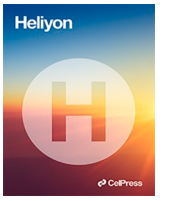
Heliyon 11 (2025) e42293

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

The neuroscience in breast cancer: Current insights and clinical opportunities

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ARTICLE INFO

Keywords:
Cancer neuroscience
Breast cancer
Innervation
Cancer treatment
Neurotransmitter

ABSTRACT

The involvement of nerves in the development of breast cancer has emerged as a significant factor. Interaction between the nervous system and breast cancer can influence tumor initiation, growth, invasion, metastasis, reverse resistance to drugs, promote inflammation in tumors, and impair the immune system's ability to combat cancer. This review examined the intricate relationship linking the nervous system with breast cancer, emphasizing both central and peripheral aspects of the nervous system. Moreover, we reviewed neural cell factors and their impact on breast cancer progression, alongside the interactions between nerves and immunology, microbiota in breast cancer. Furthermore, the study discussed the potential of nerves as biomarkers for diagnosing and prognosticating breast cancer, and evaluated prospects for improving chemotherapy and immunotherapy therapeutic outcomes in breast cancer treatment. We hope to provide a deeper understanding of the neurobiological underpinnings of breast cancer and pave the way for the discovery of innovative therapeutic targets and prognostic markers.

1. Introduction

Breast cancer is the most prevalent malignant condition among women, with 2.3 million new cases diagnosed and resulting in over 685,000 fatalities globally [1]. The five-year survival rate for breast cancer patients has improved to about 90 %, reflecting advancements in treatment and the transition of breast cancer to a more chronic disease management paradigm [2]. In breast cancer, a multitude of studies have underscored the pivotal influence of nerve-tumor crosstalk on tumor progression. The nervous system has transitioned from a passive observer to an active participant in tumor progression [3,4]. Recently, the presence of innervation and perineural invasion has been recognized as new characteristics of breast cancer within the tumor microenvironment [5,6]. Tumor innervation refers to the penetration of sympathetic, parasympathetic, and sensory nerves into the breast tumor tissue, whereas perineural invasion signifies the progression and encroachment of tumor cells along nerve fibers [7]. The central nervous system (CNS)

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https://doi.org/10.1016/j.heliyon.2025.e42293
Received 6 August 2024; Received in revised form 25 January 2025; Accepted 25 January 2025
Available online 27 January 2025

and peripheral nervous system (PNS) jointly govern the genesis, expansion, and metastasis of cancer, encompassing diverse facets of pathophysiology [8]. Additionally, neuroactive molecules, such as neurotrophins and AGMs, in breast cancer progression cannot be ignored [9]. Additionally, cancer treatments, including chemotherapy, targeted therapy, and immunotherapy, can influence and alter the nervous system, resulting in neurological impairments and possibly impacting the advancement of malignant tumors [10]. Therefore, treatment strategies based on neural tumor interactions may provide new perspectives and methods for improving the prognosis of cancer patients. Although current research has preliminarily revealed the mechanism of neural tumor interaction in cancer, its prospects in clinical applications still need further exploration.

This review seeks to offer an extensive analysis of the nerves associated with breast cancer, encompassing pertinent mechanisms related to nerve-induced carcinogenic effects, their potential as biomarkers, and future application prospects in the prevention or treatment of breast cancer. Our goal is to facilitate the clinical utilization of nerve-related strategies for breast cancer treatment moving forward.

2. Central nervous system and peripheral nervous system

The central nervous system (CNS) and peripheral nervous system (PNS) oversee the functional operations of various organs. Serving as a crucial factor in tumor development, the tumor microenvironment (TME) includes a complex array of extracellular matrix elements, fibroblasts, adipocytes, immune-inflammatory cells, along with extensive blood and lymphatic vascular systems [11]. The TME significantly influences the initiation, progression, and spread of tumors, while also promoting neural development [12]. In this context, tumor cells can secrete various cytokines and growth factors into the TME, which may encourage the proliferation of neuronal cells and facilitate the maturation of neural stem cells [13]. Simultaneously, the neural components present in the tumor microenvironment affect the progression of breast cancer by releasing a range of bioactive compounds [14]. Hence, a detailed investigation into the complex relationship between the nervous system and breast cancer may reveal new therapeutic targets, thereby offering more comprehensive and effective treatment options for breast cancer patients.

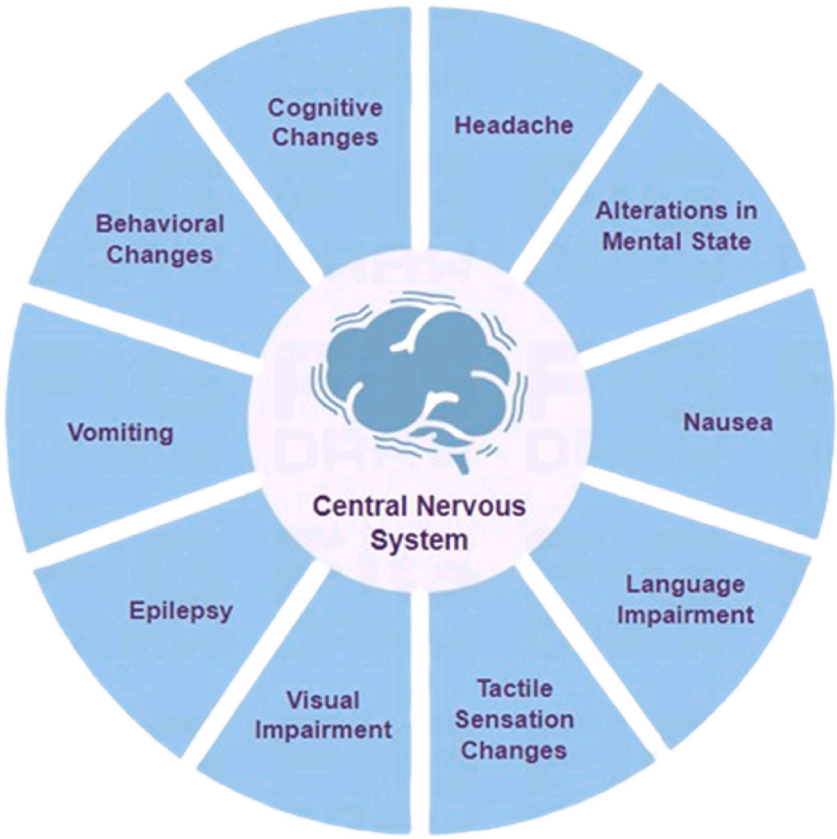

Fig. 1. CNS and breast cancer. After brain metastasis in cancer patients, various CNS clinical manifestations may occur, including nausea, vomiting, seizures, sensory, motor, speech, and visual impairments, headaches, and changes in cognition, mental state, and behavior. Metastasis involving the cerebellum and brainstem can lead to ataxia, neurological disorders, and dysfunction of upper motor neurons. Emotions are generated by CNS, which in turn can have mutual effects on the CNS, thereby affecting the progression of cancer. Negative emotions such as stress and anxiety can increase the risk of developing breast cancer.

2.1. CNS and breast cancer

2.1.1. The impact of breast cancer on the CNS

A retrospective investigation found that the occurrence rate of brain metastases among patients with breast cancer varies between 17 % and 25 % [15]. In contrast to individuals who have metastases in different areas, patients experiencing brain metastases typically face a significantly worse prognosis, which is a major factor in the mortality or recurrence of breast cancer cases [16,17]. After brain metastases develop in breast cancer patients, a range of clinical symptoms, such as headaches, changes in cognitive function, mental state, and behavior, may present [18]. Depending on the metastatic site and the extent of peritumoral brain edema, additional manifestations, such as nausea, vomiting, seizures, and sensory, motor, speech, and visual impairments, may occur. Metastasis involving the cerebellum and brainstem can lead to ataxia, cranial nerve disorders, and upper motor neuron dysfunction. Additionally, manifestations related to hydrocephalus may also come to the fore [19,20] (Fig. 1).

2.1.2. The influence of the CNS on breast cancer

The brain and spinal cord make up the central nervous system, where resident cells such as microglia, macrophages, dendritic cells, and T cells act as systemic observers of the body [21]. Research indicates that microglia, essential for the survival of neurons, can enhance anti-tumor immune responses and decrease brain metastasis in patients with cancer [22,23]. The CNS not only regulates breast cancer through resident cells but also exerts regulatory effects on breast cancer by directly stimulating the CNS [24]. Doublecortin (DCX), a microtubule-associated protein that is commonly associated with neuronal migration and maturation, has been proven to serve as a marker for neural precursor cells or newborn neurons [25].

Protein tyrosine phosphatase receptor type Z1 (PTPRZ1) functions as an enzyme associated with the development of the nervous system [26]. Studies indicate that in patients with breast cancer receiving hormone therapy, DCX does not correlate with recurrence-free survival (RFS), whereas a positive association exists between PTPRZ1 and improved RFS [27]. Additionally, Huang et al. found that chemotherapy can induce resistance in triple-negative breast cancer by stimulating the CDKN1A/PTN/PTPRZ1 pathway, resulting in enhanced expression of PTPRZ1 and its receptors [28]. The use of trastuzumab therapy has been connected to a significant rise in the occurrence of CNS metastasis among HER2-positive breast cancer patients [29,30]. In the occurrence of brain metastasis in breast cancer, tumor cell-secreted neurotrophin-3 (NT-3) can promote epithelial–mesenchymal transition, amplifying the invasive and distant metastatic capabilities of these cells [31]. Subsequently, tumor cells breach the basement membrane, infiltrate vascular or lymphatic conduits, persist within the circulatory system, and engender distant metastatic foci through endothelial migration, extravasation, and colonization [32,33]. At the same time, NT-3 exerts a suppressive effect on the cytotoxic response of microglia, fostering the propagation of breast cancer cells endowed with brain metastatic potential [34,35].

Emotions such as stress and anxiety, are generated by the CNS and can affect the progression of diseases by regulating the CNS. Research has indicated that adverse emotions such as stress and anxiety resulting from social isolation can increase the occurrence of breast cancer in rats by 135 %, increase the volume of breast cancer by 8.4-fold, and increase the relative risk of malignant tumors by 3.3-fold through regulation of the hypothalamic–pituitary–adrenal (HPA) axis [36]. Therefore, in addition to pharmacological interventions, a holistic approach integrating psychological interventions by mental health professionals should be considered. This approach aims to maintain emotional equilibrium in patients, alleviate the psychological burden imposed by the disease, and ultimately enhance therapeutic outcomes.

2.2. PNS and breast cancer

Numerous investigations have highlighted the substantial role of the PNS in breast cancer [37–53]. The PNS consists of two main divisions: the autonomic and somatic nervous systems, with the former being primarily responsible for its effects on breast cancer [14,54,55]. In a study conducted by Kamiya and his team, it was found that in a murine model of breast cancer, activation of the sympathetic nervous system facilitated tumor growth, whereas activation of the parasympathetic nervous system suppressed it [14]. Following this framework, we will individually outline the influences of both the sympathetic and parasympathetic nervous systems on breast cancer.

2.2.1. The impact of breast cancer on the PNS

The development of mammary glands is regulated by the sympathetic nervous system, which releases epinephrine and norepinephrine that subsequently interact with specific receptors found on breast cancer cells [56]. Numerous studies indicate that activating the adrenergic α2 receptor on these cancer cells may accelerate the progression of breast cancer. The use of the selective α2-adrenergic receptor (α2-ARs) agonist dexmedetomidine has been shown to significantly enhance the growth, invasion, and metastasis of breast cancer cells [57–59]. Conversely, the inactivation of α2-ARs, as achieved through tramadol administration, has proven effective in reducing the proliferation, invasion, and migration of breast cancer cells [60].

The β2-adrenergic receptor (β2-AR) activation has the potential to advance the development of breast cancer. Studies have demonstrated that chronic stress can lead to increased β2-AR activation, which in turn enhances growth, promotes angiogenesis, and augments stem-like characteristics in breast cancer cells [61,62]. In cases of HER-2-positive breast cancer, catecholamines activate the PI3K/Akt/mTOR signaling pathway through β2-AR, consequently undermining the effectiveness of trastuzumab treatment for breast cancer [63]. Additionally, retrospective analyses indicate that β-blockers may reduce the likelihood of metastasis in patients with breast cancer, yet they may also elevate the recurrence rate [64–70]. Conversely, β2-AR activation has been found to potentially hinder breast cancer progression. Rivero and colleagues reported that salbutamol, a β2-AR agonist, reduced the migration, invasion, and

metastasis of the MDA-MB-231 human breast cancer cell line [71]. Moreover, Wang et al. revealed that norepinephrine, by activating β2-AR receptors, can inhibit the invasion of MDA-MB-231 breast cancer cells, resulting in a decrease in CXCR4 expression [72]. Currently, most research indicates that the sympathetic nervous system is involved in facilitating breast cancer progression. Nonetheless, a few studies present findings that challenge this perspective, and this inconsistency may be influenced by the tumor microenvironment (TME) in which breast cancer develops.

2.2.2. *The influence of PNS on breast cancer*

Acetylcholine interacts with various receptors on breast cancer cells, such as the muscarinic acetylcholine receptor (MACHR) and the nicotinic acetylcholine receptor (NACHR), influencing multiple pathways related to breast cancer progression [73,74]. Studies indicate that the selective antagonist of the M1-acetylcholine receptor, pirenzepine, can reduce the suppressive impact of the parasympathetic nervous system on breast cancer [14]. According to Nishioka et al., nicotine binds to NACHRs present on breast cancer cells, which activates the EGFR/ERK1/2 signaling pathway, thus facilitating the proliferation of these cells [75]. Hirata et al. found that nicotine can interact with α7 NACHRs, triggering the PKC-Notch signaling pathway and boosting the stem-like properties of breast cancer cells [76]. Additionally, treatments with compounds like luteolin, which aim to obstruct nicotine's effects on α9 NACHRs, have been shown to mitigate breast cancer development [77]. Furthermore, the NACHR antagonist αO-conotoxin has been identified as effectively halting proliferation and encouraging apoptosis in breast cancer cells [78–81]. Pinnatoxin G similarly exhibits cytotoxic properties by blocking acetylcholine's binding to NACHR on breast cancer cells [82]. Collectively, these results indicate that the parasympathetic nervous system plays a role in inhibiting breast cancer advancement. This inhibition is primarily attributed to the

Table 1
The effect of neural cell-secreted bioactive factors on breast cancer.

Factor	Function	In vivo/vitro	Signaling pathways	Reference
NGF	Positively affects the migration, invasion, and proliferation of triple-negative breast cancer cells.	In vitro	TrkA/β1-integrin/FAK/Src pathway	[94]
	Enhances gene transcription and promotes breast cancer stem cells in TNBC and HER2-enriched breast cancer.	In vitro	JAK2-STAT3 and TrkA pathway	[91]
	Positively affects the migration/invasion of breast cancer cells	In vivo and vitro	CD44v3/TrkA pathway	[89,95]
	Facilitating self-renewal and plasticity in breast cancer stem cellsbreast	In vitro	NGF/proNGF/p75(NTR) pathway	[96]
	Enhancing chemoresistance in TNBC cells	In vitro	p75(NTR) pathway	[90]
BDNF	Promoting proliferation and metastasis of breast cancer cells	In vivo	BDNF/TRKB pathway	[100]
	Development of resistance to tamoxifen	In vivo and vitro	BDNF-AS/RNH1/TRIM21/ mTOR pathway	[101]
	Inhibition of apoptosis in breast cancer cells	In vitro	/	[102]
	Facilitating early recurrence in triple-negative breast cancer	In vitro	/	[103]
NTN-1	Inhibition of apoptosis in breast cancer cells	In vitro	/	[110]
	Facilitating metastasis in breast cancer	In vivo	/	[111]
NTN-4	Inhibiting migration and invasion of breast cancer cells	In vitro	/	[114]
	Promoting lymphatic vessel growth in breast cancer	In vivo	Src/FAK pathway	[115]
EPHA2	Enhancing resistance to trastuzumab	In vivo	/	[118]
EPHA10	Promoting metastasis in breast cancer	In vitro	/	[122]
EPHA2	Promoting breast cancer growth	In vivo and vitro	EPHA2/ephrin-A1 pathway	[126]
	Facilitating breast cancer recurrence	In vitro	EPHA2/ephrin-A1 pathway	[127]
Slit2	Inhibiting brain metastasis in breast cancer	In vivo and vitro	Slit2/Robo1 pathway	[130]
	Promoting breast cancer metastasis in endothelial cells, inhibiting migration in breast cancer cells	In vivo and vitro	Slit2/TLR3 pathway	[132]
SEMA7A	Promoting breast cancer growth	In vivo	SEMA7A/COX-2 pathway	[136]
SEMA4C	Promoting invasion and metastasis of breast cancer	In vivo	Sema4C/PlexinB2	[137]
	facilitating recruitment of macrophages and angiogenesis in breast cancer	In vitro	p53 and NF-κB pathways	[139]
	promoting invasion in breast cancer	In vivo	TGF-β pathway	[140]
SEMA4D	Promoting invasion and metastasis of breast cancer	In vivo and vitro	/	[141]
SEMA3B	Inhibiting breast cancer growth, promoting breast cancer metastasis	In vivo and vitro	p38–MAPK pathway	[143]
	Induces apoptosis in breast cancer cells	In vitro	PI3K/Akt pathway	[144]
	Inhibiting breast cancer growth	In vivo and vitro	GATA3 pathway	[145]
	Induces apoptosis in breast cancer cells	In vitro	VEGF pathway	[146]
SEMA3A	Inhibiting migration, tumor growth, and angiogenesis in breast cancer cells	In vivo	PTEN/FOXO 3a pathway	[147]
	Inhibiting migration, tumor growth, and angiogenesis in breast cancer cells	In vivo	Neuropilin-1 pathway	[148]
SEMA3	increasing the number of cancer stem-like cells in breast cancer cells	In vivo and vitro	NP1/MICAL3/CRMP2/Numb pathway	[149]
SEMA3C	Inhibits tumor metastasis and lymphangiogenesis	In vitro	VEGFR-3, ERK1/2 and Akt pathways	[150]

interaction of acetylcholine with MACHR. For breast cancer patients who smoke, advising them to quit smoking promptly is crucial to prevent further deterioration of their condition. Additionally, whether a combination of MACHR agonists or NACHR antagonists could yield more favorable treatment outcomes in breast cancer patients warrants further investigation during the course of therapy.

3. Neural cell factors and breast cancer

In the relationship between the nervous system and breast cancer cells, factors secreted by nerve cells play a crucial role. These secreted factors primarily consist of neurotrophic proteins and axon guidance molecules (AGMs) [83]. Examples of neurotrophic proteins are the nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin-3 (NT-3), among others. Both NGF and BDNF can be released by neural cells and directly interact with their specific receptors on breast cancer cells, influencing signaling pathways that are involved in the progression of breast cancer [84,85]. The AGM category mainly includes three significant families: netrin (NTN), ephrin, slit, and semaphorin (SEMA), all of which play a role in the growth and movement of neuronal axons [86]. In breast cancer, these molecules predominantly mediate their regulatory effects via autocrine signaling mechanisms [87]. (Table 1) (Fig. 2).

3.1. Neurotrophic proteins

3.1.1. NGF

Since its identification in the 1950s, nerve growth factor (NGF) has been recognized for its significant involvement in neurological disorders, cardiovascular illnesses, and cancerous conditions [88]. Research indicates that NGF interacts with the receptors TRKA and NGFR, thereby promoting the advancement of breast cancer, while myocardial infarction can stimulate breast tumor growth by activating the NGF-TRKA signaling pathway [89,90]. The levels of NGF and its receptors correlate with the aggressiveness of breast tumors and may act as prognostic markers for breast cancer [91–93]. Evidence suggests that TRKA activation fosters the development of triple-negative breast cancer (TNBC) by bolstering the growth, invasion, and migration of cancer cells. Additionally, the TRKA inhibitor GW441756 has demonstrated the capacity to impede cancer cell progression [94]. Elevated NGFR levels enhance the proliferation and movement of TNBC cells and provide resistance to programmed cell death [92]. The stimulation of TRKA via β-NGF also

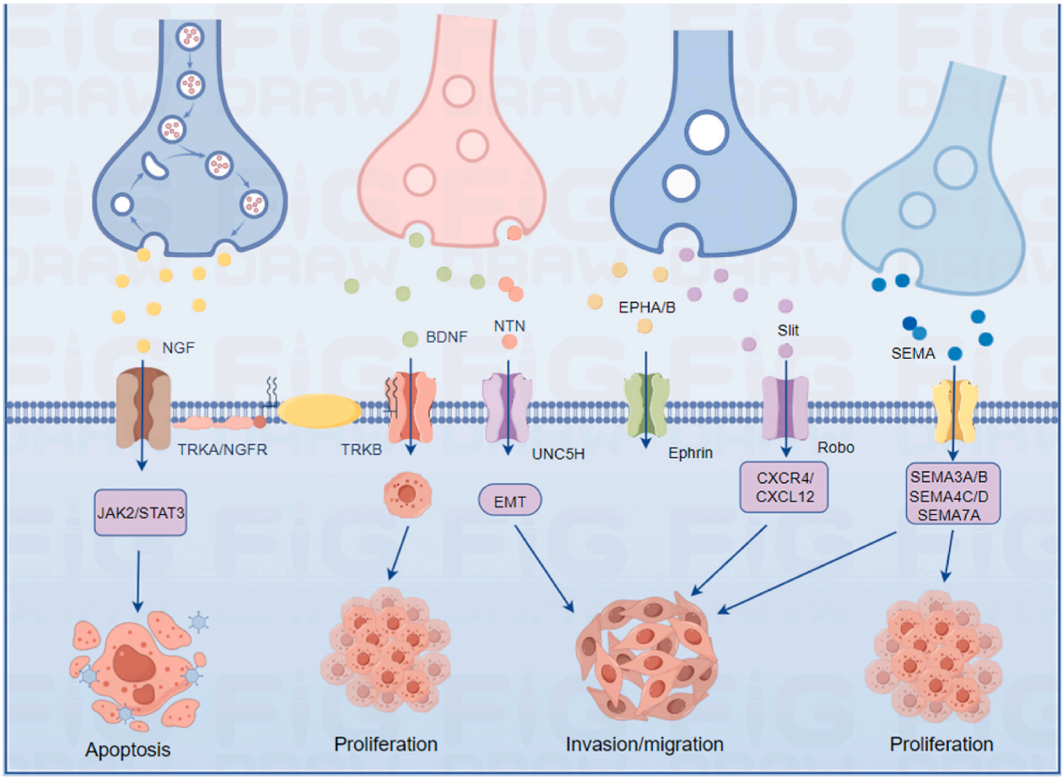

Fig. 2. Neural cell factors and breast cancer. Neural cell factors actively secreted by nerve cells play a key role in the occurrence and development of breast cancer. These active cytokines including NGF, BDNF, NTN, EPHA/B, Slit, SEMA3A/B, SEMA4C/D and SEMA7A can bind to corresponding receptors on breast cancer cells and regulate the proliferation, migration, invasion and apoptosis of breast cancer cells. The interaction between these neural factors and their receptors on cancer cells represents a complex network that integrates neuronal signaling into the tumor microenvironment, thus influencing tumor behavior and clinical outcomes.

activates the JAK2/STAT3 pathway, and the simultaneous activation of both pathways contributes to the tumorigenic potential of invasive breast tumors [91]. The interaction between TRKA and CD44 enhances the aggression and drug resistance of breast cancer cells (BCC) [89,95]. The NGF/NGFR signaling pathway is essential for cancer maintenance, as it regulates the renewal and adaptability of breast cancer stem cells (CSCs) [96]. Chakravarthy et al. found that the NGF-induced increase in NGFR expression can improve the effectiveness of chemotherapy in TNBC [90]. Collectively, the results from these studies indicate that NGF, along with its receptors TRKA and NGFR, could be promising therapeutic targets for breast cancer.

However, despite the promising anti-tumor effects of TRKA inhibitors observed in laboratory studies, their clinical application remains hindered by numerous challenges. The interaction between NGF and its receptors is not limited to tumor cells, but may also affect the surrounding tumor microenvironment, including immune cells and endothelial cells. This complexity suggests that monotherapy targeting NGF/TRKA may not be fully effective. Therefore, future research should focus more on the comprehensive role of the NGF/NGFR axis within the tumor microenvironment and explore combination therapies to better overcome the multi-drug resistance and invasiveness of tumors.

3.1.2. BDNF

BDNF is an essential neurotrophic factor that significantly contributes to the development of the central nervous system (CNS) [97]. Recent research has highlighted the involvement of BDNF along with its receptor TRKB in breast cancer development [98]. It has been reported that the BDNF/TRKB pathway can enhance breast cancer progression by promoting proliferation and migration of tumor cells [99,100], triggering resistance to treatments [101], preventing apoptosis in cancer cells [102], and increasing recurrence rates [103]. The administration of miR-206, miR-107, and miR-204 has been found to influence BDNF expression and can either inhibit or stimulate breast cancer progression [104–106]. However, while miR-206, miR-107, and miR-204 regulate BDNF expression and influence breast cancer progression, their clinical translation potential is still limited. Applying these microRNAs in therapy faces challenges, particularly in effectively targeting them and addressing tumor heterogeneity. Studies indicate that estrogen may enhance the invasiveness and tumor development of TNBC through the activation of TRKB and its associated downstream pathways, which, in turn, facilitates the metastasis of breast cancer to the brain [107]. Collectively, these findings suggest that developing interventions aimed at the BDNF/TRKB signaling pathway could play a role in the creation of novel cancer therapies, including mRNA vaccines and small molecule proteins.

3.2. AGMs

3.2.1. NTN

NTN plays a vital role in guiding the development and movement of neuronal axons by offering migration signals during CNS development [108]. Studies suggest that NTN-1, along with its receptors UNC5H (which includes UNC5H1, UNC5H2, and UNC5H3), are essential in managing apoptosis in basal cell carcinoma (BCC) [109,110]. Additionally, in the context of metastatic breast cancer, there is a notable rise in NTN-1 expression, which implies a strong link between NTN-1 levels and the prognosis for patients with breast cancer [111]. Moreover, research indicates that decitabine enhances the responsiveness of cancer cells exhibiting low NTN-1 expression to anti-NTN-1 treatments [112]. Beyond NTN-1, findings reveal that breast cancer patients with NTN-4 expression experience longer disease-free survival (DFS) and overall survival (OS) compared to those who do not express NTN-4 [113]. Another investigation found that increased levels of NTN-4 reduce the invasiveness and mobility of BCC cells by obstructing the epithelial–mesenchymal transition (EMT) process [114]. Conversely, Larrieu et al. noted that elevated NTN-4 levels can trigger both lymphangiogenesis and angiogenesis in breast cancer, which leads to increased lymphatic permeability and facilitates cancer metastasis [115].

Although the role of NTN-1 and its receptor UNC5H in regulating apoptosis in breast cancer cells (BCC), as well as the potential prognostic impact of NTN-4, have garnered significant attention, there are still notable limitations in current research. First, NTN-1's involvement in breast cancer metastasis has been shown to correlate with patient prognosis. However, the specific molecular mechanisms remain unclear. While demethylating agents like decitabine enhance the sensitivity to anti-NTN-1 treatment in NTN-1-low-expressing cancer cells, it remains uncertain whether this strategy can be widely applied in clinical settings. More clinical data and long-term follow-up are needed for validation. Additionally, the research on NTN-4 yields contradictory findings. High NTN-4 expression is associated with longer disease-free survival (DFS) and overall survival (OS) in breast cancer patients. However, other studies suggest that overexpression of NTN-4 promotes cancer metastasis by inducing lymphangiogenesis and angiogenesis, thus increasing lymphatic permeability. These conflicting results highlight that NTN-4's role in breast cancer progression may depend on the tumor's microenvironment and molecular context. Further research is required to clarify its dual effects.

3.2.2. Ephrin

Ephrin type-A receptor 2 (EPHA2) functions as a receptor tyrosine kinase and is found to be overexpressed in multiple types of cancer, such as breast cancer [116]. In breast cancer, the expression of Epha2 and Epha10 is significantly upregulated [117–123], while the expression of EPHB4 is markedly downregulated [124]. Compared with that in the primary tumor site, the expression of Epha3 is significantly elevated in metastatic breast cancer, while the expression of Ephrin-A1 is notably decreased, indicating a poorer prognosis [125–127]. Conversely, additional research has shown that the expression levels of EPHA2, EPHA3, EPHA4, and EPHA5 are reduced in cases of breast cancer, implying that these genes might have roles in tumor suppression [128]. Additionally, research has reported that EPHB2 and its homologous ephrin ligands exhibit dual antitumor effects in breast cancer [129]. Conflicting evidence exists regarding the role of EPHA2 in breast cancer progression, potentially stemming from variations in experimental models and

analytical approaches. Therefore, a thorough investigation into the spatiotemporal regulation and therapeutic potential of EPHA2 within specific breast cancer subtypes is warranted.

3.2.3. Slit

Studies have indicated that reduced levels of Slit and its receptor Robo are linked to an unfavorable prognosis and a higher probability of brain metastasis in breast cancer patients [130]. It has been demonstrated that an increased expression of SLIT2 elevates the presence of β-catenin at the membranes of breast cancer cells (BCCs), which enhances cell-to-cell adhesion and mitigates cancer invasion [131]. Moreover, elevated SLIT2 levels can lead to a decrease in the nuclear translocation of β-catenin, further hindering the proliferation of cancer cells [131]. Enhancing the functionality of the Slit/Robo pathway appears to downregulate the CXCR4/CXCL12 signaling axis, effectively reducing the metastasis of breast cancer [131]. In addition, SLIT2 can boost the body's antitumor immune response and limit metastasis by stimulating antitumor M1-type tumor-associated macrophages (MI-TAMs) as well as reprogramming macrophages derived from bone marrow [132,133]. However, other studies have indicated that SLIT2 can promote breast tumor growth, invasion, and metastasis by stimulating the release of the neuropeptide substance P, which contradicts the aforementioned findings [134].

Although Slit/Robo signaling, particularly SLIT2, shows promise in inhibiting breast cancer progression, the literature presents several contradictions. While SLIT2 overexpression can suppress invasion and proliferation by modulating β-catenin and inhibiting metastasis via the CXCR4/CXCL12 axis, these effects may be context-dependent and vary across different cancer subtypes and stages. Additionally, SLIT2's ability to enhance antitumor immunity by activating M1-type macrophages is promising but may be limited by the plasticity of tumor-associated macrophages, which can shift to a pro-tumor phenotype. Furthermore, studies suggesting that SLIT2 promotes tumor growth through the release of substance P highlight its potentially dual role in cancer progression. These contradictions underscore the need for more comprehensive research to better understand the complex, stage- and context-dependent functions of SLIT2 in breast cancer.

3.2.4. SEMA

The SEMA gene family consists of several members. Elevated expression levels of SEMA4C and SEMA7A have been notably observed in breast cancer cases. Additionally, research has shown that SEMA4C can significantly improve the diagnostic accuracy for breast cancer lesions categorized as BI-RADS 3 or 4 [135–138]. Both SEMA4C and SEMA4D are believed to play a role in the advancement of breast cancer by facilitating processes such as cancer cell proliferation, growth, invasion, and metastasis [137, 139–142]. In a related manner, SEMA7A not only serves similar functions but also encourages lymphangiogenesis and has a strong

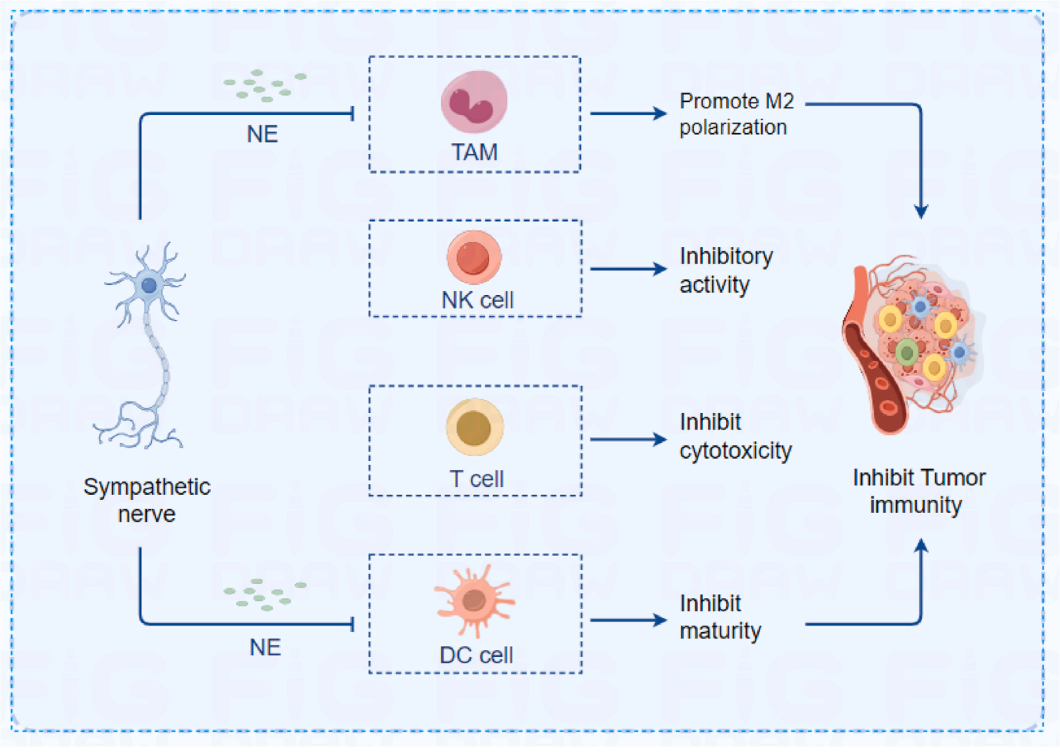

Fig. 3. Sympathetic nervous system and tumor immunity in breast cancer. The sympathetic nervous system plays a role in anti-tumor immune responses by modulating immune cells. It can promote M2 polarization in TAMs, inhibit T cell cytotoxicity, suppress NK cell activity, hinder DC cell maturation, thereby achieving tumor immune suppression, and promoting the progression of breast cancer.

correlation with breast cancer arising postpartum [136,137,139–142]. Furthermore, SEMA3B has been recognized as a factor that inhibits the progression of breast cancer by promoting cellular apoptosis, blocking cancer cell growth, and curbing metastasis [143–146]. On a different note, SEMA3A has the capacity to hinder both the growth and spread of breast cancer while also fostering its progression by enhancing the stemness of cancer cells [147–149]. Notably, the presence of breast cancer may induce changes in SEMA that further stimulate its progression. For example, SEMA3C can be cleaved by furin-like pro-protein convertases, which results in the loss of its ability to inhibit cancer cell migration and lymphangiogenesis, thereby facilitating breast cancer progression [150].

Current research indicates that targeting members of the SEMA family can exert inhibitory effects on the progression of breast cancer or modulate sensitivity to therapeutic agents. miR-138 has been found to inhibit breast cancer invasion by targeting SEMA4C [151]. miR-195 can influence the therapeutic efficacy of chemotherapy drugs by targeting SEMA6D [152]. Antibodies against SEMA4D significantly suppresses the progression of breast cancer [136]. Although targeting members of the SEMA family—such as SEMA4C and SEMA6D—has shown promise in modulating cancer cell behavior and enhancing sensitivity to therapies, the translation of these findings into clinical practice remains a challenge. The therapeutic potential of miRNAs like miR-138 and miR-195 and monoclonal antibodies targeting SEMA4D has yet to be confirmed in large-scale clinical trials. The complexity of the SEMA family's interactions with other signaling pathways and its varied functions across different cancer types underscores the need for further studies to refine therapeutic strategies targeting these molecules.

4. Nerves and immunology

4.1. Sympathetic nervous system and tumor immunity in breast cancer

Research has shown that both primary and secondary immune organs receive input from the sympathetic nervous system (SNS) [153]. Therefore, the SNS is essential in the regulation of immune functions. Numerous studies have demonstrated that the SNS is capable of influencing the tumor microenvironment (TME) through various mechanisms, thus fostering tumor progression. It has the ability to dampen innate immunity by encouraging M2 polarization in tumor-associated macrophages (TAMs) and reducing the effectiveness of natural killer (NK) cells [154–156]. Furthermore, the SNS can impede adaptive immunity by blocking dendritic cell (DC) maturation and diminishing the cytotoxic activities of T cells [157,158]. Additionally, the SNS may enhance both the activity and numbers of immunosuppressive regulatory T cells and myeloid-derived suppressor cells (MDSCs), which leads to further suppression of antitumor immune responses [159]. Beyond these mechanisms, the SNS can also facilitate the growth of breast cancer by decreasing the expression of immune checkpoint molecules, which aids in the development of an immunosuppressive TME [14] (Fig. 3).

4.2. Parasympathetic nervous system and tumor immunity in breast cancer

Unlike the sympathetic nervous system, the parasympathetic nervous system has opposing effects on the antitumor immune response. Activation of the tumor-associated parasympathetic nervous system can lead to a reduction in PD-1 expression on $CD4^+$ tumor-infiltrating lymphocytes (TILs), while simultaneously increasing IFN-γ levels in both $CD4^+$ and $CD8^+$ TILs, which enhances antitumor immune responses [14]. Additionally, stimulation of the vagus nerve boosts the activity and proportion of $CD8^+$ T cells and natural killer (NK) cells, while diminishing the accumulation and activity of myeloid-derived suppressor cells (MDSCs), contributing to effective antitumor immunity [160]. Furthermore, it lowers the concentrations of proinflammatory mediators in the serum [160].

4.3. Sensory nervous system and tumor immunity in breast cancer

In addition to the autonomic nervous system, the sensory nervous system significantly contributes to tumor immunity. Erin et al. found that Olvanil, which stimulates sensory nerves, increases the quantity and infiltration of $CD8^+$ T cells and concurrently hinders lung and liver metastasis in breast cancer [161]. Furthermore, studies indicate that activating sensory fibers of the left vagus nerve using capsaicin may reduce breast cancer metastasis [162].

The studies mentioned above suggest that the sympathetic nervous system has an inhibitory influence on the tumor immune system, which facilitates the advancement of breast cancer. In contrast, the parasympathetic and sensory nervous systems may hinder breast cancer progression by enhancing the tumor immune response. This observation is consistent with the previously outlined functions of the nervous system related to breast cancer. This provides a theoretical basis for the addition of relevant neural blockers or stimulants in future therapeutic approaches for breast cancer. These insights also imply that the pain experienced by breast cancer patients might be a mechanism through which the body initiates self-recovery and healing processes.

5. Nerves and microbiota

5.1. Nerves and gut microbiota

The gut microbiota works alongside the nervous, immune, and endocrine systems to manage reactions to pathophysiological stressors in the intestine. While there is presently insufficient experimental evidence to directly link the nervous system, microbiota, and cancer, new research findings suggest a functional relationship among these components.

The composition and functionality of both the nervous system and the microbial community influence one another in states of health and disease. The gut microbiota plays a role in the modulation of social, psychological, and emotional shifts via the microbiota-

brain axis, being linked to feelings of anxiety, fatigue, and depression [163]. Furthermore, there is a connection between sleep disturbances, fatigue intensity, and the microbiota [164]. Importantly, chemotherapy-induced modifications in the gut microbiota are correlated with anxiety regarding cancer recurrence [165]. These mechanisms are facilitated by pathways that connect to the brain, involving endocrine signaling and the activation of the immune system. Changes in the gut microbiota's composition can influence the development of breast cancer and affect patients' psychosocial health through multiple pathways [166]. For example, chronic inflammation within the intestines can lead to anxiety-like behaviors in mice, alongside a decrease in brain-derived neurotrophic factor (BDNF) levels in the hypothalamus, a condition that may be alleviated by the administration of bifidobacteria [167]. Additionally, research by Kim et al. demonstrated that a 12-week regimen of probiotic capsules (Bifidobacterium bifidum BGN4 and Bifidobacterium longum BORI) in healthy individuals aged 65 and over notably raised serum BDNF levels [168]. Likewise, in breast cancer patients undergoing chemotherapy, probiotic capsules containing Bifidobacterium longum, Lactobacillus acidophilus, and *Enterococcus faecalis* were shown to significantly reduce cognitive impairment related to chemotherapy [169].

The gut microbiota influences the functioning of the nervous system via immune-related factors, which in turn regulates stress levels. Chronic stress, driven by catecholamines and hormones from the adrenal cortex originating from the sympathetic nervous system and the neuroendocrine system, has a substantial impact on the onset, progression, and outcome of breast cancer [170]. The hypothalamic-pituitary-adrenal (HPA) axis, an essential element of the neuroendocrine pathway, plays a vital role in the release of adrenal cortex hormones during stress and depends on a healthy gut microbiota for its proper development [171]. Probiotics, including *lactobacilli and bifidobacteria*, produce neurotransmitters such as GABA that act on the brain-gut axis, thereby inhibiting stress-related hormone levels, suppressing the HPA axis and sympathetic nervous system pathways, reversing the body's chronic stress state, thereby potentially consequently inhibiting tumor development [172]. In addition, the vagus nerve serves as a crucial link between intestinal and brain nerve functions, transmitting information regarding gut microbiota dysbiosis to the brain, thereby inducing chronic stress-related emotions such as anxiety and depression that impact tumor progression [173]. Research has demonstrated the potential of *Lactobacillus rhamnosus* to ameliorate anxiety and depressive behavior in rats, while an effect inhibited by vagotomy [174]. Recent research has emphasized that short-chain fatty acids (SCFAs), which are produced by bacteria, play crucial roles in intestinal health and immune modulation, interacting with nerve cells by activating both the sympathetic and autonomic nervous systems [175]. SCFA supplementation ameliorates anxiety and depressive-like behaviors and reduces stress-related receptor gene expression in the hypothalamus, hippocampus, and colon [176] (Fig. 4).

5.2. Nerves and intratumoral microbiota

Previous research has established a connection between dysbiosis of gut bacteria, fungi, and viruses and the onset of breast cancer [177]. In rece nt years, the once prevalent belief in the sterility of organs and tumor tissues has been debated. Importantly, the human breast is not sterile, and the microbiota in breast tissue can ingress through endogenous pathways such as the skin, nipple areola, blood circulation, and gut microbiota. *Fusobacterium, Atopic, Glucobacillus, Hydrophilic,* and *Lactobacillus* are notably enriched in breast cancer tissue [178]. Similar to the gut microbiota, the intratumoral microbiota can modulate the function of the nervous system through immune-related factors [179]. Significantly, it has become more apparent that the intratumoral microbiota affects carcinogenesis, cancer advancement, treatment, and even resistance to drugs [180]. Urbaniak and colleagues found that Bacillus,

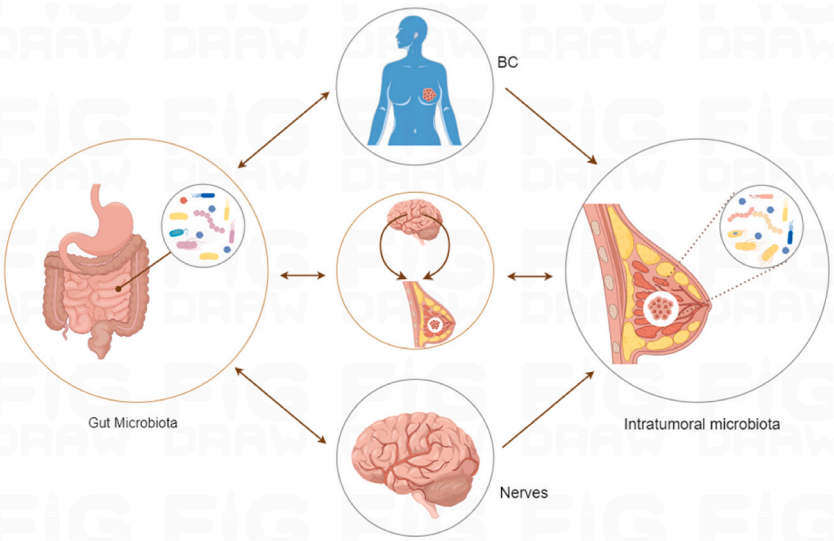

Fig. 4. Nerves and microbiota in breast cancer. There is a functional connection between the nervous system, microbiota, and cancer. Gut microbiota and intratumoral microbiota participate in the regulation of social, psychological, and emotional changes through various mechanisms such as microbiota visceral brain axis, regulating breast cancer development and affecting the mental health of breast cancer patients.

Enterobacteriaceae, and Staphylococcus *Escherichia coli* were found in greater quantities in healthy tissues compared to breast cancer tissues. Furthermore, *Staphylococcus* was found to promote the activation of NKT cells, leading to cellular immunity and aiding in the prevention of cancer development [181]. Furthermore, an increased occurrence of Prevotella in healthy tissues has been observed, with this microorganism capable of generating SCFAs that interact with nerve cells by activating both the sympathetic and autonomic nervous systems to exert effects that suppress tumors [175,181]. Fu et al. indicated that, despite the low biomass of the intratumoral microbiota, it improves resilience against fluid shear stress via the recombinant actin cytoskeleton, thereby aiding the survival of host cells and contributing to cancer metastasis [182].

In summary, the microbiota within tumors is prevalent in breast cancer tissues, and these microbes could play a role in the initiation, progression, and outcomes of the disease. Previous research has highlighted a strong connection among microorganisms, the nervous system, and breast cancer, with early advancements observed in enhancing cognitive abilities and managing weight in patients with breast cancer. Future research could explore whether microorganisms can enhance the mental health of breast cancer patients by modulating neural pathways, alleviate neurotoxicity during treatment, and potentially directly influence the progression of breast cancer.

6. Potential clinical applications of nerves in breast cancer

6.1. Nerves as potential biomarkers for breast cancer diagnosis and prognosis

Assessing the role of neuroscience in cancer treatment is crucial, particularly emphasizing the advancement of imaging and electrophysiological biomarkers. The relationship between nerves and tumors has been explored at cellular and subcellular levels through high-resolution optical and electron microscopy techniques, alongside electrophysiological patch clamp recordings [183]. While these techniques yield accurate information, their application in larger clinical trials poses challenges. Additionally, investigating molecular and structural biomarkers in tumor biopsy samples regarding the interplay between the nervous system and cancer may provide deeper understanding. Neuronutrients, including NGFR and BDNF, are vital for neuron development, survival, and apoptosis. Research indicates that NGFR levels in BLBC are considerably elevated compared to other subtypes, and BDNF produced by cancer cells enhances axon formation, aiding tumor cell invasion [184,185]. Increased BDNF levels have been associated with adverse clinical outcomes and lower survival rates among breast cancer patients [186]. Furthermore, the upregulation of Trk B, a neurotrophic receptor, has been linked to unfavorable survival outcomes for TNBC patients [187,188].

A research investigation involving 114 patients diagnosed with breast cancer indicated that interventions promoting physical activity can enhance both life quality and emotional health, with the endorphins released during physical activity acting as a significant biomarker [189,190]. The role of catecholamine-mediated β-activation of adrenergic signals has been demonstrated to be vital in the processes of cancer growth, invasion, metastasis, and angiogenesis [191]. The length of treatment involving β-blockers has a

Table 2
Potential clinical applications of nerves in breast cancer.

Clinical applications	Nerves	Mechanism	Reference
As a biomarker	NGFR	The level of NGFR in BLBC was significantly higher than in other subtypes.	[184,185]
	BDNF	Elevated BDNF levels were associated with reduced clinical survival in breast cancer patients.	[186]
	Trk B	Elevated Trk B levels were associated with poor survival outcomes in TNBC patients.	[188]
	Endorphins	Improved mood and quality of life of patients with breast cancer.	[189,190]
	β-activation of adrenergic signals	The time of β-blocker was closely related to the prognosis of breast cancer treatment.	[191–194]
	5-HT	5-HT had a stronger effect in the early stage of metastasis than in the later stage.	[196]
	mGluR1	Elevated mGluR1 levels were associated with MFS and poor OS in ER-negative breast cancer patients.	[197]
Improving chemotherapy efficacy	Antidepressants Sertraline	Enhanced docetaxel sensitivity and alleviated the side effects of hot flashes after taking tamoxifen.	[198,199]
	Trk inhibitors (AZD6918, CEP-701)	Enhanced etoposide sensitivity.	[200]
	Glutamate	Heightened sensitivity to cytotoxic chemotherapy.	[201]
	Dopamine or dopamine receptor agonists	Enhanced doxorubicin or 5-FU sensitivity.	[202]
	miR-195	Influence the efficacy of epirubicin/cyclophosphamide chemotherapy by targeting SEMA6D	[152]
	β-blockers	Reversed trastuzumab resistance.	[206]
Improving immunotherapy efficacy	CNS-myeloids	Downregulated of CX3CR1 and upregulated of CXCL10, then inhibited PD-L1-signaling relieved immune suppression.	[210]
	Vagus nerve	Inhibited breast cancer by reducing PD-1 levels in $CD4^+$ and $CD8^+$ lymphocytes.	[211]
	Sympathetic denervation	Downregulated the expression of PD-1, PD-L1, and FOXP3.	[212]
	Neural signaling that controls the retention or release of T cells	Regulated the native immune response as well as the immune checkpoint blockade-induced immune response.	[213]

strong correlation with the prognosis for breast cancer patients. Those who utilized β-blockers saw their risk of metastasis decrease by 57 % and their mortality rate drop by 71 % [192]. When administered at the start of neoadjuvant therapy, β-blockers are linked to marginally improved recurrence-free survival rates [193,194]. Furthermore, prior to or following a breast cancer diagnosis, the adoption of selective SSRIs has been found to elevate the overall mortality rate [195].

Serotonin (5-HT) serves as an important local regulator of epithelial balance within the breast, exerting a more pronounced effect during the initial phases of metastasis compared to subsequent stages, thereby emphasizing its involvement in the progression of breast cancer [196]. Metabotropic glutamate receptor 1 (mGluR1), classified within the GPCR superfamily, plays a role in synaptic signaling and the excitability of neurons. Notably, the expression of mGluR1 has shown a significant correlation with metastasis-free survival (MFS) and reduced overall survival (OS) in patients with ER-negative breast cancer [197]. Finally, the utilization of multiomics methods can serve as alternative parameters for clinical trials, expanding our understanding of cancer cells related to cancer neuroscience and the molecular heterogeneity and plasticity of cancer (Table 2).

6.2. *Nerves improve the efficacy of chemotherapy*

At present, chemotherapy remains the cornerstone of drug treatment for breast cancer. However, chemotherapy is usually associated with numerous side effects, particularly gastrointestinal reactions such as nausea, vomiting, and anorexia. The negative impacts not only diminish the effectiveness of chemotherapy but also influence patient adherence. Importantly, these reactions are regarded as preliminary signs of chemotherapy's adverse effects on the brain-gut axis, suggesting the involvement of the brain-gut axis, the function of the vagus nerve, and the dynamics of neurotransmitters.

Frontline antidepressants have been associated with cancer progression by elevating prolactin levels and inhibiting tamoxifen metabolism. For example, research has indicated that sertraline can improve the effectiveness of docetaxel in managing the growth of breast tumors and reducing hot flashes in cancer survivors who are on tamoxifen, consequently lessening the related depression [198, 199]. Furthermore, Trk inhibitors, including AZD6918 and CEP-701, alongside RNA interference, have been found to increase the sensitivity of xenograft tumors to etoposide, a drug that inhibits topoisomerase II [200]. An analysis of 270 breast cancer clinical samples showed elevated levels of glutamate in 56 % of ER + tumor tissues and 88 % of ER-tumor tissues, indicating that patients with tumors that are high in glutamate might demonstrate an increased susceptibility to cytotoxic chemotherapy [201].

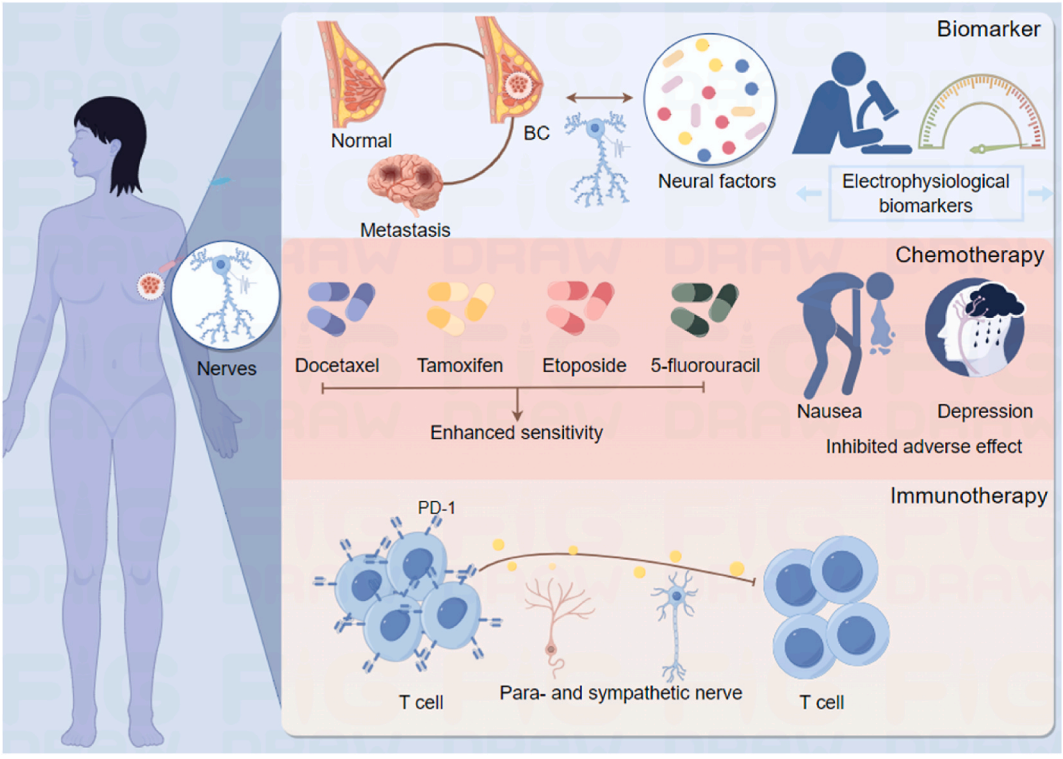

Fig. 5. Potential clinical applications of nerves in breast cancer. Firstly, the development of imaging and electrophysiological biomarkers and neural factors provide further insights into the molecular and structural biomarkers of the interaction between the nervous system and breast cancer. Secondly, the nerves significantly enhance the efficacy of chemotherapy drugs such as docetaxel, 5-fluorouracil, tamoxifen, and etoposide in treating breast cancer, and alleviate adverse effects such as nausea and vomiting caused by chemotherapy. Thirdly, the interaction between the nervous system and immune system in breast cancer points out potential pathways for therapeutic interventions through targeted neuro-immune interactions.

Additionally, it has been shown that combining dopamine or dopamine receptor agonists with anticancer medications, like doxorubicin or 5-fluorouracil (5-FU), can significantly improve the effectiveness of chemotherapy [202]. Clinical trials have demonstrated that psychological interventions can significantly increase dopamine receptor expression in breast cancer patients [203], indirectly providing experimental evidence for the potential use of dopamine receptor agonists in combination with chemotherapy drugs for breast cancer treatment. Moreover, microRNAs and their targets influence the chemoresponse. miR-195 can influence the therapeutic efficacy of epirubicin/cyclophosphamide chemotherapy by targeting SEMA6D [152].

Trastuzumab serves as the primary treatment option for HER2-positive breast cancer [204]. Nevertheless, the emergence of resistance to trastuzumab presents a considerable clinical issue. Research has demonstrated that β2-AR plays a role in mediating trastuzumab resistance via the PI3K/AKT/mTOR signaling pathway [205]. Clinical investigations have revealed that the combination of β-blockers and docetaxel leads to a notable enhancement in progression-free survival among patients with advanced breast cancer that is HER2-negative [206,207]. While certain neurotrophic factors have been found to facilitate breast cancer progression in experimental models involving animals or cell cultures, their effectiveness must be further assessed within the intricate framework of clinical treatment. For example, among several clinical trials investigating the use of β-receptor blockers in combination with chemotherapy for breast cancer, only the combination with docetaxel has been found to significantly improve patients' PFS to date. Further exploration of additional combination therapy strategies could contribute to improving treatment efficacy and patient outcomes (Fig. 5).

6.3. *Nerves improve the efficacy of immunotherapy*

Immunotherapy has recently received approval for a select group of patients diagnosed with advanced TNBC [208]. Investigations conducted prior to clinical trials regarding the neuro-immune axis have revealed numerous mechanisms through which the nervous system influences the functions of both lymphatic and tissue-resident immune cells [209]. In particular, myeloid cells located within the central nervous system (CNS-myeloids) have been observed to facilitate the spread of breast cancer to the brain by reducing the expression of CX3CR1. This reduction subsequently causes an increase in the chemokine ligand CXCL10. Notably, research suggests that neutralizing CXCL10 could potentially lower the rates of breast cancer metastasis to the brain, while excessive CXCL10 expression seems to promote metastasis by attracting VISTA Hi PD-L1+ CNS myeloid cells to areas of metastasis. Additionally, studies have shown that inhibiting both VISTA and PD-L1 signaling can mitigate immunosuppression and reduce the chances of breast cancer brain metastasis [210]. Recent research has pinpointed particular neurotransmitters, including norepinephrine and acetylcholine, which significantly influence the functioning of immune cells during immunotherapy. For instance, norepinephrine has been found to boost the cytotoxic effectiveness of $CD8^+$ T cells and natural killer (NK) cells, thereby enhancing treatment results [56].

The vagus nerve, an essential component of the parasympathetic nervous system, directly contributes to suppressing tumorigenesis in breast cancer via cholinergic mechanisms. Studies indicate that cholinergic activation can lower PD-1 expression on $CD4^+$ and $CD8^+$ lymphocytes, thus impeding the progression of breast cancer [211]. Furthermore, tumor-specific sympathetic denervation has been demonstrated to significantly obstruct tumor growth while decreasing the expression of crucial immune checkpoint proteins, such as PD-1, PD-L1, and FOXP3 [212]. This suggests that stimulating the vagus nerve may boost the anti-tumor immune response, underscoring the groundbreaking prospects of neural regulation techniques like VNS in enhancing the effectiveness of immunotherapy.

Recent findings reveal that a significant portion of the immune checkpoint blockade response takes place outside the tumor microenvironment. As a result, the modulation of neural signaling pathways that affect T cell retention or release can significantly influence both the innate immune response and the immune responses elicited by checkpoint inhibitors [213]. These results emphasize the link between the nervous system and the immune system in the context of breast cancer, proposing promising opportunities for therapeutic interventions through the targeting of neuroimmune interactions. There is optimism for the future in developing more personalized immunotherapy strategies by incorporating neuroimmune methodologies.

Table 3
Clinical trials on the effect of neurotransmitter drugs on breast cancer patients.

Drug	Promoter/Suppressor	Clinicaltrials	Function	Reference
Venlafaxine	Serotonin and Norepinephrine Suppressor	NCT00198250	Reduced symptoms of hot flashes	215
Olanzapine	Dopamine Suppressor	NCT02861859	Improved nausea and vomiting caused by chemotherapy	216
Duloxetine	Serotonin and Norepinephrine Suppressor	NCT01598298	Treatment of early breast cancer aromatase inhibitor related arthralgia	217
Propranolol	Epinephrine and norepinephrine Suppressor	NCT01847001)	Reduced distant breast cancer metastases	218
Dexmedetomidine	Epinephrine and norepinephrine Suppressor	NCT05283408	Improved postoperative recovery quality and decreased the incidence of bradycardia	219
Cabergoline	Dopamine Promoter	Open-label single arm pilot phase II	Inhibited excessive secretion of prolactin and control disease progression	220
Nicotine	Dopamine, serotonin, norepinephrine, acetylcholine, gamma-aminobutyric acid Promoter	NCT02312943	Improved persistent chemotherapy-related cognitive impairment	221

7. Conclusion

In recent years, the burgeoning discipline of cancer neuroscience has achieved notable advancements, illuminating the direct and indirect influences of the nervous system on the initiation, progression, dissemination, and resistance to therapeutic drugs in breast cancer. Investigating the mechanisms underlying neural infiltration and its role in the interconnected network among tumors, immune responses, and endocrine cells can yield important insights for developing targeted treatments. Furthermore, existing evidence suggests that the nervous system may be linked to drug resistance in the treatment of breast cancer [214]. Focusing on nerves could present a novel approach for managing breast cancer characterized by high levels of innervation. Considering the importance of neural regulation in tumor angiogenesis and immunity, strategies aimed at neural targeting could be integrated with antivascular therapies or immunotherapies to enhance the outcomes of cancer treatment.

At present, some clinical trials are currently investigating these possibilities in this regard (Table 3) [215–221]. A randomized controlled crossover trial has demonstrated that venlafaxine can lead to a moderate and acute reduction in hot flashes, with some women reporting significant improvements in fatigue, sleep quality, and overall quality of life; however, the duration of its efficacy on hot flashes varies with dosage [215]. Nausea and vomiting induced by chemotherapy continue to pose significant challenges for patients with breast cancer. A multicenter investigation revealed that incorporating 5 mg of olanzapine daily into conventional antiemetic therapy significantly improves symptom control and health-related quality of life for those at high risk, all while showing no unforeseen toxic effects [216]. Furthermore, duloxetine has proven effective in relieving joint pain linked to aromatase inhibitors in patients with early-stage breast cancer [217]. In modern clinical practice, in addition to standard treatment protocols, stress management techniques like β-blockers, physical activity, and relaxation methods are acknowledged as safe and beneficial supplements for breast cancer patients. A Phase II trial examining the use of propranolol alongside neoadjuvant chemotherapy in newly diagnosed breast cancer patients indicated high adherence rates and a decrease in the spread of cancer to distant sites [218]. Moreover, the combination of dexmedetomidine and esketamine has been found to improve the quality of postoperative recovery and reduce the occurrence of bradycardia in patients with breast cancer undergoing modified radical mastectomy [219]. In a Phase II study, cabergoline, a strong dopamine receptor agonist, was shown to effectively manage long-term disease progression in individuals with metastatic breast cancer while maintaining good tolerability [220]. Furthermore, a pilot study indicated that nicotine may alleviate subjective cognitive impairment post-chemotherapy and enhance cognitive function [221]. This complex treatment interaction and variability in patient response to treatment emphasize the necessity of personalized medical methods. Future research should focus on elucidating biomarkers that predict treatment efficacy and tolerance, as well as exploring novel therapeutic agents targeting potential mechanisms of cancer-related symptoms. The integration of multidisciplinary treatment and continuous innovation in drug therapy are crucial for enhancing the overall treatment model for cancer patients.

Although the latest advances in genetic engineering technology, there are still some unsolved mysteries that need to be further explored. To begin with, the precise functions of various types of nerves, along with their interactions during different phases of cancer progression and treatment, as well as in response to changing stress levels in patients, require deeper exploration in complex neural networks. For example, while there is an increase in nerve density and levels of neurotrophic factors during the initial phases of cancer, the origins of these factors and the triggers that lead to their production are still unclear. The neurotrophic factors such as NGF, BDNF, and TrK receptors have become focal points in current research. Nevertheless, targeting TrK receptors with small molecules has demonstrated some adverse effects by influencing other tyrosine kinases. More targeted research is essential to uncover more precise mechanisms for neural pathway targeting. Additionally, surgical denervation has been found to lessen the incidence and advancement of cancer by 50 % [222]. However, additional studies are necessary to assess the advantages and potential adverse effects associated with surgical denervation. The technology and transformation of surgical denervation are still in the early stages, and interdisciplinary collaboration is required to develop feasible neurobased therapies for clinical practice. Thirdly, the nervous system is quite complex and requires the establishment of more suitable models to simulate the interaction between neurons and tumor cells, but the cultivation of mature neurons is challenging in vitro. Researchers typically study neural effects by gene editing mouse models and transplanting tumors with or without metastatic sites, but the effects are still limited. Finally, it has been proven that relaxation and physical activity are beneficial for the survival of breast cancer patients, but it is necessary to elaborate on the mechanism and specific methods that can achieve the greatest effects when combined with clinical treatment. Therefore, conducting multicenter clinical research and developing standard guidelines as a supplement to clinical treatment will be instrumental in advancing the field and improving outcomes for breast cancer patients.

CRediT authorship contribution statement

Jia-feng Wang: Writing – original draft. **Meng-chuan Wang:** Writing – original draft. **Lei-lei Jiang:** Writing – review & editing. **Neng-ming Lin:** Writing – review & editing.

Ethical approval

Not applicable.

Availability of data and materials

No data and materials are available in the research described in the article.

Funding

This study was funded by Key Laboratory of Clinical Cancer Pharmacology and Toxicology Research of Zhejiang Province (2020E10021), Zhejiang Provincial Program for the Cultivation of High-level Innovative Health Talents (ZWB-2020-18), Zhejiang Medical Key Discipline Foundation (ZWB-2018-02-03), Hangzhou Medical Key Discipline Foundation (HWF-2021-21-16).

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Nengming Lin reports article publishing charges was provided by Hangzhou First People's Hospital. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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