findings across tumor subtypes and the lack of standardized methods for assessing neural involvement, are critically discussed. Future directions emphasize the integration of neural-targeted therapies with existing modalities and developing biomarkers to optimize patient outcomes. This review underscores the importance of a multidisciplinary approach in advancing our understanding of EC and addressing its clinical challenges.

Keywords: ***esophageal neoplasms, nervous system physiological phenomena, neurotransmitter agents, tumor microenvironment, biomarkers, tumor, immune tolerance***

Introduction

Esophageal cancer (EC) remains a formidable global health challenge, ranking as the eighth most common cancer and the sixth leading cause of cancer-related mortality worldwide. According to recent epidemiological data, over 600,000 new cases and nearly 550,000 deaths are reported annually, reflecting its aggressive nature and the limited effectiveness of current therapeutic strategies [1-3].

The disease is primarily presented in two histological subtypes: esophageal squamous cell carcinoma (ESCC), which predominates in Asia and Africa, and esophageal adenocarcinoma (EAC), whose incidence is increasing rapidly in Western nations due to risk factors such as gastroesophageal reflux disease (GERD), Barrett's esophagus, and obesity [2-4].

Despite advances in early detection, surgical techniques, and multimodal therapies, the five-year survival rate remains dismal, often below 20%, emphasizing the urgent need for innovative approaches to improve outcomes [3-5].

The pathogenesis of EC is multifactorial, involving genetic mutations, epigenetic alterations, and interactions within the tumor microenvironment (TME). The TME, a complex network of cellular and non-cellular components, plays a critical role in tumor progression and therapeutic resistance [4-6].

Immune cells, cancer-associated fibroblasts (CAFs), endothelial cells, extracellular matrix (ECM) components, and soluble factors interact dynamically with cancer cells, promoting proliferation, invasion, angiogenesis, and immune evasion. In recent years, the nervous system has emerged as a critical yet underexplored component of TME, influencing tumor biology through intricate neural-cancer crosstalk [5-7].

Neuroregulation in cancer refers to the bidirectional interactions between the nervous system and tumor cells. This

phenomenon has been well-documented in several malignancies, including prostate, gastric, and pancreatic cancers, where neural signaling actively supports tumor growth, metastasis, and resistance to treatment [6-8].

Neural remodeling, characterized by increased nerve density and altered neural architecture within the TME, has been identified as a hallmark of aggressive cancers. Neural elements release neurotransmitters, neurotrophic factors, and other bioactive molecules that interact with tumor cells, creating a "neurogenic niche" that facilitates disease progression. Despite these advances in understanding the neurobiology of cancer, the role of neural regulation in EC remains uncharted mainly, representing a critical gap in oncological research [7-10].

Perineural invasion (PNI), a process wherein cancer cells invade surrounding nerve fibers, is a recognized pathological feature of aggressive malignancies. In EC, PNI correlates with poor prognosis, increased recurrence rates, and reduced survival. The molecular mechanisms underlying PNI in EC are complex and multifaceted, involving signaling pathways such as the nerve growth factor (NGF)/TrkA axis, the glial cell line-derived neurotrophic factor (GDNF)/RET axis, and various neurotransmitter pathways [9-12].

These pathways facilitate tumor-nerve interactions and contribute to the recruitment of immune and stromal cells, further enhancing the pro-tumorigenic microenvironment. Recent advances in imaging and molecular profiling have begun to shed light on the neural contributions to tumor biology [13,14].

High-resolution imaging techniques, such as confocal laser endomicroscopy and PET-MRI, have demonstrated increased neural innervation within tumor tissues. Molecular studies have identified overexpression of neurotrophic factors and their receptors, such as NGF, brain-derived neurotrophic factor (BDNF), and RET, in EC tissues. These findings suggest that neural signaling is pivotal in modulating tumor growth, invasion, and therapeutic response, underscoring the need for targeted interventions [15-17].

Emerging evidence has also highlighted the interplay between neural signaling and immune modulation within the TME. The nervous system influences immune cell recruitment, activation, and function through neurotransmitters such as norepinephrine and acetylcholine [18,19].

In EC, these interactions may contribute to immune evasion and resistance to immunotherapy. For example, the adrenergic signaling pathway has been implicated in suppressing cytotoxic T-cell activity and enhancing the recruitment of regulatory T-cells and myeloid-derived suppressor cells (MDSCs). These findings underscore the importance of exploring neural-immune crosstalk as a potential therapeutic target in EC.

The therapeutic implications of neuroregulation in EC are profound [20-22].

Preclinical studies in other cancers have demonstrated that pharmacological blockade of neural signaling pathways, such as beta-adrenergic receptor antagonists, can significantly inhibit tumor growth and metastasis. Neuromodulatory techniques, including vagus nerve stimulation and surgical denervation, have shown promise in altering the course of disease progression. However, the clinical application of these strategies in EC remains in its infancy, necessitating rigorous investigation through translational and clinical research [23-26].

Despite these advances, significant challenges remain. The heterogeneity of neural involvement across different cancer types and within individual tumors poses a barrier to the development of universal therapeutic approaches. Furthermore, preclinical and clinical studies must carefully evaluate the potential side effects of disrupting neural signaling, such as impaired physiological functions and systemic impact. Addressing these challenges requires a multidisciplinary approach, integrating insights from oncology, neuroscience, immunology, and bioengineering [27-30].

Exploring neural regulation in EC is an academic exercise and a translational imperative. Understanding the molecular and cellular mechanisms of neural-tumor interactions can revolutionize the management of EC, offering new avenues for early detection, prognostication, and therapy. Targeting neural pathways may disrupt the pro-tumorigenic environment, enhance the efficacy of existing treatments, and improve patient outcomes [31-33].

This review aims to provide a comprehensive synthesis of current knowledge on the role of neural regulation in esophageal cancer. Specifically, it seeks to elucidate the mechanisms through which neural signaling influences tumor progression, examine the impact of neural elements on the tumor microenvironment, and explore innovative therapeutic strategies that leverage neuromodulation. By addressing these objectives, this work aspires to contribute to the growing field of neuro-oncology and inspires future research to integrate neuroregulation into the therapeutic paradigm for esophageal cancer [34,35].

Methods

This review explored the role of nervous system physiological phenomena, neurotransmitter agents, and the tumor microenvironment in the progression and treatment of esophageal neoplasms, emphasizing identifying tumor biomarkers and the impact of immune tolerance. A systematic and comprehensive search was performed across leading scientific databases, including PubMed, Embase, Scopus, Web of Science, SciELO, and gray literature accessed through Google Scholar. The search included studies published up to date to ensure a thorough assessment of the available evidence.

The search strategy used keywords and MeSH terms tailored to the review's primary focus areas. The terms employed included "Esophageal Neoplasms," "Nervous System Physiological Phenomena," "Neurotransmitter Agents," "Tumor Microenvironment," "Biomarkers, Tumor," and "Immune Tolerance." Boolean operators (AND, OR) created precise and efficient search strings that included a broad spectrum of relevant studies while maintaining specificity. Eligibility criteria were predefined to include various study designs, such as randomized controlled trials, cohort studies, case-control studies, cross-sectional studies, systematic reviews, and meta-analyses. Studies were selected if they provided data on the interactions between neural activity, neurotransmitters, immune modulation, and the tumor microenvironment in esophageal cancer. Particular attention was given to studies examining the role of biomarkers in tumor progression and therapeutic responses, as well as those addressing the nervous system's influence on immune and cellular processes within the tumor microenvironment. Articles were included regardless of the type of esophageal cancer studied, provided they contained relevant information about neural or immune regulatory mechanisms. The screening process involved two independent reviewers who assessed titles and abstracts to identify potentially relevant studies. Any disagreements with the reviewer were resolved through discussion, with a third reviewer consulted when necessary to achieve consensus. Reviewers remained blind to the authorship and institutional affiliations of the studies to minimize potential bias during the selection process. Subsequently, full-text articles meeting the inclusion criteria were retrieved and assessed for eligibility based on their relevance to the review's objectives. Data extraction was

conducted systematically using a standardized protocol to ensure consistency and reproducibility.

Extracted data included study design, sample size, characteristics of the population studied, investigated mechanisms related to neural regulation, tumor microenvironment interactions, immune modulation, and primary findings relevant to clinical outcomes. Thematic analysis was used to categorize the findings, focusing on neural signaling, neurotransmitter pathways, biomarkers for diagnosis and prognosis, and immune regulation. Special emphasis was placed on identifying research gaps, such as the limited studies addressing the longitudinal impact of neural signaling in esophageal cancer and the variability of findings across tumor subtypes. Methodological limitations in the existing literature, including small sample sizes and inconsistent approaches to evaluating neural interactions, were critically analyzed. The review also proposed future directions for research, including the need for standardized protocols to study neural and immune interactions in esophageal cancer and the development of targeted therapies that leverage these pathways. This review provides a comprehensive synthesis of current knowledge, emphasizing the importance of nervous system regulation, immune mechanisms, and the tumor microenvironment in esophageal cancer. By highlighting areas for further investigation and offering insights into potential diagnostic and therapeutic advancements, this work aims to improve the management of esophageal neoplasms and advance the understanding of tumor biology.

Results and Discussion

Table 1: Neuroregulation in Esophageal Cancer

Author(s)	Study	Results
Yang C, Chen K (2022) [1]	**Literature Review**	Highlighted the critical role of long non-coding RNAs (lncRNAs) in modulating tumorigenesis and therapy resistance. This study emphasized how specific lncRNAs, such as HOTAIR and MALAT1, influence tumor cell proliferation, invasion, and apoptosis pathways, underscoring their diagnostic and therapeutic potential.
Xing C et al. (2025) [2]	**Experimental Study**	Demonstrated that targeting neural components in the tumor microenvironment can suppress tumor growth and angiogenesis. The study identified nerve-derived growth factors as key mediators in tumor progression, suggesting therapeutic inhibition of neurotrophic signaling pathways as a novel approach.
Jayaprakash S et al. (2022) [3]	**Mechanistic Analysis**	Investigated the interplay between nuclear receptors and neural pathways in esophageal cancer. Found that nuclear receptor signaling regulates neurotransmitter release, which in turn promotes tumor cell proliferation and immune suppression within the tumor microenvironment.
Zhang Y et al. (2024) [4]	**Epigenetic Research**	Revealed that epigenetic regulation, particularly methylation and acetylation of p63, prevents squamous-to-neuroendocrine differentiation. This finding provides insights into maintaining tissue homeostasis and potential targets to prevent aggressive neuroendocrine tumor phenotypes.
Lyu Y et al. (2024) [5]	**Molecular Study**	Showed that nerve cells significantly influence the tumor microenvironment by enhancing angiogenesis, immune suppression, and tumor invasion. Identified that adrenergic and cholinergic signaling pathways are critical in maintaining these tumor-promoting effects.
Chen D et al. (2023) [6]	**Translational Study**	Demonstrated that adrenergic signaling increases resistance to chemotherapy and radiotherapy in esophageal cancer. Found that beta-adrenergic receptor blockers, such as propranolol, could mitigate these effects by reducing tumor-promoting signaling and enhancing therapeutic sensitivity.
Patel M et al. (2023) [7]	**Immunological Study**	Explored the neural regulation of immune tolerance in esophageal cancer. Discovered that neural inputs increase T-regulatory cell activity and reduce cytotoxic T-cell infiltration, contributing to tumor immune evasion. Suggested combining immune checkpoint inhibitors with neural modulation for improved outcomes.
Zhang J et al. (2024) [8]	**Clinical Study**	Evaluated the influence of neurotransmitter agents, such as dopamine and serotonin, on tumor progression. Reported that altered neurotransmitter levels correlated with poorer survival outcomes, highlighting their potential as prognostic biomarkers and therapeutic targets.
Sun Y et al. (2023) [9]	**Mechanistic Review**	Discussed mechanisms by which neural signaling modulates immune evasion in esophageal squamous cell carcinoma. Found that neural inputs regulate PD-L1 expression and macrophage polarization, fostering an immune-suppressive microenvironment.
Fang J et al. (2024) [10]	**Cellular and Molecular Study**	Examined the dual role of adrenergic and cholinergic signaling in shaping the tumor microenvironment. Reported that adrenergic pathways promote angiogenesis and metastasis, while cholinergic signaling modulates tumor cell proliferation and immune cell recruitment. Proposed targeting these pathways to disrupt tumor progression.
He J et al. (2024) [12]	**Therapeutic Research**	Highlighted novel therapies targeting tumor-neural crosstalk. Found that targeting neurotrophic factors, such as NGF and BDNF, inhibited tumor growth in preclinical models. Explored the potential of combining these therapies with immune checkpoint inhibitors to enhance efficacy.
Zhao Q et al. (2024) [15]	**Translational Study**	Demonstrated that neurotransmitter signaling influences tumor plasticity and therapy resistance in esophageal adenocarcinoma. Identified serotonin receptor antagonists as potential therapeutic agents to reduce therapy resistance and improve outcomes.
Chen L et al. (2023) [16]	**Comprehensive Review**	Analyzed neuroimmune interactions in esophageal cancer, emphasizing the role of neural remodeling in creating an immune-suppressive microenvironment. Identified gaps in understanding the variability of neural influences across different tumor subtypes and their implications for personalized therapies.
Fang Z et al. (2024) [20]	**Imaging Study**	Advanced imaging modalities, such as PET and MRI, were employed to assess neural involvement in esophageal cancer. It revealed that higher neural density correlates with more aggressive tumor behavior and poorer prognosis. Proposed neural density as a biomarker for stratifying patients for therapy.

Zhao F et al. (2023) [22]	**Experimental Study**	Found that adrenergic and cholinergic signaling pathways modulate angiogenesis and tumor invasiveness. Demonstrated that targeting these pathways reduces metastatic spread and enhances the efficacy of systemic therapies in animal models.

Source: Authors.

The Role of Neural Pathways in Tumor Progression

Neural innervation has emerged as a significant driver of tumor progression in esophageal cancer (EC). The increased density of nerve fibers observed in EC tissues compared to normal esophageal tissues has been strongly associated with advanced disease stages and poor prognosis (Table 1) [36,37].

These nerve fibers serve as conduits for bi-directional communication between the nervous system and tumor cells, creating a pro-tumorigenic microenvironment. Sympathetic nerve fibers release catecholamines, such as norepinephrine and epinephrine, which interact with beta-adrenergic receptors in cancer cells [38].

This interaction activates cyclic AMP (cAMP)-dependent pathways that drive cellular proliferation, migration, and angiogenesis. These findings suggest that tumor innervation is not merely a reactive phenomenon but a critical process orchestrating tumor growth [39].

In parallel, parasympathetic innervation, mainly via the vagus nerve, has been implicated in modulating tumor behavior. Acetylcholine, released by parasympathetic nerves, binds to nicotinic and muscarinic receptors on tumor cells, influencing survival pathways such as MAPK and PI3K/AKT. This interaction promotes resistance to apoptosis and enhances metastatic potential, particularly in hypoxic tumor regions where neural inputs are further upregulated [40,41].

Neurotransmitters as Tumor Modulators

Neurotransmitters' role in EC extends beyond their conventional neural signaling functions. Dopamine, serotonin, and glutamate have all promoted tumor cell proliferation, invasion, and immune modulation. Dopamine receptor D2 activation has been linked to reduced antitumor immune activity, primarily by suppressing effector T-cell responses. Glutamate, acting through its ionotropic and metabotropic receptors, enhances the invasive capacity of EC cells by activating matrix metalloproteinases (MMPs) and degrading the extracellular matrix (ECM) [42-44].

Serotonin, another key neurotransmitter, is upregulated in several cancers, including EC, and has been shown to contribute to angiogenesis and immune evasion. The serotonergic system's involvement in regulating tumor-associated vasculature suggests its potential as a therapeutic target for mitigating EC progression [45].

Molecular Alterations in Driving Neural Involvement

Molecular analyses of EC tissues have revealed dysregulated expression of neurotrophic factors such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and glial cell-derived neurotrophic factor (GDNF). These molecules, primarily secreted by cancer cells, promote neural sprouting and remodeling within the TME. TrkA, TrkB, and RET, the receptors for NGF, BDNF, and GDNF, respectively, are frequently overexpressed in EC and serve as critical mediators of tumor-nerve crosstalk. Activation of these receptors induces downstream signaling cascades, including RAS/MAPK and PI3K/AKT, which enhance tumor cell survival, proliferation, and motility [46-48].

Perineural invasion (PNI) is a hallmark of aggressive EC and is frequently observed in advanced cases. PNI facilitates local tumor spread along nerve sheaths, bypassing conventional anatomical barriers. Clinically, the presence of PNI correlates with higher rates of recurrence and reduced survival [49].

PNI involves reciprocal signaling between cancer cells and Schwann cells. Cancer-derived neurotrophic factors induce Schwann cell migration, and Schwann cells, in turn, secrete pro-invasive factors such as laminin and fibronectin [50].

In advanced EC, neural signaling contributes significantly to epithelial-mesenchymal transition (EMT), a process critical for metastasis. Catecholamines released by sympathetic nerves upregulate EMT transcription factors such as Snail and Twist while simultaneously downregulating E-cadherin, a key adhesion molecule. These changes enhance cancer cells' migratory and invasive capabilities, facilitating systemic dissemination [51,52].

Interactions Between the Nervous System and Tumor Microenvironment

The interplay between tumor cells and the nervous system creates a self-reinforcing feedback loop that drives EC progression. Cancer cells secrete neurotrophic factors that induce axonal sprouting and increased nerve density within the TME. These newly formed nerve fibers release neurotransmitters and neuropeptides that further stimulate tumor growth. This bidirectional crosstalk amplifies the aggressiveness of the tumor, promoting resistance to therapy and creating new avenues for tumor dissemination [53-55].

Neural regulation exerts profound effects on the immune landscape of the TME. Through adrenergic signaling, sympathetic nerves suppress cytotoxic T lymphocyte activity and enhance the recruitment of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs). These immunosuppressive populations facilitate immune evasion, a hallmark of cancer progression. Additionally, adrenergic signaling has been shown to inhibit dendritic cell maturation and impair antigen presentation, further weakening the host immune response against EC [56-58].

Neural inputs significantly influence angiogenesis within TME. Norepinephrine, acting through beta-adrenergic receptors on endothelial cells, upregulates vascular endothelial growth factor (VEGF) production. This leads to the formation of aberrant and dysfunctional vasculature, which not only supports tumor growth but also creates hypoxic conditions that exacerbate neural involvement and tumor aggressiveness [58,59].

The immunosuppressive effects of neural signaling pose significant challenges for immunotherapy. By promoting an environment rich in Tregs and MDSCs, neural input diminishes the efficacy of immune checkpoint inhibitors (ICIs). Moreover, adrenergic signaling directly reduces the expression of PD-L1 on cancer cells, potentially altering the dynamics of ICI response in EC [60,61].

Pharmacological interventions targeting neural pathways have demonstrated promise in preclinical models. Beta-blockers, such as propranolol, effectively reduce adrenergic signaling, restoring immune competence and enhancing the efficacy of ICIs. These findings highlight the potential of integrating neural modulators into standard EC treatment protocols [62,63].

Impact of Neural Signaling on Therapeutic Response

Neural signaling is pivotal in mediating resistance to conventional therapies such as chemotherapy, radiotherapy, and immunotherapy in esophageal cancer (EC). Catecholamines released by sympathetic nerve terminals activate beta-adrenergic receptors on cancer cells, upregulating anti-apoptotic pathways such as Bcl-2 and surviving [64,65].

These pathways impair the cytotoxic effects of chemotherapeutic agents, reducing their efficacy. Furthermore, adrenergic signaling enhances the activity of efflux transporters, such as P-glycoprotein, which actively pump chemotherapeutic agents out of cancer cells, lowering intracellular drug concentrations. This mechanism contributes significantly to multidrug resistance, a common challenge in advanced EC [66,67].

Neural signaling has been shown to promote DNA repair mechanisms, countering the genotoxic effects of radiotherapy. Catecholamine-induced activation of the ATM/ATR pathway facilitates the repair of DNA double-strand breaks, a primary mechanism of radiotherapy-induced cell death. This neural influence on DNA repair underscores the importance of addressing neural contributions to therapeutic resistance to improve treatment outcomes [68-70].

Combining neural modulation with existing therapies has emerged as a promising strategy to overcome resistance. Beta-blockers, such as propranolol, have effectively reduced catecholamine-driven resistance mechanisms [8-10]. Preclinical studies demonstrate that beta-blockers enhance the cytotoxic effects of chemotherapeutic agents by downregulating anti-apoptotic signaling and inhibiting efflux transporters. Furthermore, beta-blockers synergize with radiotherapy by suppressing DNA repair pathways, increasing cancer cell susceptibility to radiation-induced damage [11-13].

Immunotherapies, particularly immune checkpoint inhibitors (ICIs), have also been explored with neural modulators. Beta-blockers improve T-cell activation and restore effective antitumor immunity by countering the immunosuppressive effects of adrenergic signaling. Early-phase clinical trials evaluating the combination of beta-blockers and ICIs in various cancers have yielded promising results, warranting further investigation in EC [25-27].

Role of Neuromodulation in Enhancing Therapeutic Outcomes

Neuromodulation techniques, including vagus nerve stimulation and surgical denervation, offer novel approaches to enhance therapeutic outcomes in EC. Vagus nerve stimulation, for instance, has been shown to modulate the TME by reducing inflammation and improving immune surveillance. In preclinical models, vagus nerve stimulation enhances the efficacy of both chemotherapy and immunotherapy, providing a strong rationale for its integration into multimodal treatment regimens [37-40].

Though less commonly explored, surgical denervation has demonstrated potential in preclinical studies by disrupting neural inputs to the tumor. This technique reduces catecholamine release, alters the TME, and sensitizes tumors to therapy. However, the clinical translation of surgical denervation faces challenges, including technical feasibility and potential systemic effects [14,48,49].

Biomarkers associated with neural activity have emerged as potential predictors of therapy response in EC. Elevated levels of neurotrophic factors such as NGF and BDNF and overexpression of their receptors correlate with resistance to chemotherapy and radiotherapy. Biomarkers of adrenergic signaling, including norepinephrine levels and beta-adrenergic receptor expression, have been linked to therapeutic resistance. These biomarkers hold promises for guiding personalized treatment strategies by identifying patients who may benefit from neural modulation [26,53-56].

Research should focus on integrating neural-targeted therapies into standard treatment protocols for EC. Advanced molecular profiling techniques, such as single-cell RNA sequencing and spatial transcriptomics, can provide insights into the neural landscape of EC and identify novel therapeutic targets. Furthermore, clinical trials evaluating the safety and efficacy of neural modulators in combination with standard therapies are critical for translating preclinical findings into clinical practice [34,59-61].

Therapeutic Potential of Neural Modulation

Pharmacological targeting of neural pathways represents a promising avenue for enhancing therapeutic efficacy in EC. Beta-adrenergic antagonists, such as propranolol, inhibit catecholamine signaling, disrupting pro-tumorigenic pathways within the TME. Preclinical studies have demonstrated that beta-blockers reduce tumor cell proliferation, angiogenesis, and metastasis in EC models. Additionally, beta-blockers restore immune competence by facilitating the recruitment of immunosuppressive cells, such as Tregs and MDSCs, within the TME [42,64-66].

Cholinergic modulators, targeting nicotinic and muscarinic acetylcholine receptors, also show potential in mitigating neural contributions to EC progression. These agents inhibit acetylcholine-induced activation of survival pathways, enhancing tumor cell susceptibility to apoptosis. Furthermore, cholinergic modulators may synergize with other therapies by modulating neural-immune crosstalk, improving antitumor immune responses [18-22].

Non-pharmacological approaches, such as vagus nerve stimulation and transcutaneous electrical nerve stimulation (TENS), offer innovative strategies for modulating neural activity in EC. Vagus nerve stimulation reduces systemic inflammation and alters the TME by suppressing pro-inflammatory cytokine production and enhancing immune surveillance. In preclinical studies, vagus nerve stimulation improves response to chemotherapy and ICIs, highlighting its potential as an adjunctive therapy [53,68-70].

Though technically challenging, surgical denervation disrupts neural inputs to the tumor, reducing catecholamine release and altering the TME. Preclinical evidence suggests that it enhances the efficacy of chemotherapy and radiotherapy in EC models. However, the clinical feasibility and long-term effects of surgical denervation remain to be fully elucidated [50-53].

Integrating neural modulation into multimodal treatment regimens offers a comprehensive approach to managing EC. By addressing neural contributions to tumor progression and therapeutic resistance, neural modulators can enhance the efficacy of chemotherapy, radiotherapy, and immunotherapy. Furthermore, combining pharmacological and neuromodulatory techniques may provide synergistic effects, maximizing therapeutic outcomes [38-40].

Despite its potential, the clinical translation of neural modulation in EC faces significant challenges. The heterogeneity of neural involvement across tumors and individual patients necessitates personalized approaches to therapy. Additionally, the potential systemic effects of neural modulation, such as cardiovascular or gastrointestinal complications, must be carefully evaluated in clinical trials [19,24-26].

Advancing neural-targeted therapies requires a multidisciplinary approach, integrating insights from oncology, neuroscience, and immunology. Collaborative efforts between researchers, clinicians, and industry stakeholders are essential for developing and validating neural modulators as standard components of EC treatment. Future studies should prioritize identifying novel neural targets and optimizing combinatorial therapies to improve patient outcomes [58,64-67].

Neural Biomarkers and Prognostic Tools in Esophageal Cancer

Exploring neural biomarkers in esophageal cancer (EC) has provided a novel dimension to early detection strategies. Elevated levels of neurotrophic factors such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and glial cell-derived

neurotrophic factor (GDNF) have been consistently identified in the serum and tumor tissues of EC patients [7-10,60].

These neurotrophic factors are critical mediators of tumor-neural interactions and are significantly associated with aggressive tumor behavior. Immunohistochemical analysis of Trk receptors (TrkA, TrkB, and TrkC) reveals overexpression in EC, indicating their potential as diagnostic biomarkers. nerve density measurements within tumor biopsies, facilitated by advanced imaging modalities such as confocal laser endomicroscopy, have shown promise in differentiating between benign and malignant lesions [56-59,66].

Neural activity-related biomarkers also hold prognostic value in EC. High expression levels of adrenergic and cholinergic receptors, such as beta-adrenergic receptor 2 (ADRB2) and muscarinic acetylcholine receptor M3 (CHRM3), correlate with reduced overall survival and increased metastatic potential. Moreover, perineural invasion (PNI) in surgical specimens is a well-established marker of poor prognosis [24-27,55].

Advanced techniques, such as multiplex immunofluorescence and spatial transcriptomics, have further enabled the assessment of neural involvement in the tumor microenvironment (TME), enhancing the precision of prognostic predictions. The integration of neural biomarkers into therapeutic decision-making is an emerging field [48-50,69].

Patients with elevated levels of beta-adrenergic receptor expression may benefit from beta-blocker therapy as an adjunct to standard chemoradiotherapy. Similarly, markers of cholinergic signaling, including acetylcholinesterase activity, may predict responsiveness to cholinergic modulators. These findings highlight the potential of neural biomarkers in guiding personalized treatment strategies for EC [33-35,42].

Recent advancements in imaging technology have facilitated the non-invasive assessment of neural involvement in EC. Positron emission tomography-magnetic resonance imaging (PET-MRI) using radiolabeled tracers targeting neural markers has emerged as a powerful tool for visualizing neural-tumor interactions. Functional MRI techniques, such as diffusion tensor imaging (DTI), enable the mapping of neural remodeling within the TME, providing insights into tumor aggressiveness and treatment response [47-49,58].

Developing robust and reliable neural biomarkers for EC requires a multidisciplinary approach. Collaborative efforts involving oncologists, neuroscientists, and bioinformaticians are essential to validate existing biomarkers and identify novel targets. Moreover, integrating machine learning algorithms into biomarker discovery and imaging analysis holds promise for enhancing diagnostic accuracy and prognostic precision [60, 68-70].

Neural Dynamics in Tumor-Immune Interactions

Neural signaling significantly influences the immune landscape of the TME in EC. Sympathetic nerve-derived catecholamines suppress cytotoxic T-cell activity by upregulating the expression of inhibitory immune checkpoints, such as PD-1 and CTLA-4, on T cells [17,18].

This neural-driven immune suppression facilitates immune evasion, a hallmark of cancer progression. Adrenergic signaling promotes the recruitment of immunosuppressive cell populations, including regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), further inhibiting antitumor immunity [1-3].

Neural regulation extends to antigen presentation by dendritic cells (DCs). Catecholamines impair DC maturation and antigen presentation capacity by downregulating major histocompatibility complex (MHC) class II expression. This neural influence disrupts the activation of naive T cells, thereby attenuating adaptive immune responses against the tumor. Cholinergic signaling mediated by acetylcholine reduces the production of pro-inflammatory cytokines, such as interleukin-12 (IL-12), by DCs, further compromising immune activation [55-58,69].

The neural-driven immunosuppressive environment poses significant challenges for immunotherapy in EC. Immune checkpoint inhibitors (ICIs), which have shown efficacy in various cancers, often exhibit limited success in EC due to the dominance of neural-immune crosstalk. Adrenergic signaling reduces the expression of tumor antigens and MHC molecules on cancer cells, diminishing their visibility to the immune system. This neural influence highlights the need for combinatorial approaches that integrate neural modulation with ICIs [20-22,67].

Targeting neural pathways offers a promising strategy to enhance the efficacy of immunotherapy in EC. Beta-blockers, by inhibiting adrenergic signaling, restore T-cell activity and reduce the recruitment of immunosuppressive cells, creating a more favorable immune milieu. Preclinical studies have demonstrated that combining beta-blockers with ICIs significantly enhances antitumor responses, providing a rationale for clinically evaluating such combinations in EC [40, 58-60].

Advancing our understanding of neural-immune interactions in EC requires sophisticated experimental models and translational studies. A promising approach for unraveling these complex interactions is the development of three-dimensional organoid systems incorporating neural and immune components of the TME. Integrating single-cell transcriptomics and proteomics into neural-immune research will provide deeper insight into the molecular mechanisms underlying neural regulation of immunity in EC [22,36,48].

Challenges and Opportunities in Neural Modulation

The heterogeneity of neural involvement across different EC subtypes poses a significant challenge for developing neural-targeted therapies. While squamous cell carcinoma and adenocarcinoma of the esophagus exhibit distinct biological behaviors, the extent and nature of neural interactions within the TME remain incompletely understood. Studies should prioritize comparative analyses of neural involvement across these subtypes to identify shared and unique therapeutic targets [10,27,69].

The clinical translation of neural-targeted therapies is hindered by several factors, including the potential systemic effects of neural modulation and the lack of standardized protocols for assessing neural involvement. Addressing these barriers requires rigorous preclinical validation of neural modulators, coupled with the design of carefully controlled clinical trials to evaluate their safety and efficacy [58-60].

Leveraging Advanced Technologies

Technological advancements, such as spatial transcriptomics, single-cell RNA sequencing, and advanced imaging modalities, offer unprecedented opportunities for characterizing neural involvement in EC. These tools enable the identification of novel neural biomarkers and therapeutic targets, paving the way for personalized approaches to neural modulation [12,34,65].

Implementing neural-targeted therapies in EC requires collaboration across disciplines, including oncology, neuroscience, immunology, and bioinformatics. Interdisciplinary research initiatives should focus on developing integrated treatment regimens that address neural regulation's multifaceted contributions to tumor progression and therapy resistance [9,16,30].

Future research should explore the potential of artificial intelligence and machine learning to analyze complex datasets generated from neural studies in EC. These computational approaches can facilitate the discovery of novel therapeutic targets

and predictive biomarkers, accelerating the translation of neural-targeted therapies into clinical practice [48,54,70].

Conclusion

The intricate interplay between neural signaling and esophageal cancer (EC) progression has emerged as a critical frontier in oncology. This review highlights the multifaceted role of the nervous system in shaping the tumor microenvironment (TME), influencing tumor proliferation, angiogenesis, immune modulation, and therapeutic resistance. Neural elements, by releasing neurotransmitters and neurotrophic factors, establish a "neurogenic niche" that fosters tumor aggressiveness and compromises treatment efficacy. The identification of these pathways offers a promising avenue for therapeutic innovation.

Advancements in understanding tumor innervation and neural remodeling have underscored the significance of perineural invasion (PNI) and adrenergic and cholinergic signaling in EC biology. These processes facilitate local invasion and metastasis, creating barriers to effective immune responses and conventional therapies.

The emerging field of neural-targeted interventions, including beta-adrenergic antagonists, cholinergic modulators, and neuromodulation techniques, has demonstrated significant preclinical promise. These approaches, particularly when integrated with immunotherapy, chemotherapy, and radiotherapy, can enhance treatment outcomes and improve survival rates in both early and advanced stages of EC.

Biomarker development for neural activity, such as neurotrophic factors and neurotransmitter receptors, has opened new possibilities for early diagnosis, prognostic assessment, and personalized treatment strategies. Imaging advances, including PET-MRI and functional MRI, further strengthen the ability to non-invasively assess neural contributions to tumor behavior non-invasively, providing a foundation for precision oncology.

Despite these advances, significant challenges persist. The heterogeneity of neural involvement across histological subtypes of EC and the lack of standardized protocols for assessing neural interactions underscore the need for further research. Moreover, the translational potential of neural-targeted therapies must be rigorously evaluated through well-designed clinical trials to ensure their safety and efficacy.

Future robust assays should address these gaps by leveraging cutting-edge technologies, such as single-cell RNA sequencing, spatial transcriptomics, and artificial intelligence, to elucidate the molecular mechanisms underlying neural regulation in EC. Collaborative efforts integrating oncology, neuroscience, immunology, and bioinformatics will be essential to fully realize the therapeutic potential of targeting neural pathways.

In conclusion, the convergence of neuroscience and oncology provides an unprecedented opportunity to transform the clinical management of esophageal cancer. By disrupting neural contributions to tumor progression and therapy resistance, neural-targeted strategies offer hope for improved outcomes in this devastating disease. As this field continues to evolve, it is imperative to translate these insights into clinical applications that benefit patients worldwide.

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Conflict of interest

The authors declare that there is no conflict of interest.

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