The interplay between breast cancer and the nervous system during the progression of breast cancer and implications for its targeted therapy

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Abstract: Breast cancer ranks as a leading cause of cancer-related deaths in women globally. Current treatments often fall short in eradicating it completely, posing challenges in managing its incidence and mortality rates. The nervous system significantly influences breast cancer initiation, progression, and metastasis. The review highlights how the hypothalamic-pituitary-adrenal axis in the central nervous system and peripheral nerves, such as parasympathetic and sympathetic nerves, can either promote or inhibit cancer development through neurotransmitter release. Understanding these mechanisms offers new therapeutic targets, potentially improving breast cancer diagnosis and treatment strategies.

1. Introduction

Breast cancer is one of the most prevalent types of cancer. It is estimated that approximately 2.26 million cases were recorded in 2020, making it as a prominent cause of cancer-related fatalities among women[1]. According to a survey of Chinese women, breast cancer is increasingly prevalent and its occurrence is rising annually. Early diagnosis and prompt treatment are crucial in lowering the death rate associated with breast cancer. Current approaches for diagnosing and treating breast cancer primarily consist of surgical procedures and subsequent therapies, such as excision, radiotherapy, chemotherapy, endocrine therapy, and other means. However, due to limitations in medical conditions, breast cancer often progresses to advanced stages because of difficulties in early detection, leading to systemic metastasis that is difficult to intervene. Breast cancer recurrence is also a key factor contributing to increased postoperative mortality rates.

Recently, there has been a growing emphasis in cancer research on investigating the involvement of the nervous system in many stages of cancer, including its initiation, development, and metastasis. Emerging data suggests that the central nervous system (CNS) and the peripheral nervous system (PNS) are crucial in regulating tissue growth, organ development, stability, adaptability, renewal, and immune response. The nervous system is also implicated in the development, growth, and progression of cancer simultaneously. Conversely, cancer can also affect and reshape the nervous system, causing abnormal feedback loops that lead to both neurological dysfunction and the development of malignant tumors[2]. These recent insights have sparked interest in the correlation between cancer and the nervous system.

In this review, we explore the relationship between breast cancer and the nervous system, focusing on how CNS and PNS regulate the onset and progression of breast cancer brain metastasis. Additionally, we discuss the impact of breast tumors on the nervous system, highlighting how breast tumors create a conducive environment for their own survival by inducing neural infiltration, promoting axonal growth, and causing neural reprogramming. Furthermore, these tumors also provide opportunities for breast cancer metastasis. Finally, this review summarizes traditional methods for treating breast cancer and explores novel therapeutic approaches, including targeted therapy. It also investigates the impact of psychological factors like depression and anxiety on breast cancer patients, proposing potential treatment strategies.

2. The pathogenesis, progression, and associated cell types of breast cancer

2.1. Classification and subtypes of breast cancer

Breast cancer is a prevalent cancer type originating from either ductal or lobular cells. It constitutes approximately 11.6% of all cancer cases[3]. The incidence of breast cancer exhibits two notable characteristics: a consistent rise in the number of individuals affected each year and a tendency towards detection at a younger age. Consequently, breast cancer is a major issue in terms of public health worldwide.

Molecular subtyping is a method of categorizing breast cancer by analyzing gene mutations and protein expression by genetic and protein-level testing. Classification of cancer cells is determined by the presence of three specific proteins: estrogen receptor (ER),

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progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). ER and PR can be collectively referred to as hormone receptors (HR). Different subtypes of breast cancer are established based on the positive or negative expression of certain combinations. Generally, breast cancer is classified into three categories: hormone receptor-positive breast cancer, HER2-positive breast cancer, and triple-negative breast cancer. Notably, the most frequently occurring type of breast cancer is hormone receptor-positive breast cancer (ER+/PR+; HER2-). This particular category represents the majority, comprising 60% to 70%, of instances of breast cancer and is distinguished by its slow progression. The classification can be further subdivided into two subtypes: Luminal A (ER+/PR+, HER2-) and Luminal B (ER+/PR+, HER2+). Luminal A is primarily treated with endocrine therapy, while Luminal B may require a combination of various adjunctive approaches depending on the particular subtype. Furthermore, HER2-positive breast cancer, which is characterized by being negative for estrogen receptors (ER-) and progesterone receptors (PR-) but positive for HER2, accounts for approximately 20% of all cases. This type of breast cancer exhibits an overexpression of the HER2 protein, indicating a greater level of aggressiveness and a propensity for metastasis. Typically, targeted therapy against HER2 is administered. Last but not least, triple-negative breast cancer (ER-/PR-; HER2-) is the least prevalent subtype, comprising about 10% to 15% of cases. This subtype is the most aggressive, characterized by rapid progression, high metastatic potential, and a lack of identifiable treatment targets in cancer cells. Currently, chemotherapy remains the primary treatment option, but its effectiveness is limited.

2.2. Pathogenesis and progression of breast cancer

Breast cancer can manifest through two potential pathways. Firstly, breast tissue may undergo carcinogenesis through accumulated mutations. Mutation accumulation is a characteristic of all normal cells. The progression of breast cancer is linked to the accumulation of mutations in numerous functional genes within cells, leading to the transition of normal breast tissue into malignant breast cancer[4]. Additionally, breast cancer has the potential to start and persist due to a small subset of cells that resemble stem cells, commonly known as ‘cancer stem cells’ or CSCs. This notion has received increasing support in recent years. Luminal and myoepithelial cells in the breast derive from a single multipotent progenitor cell known as the mammary stem cell. This stem cell has the capacity to maintain organogenesis and self-renewal. When mammary stem cells acquire gene mutations that enhance specific functions, they can develop into cancer stem cells, initiating breast cancer. These cells are known as breast cancer stem cells (BCSCs). Disruption of certain signaling pathways that regulate and maintain the phenotype of BCSCs may lead to the development of breast cancer. The Hedgehog, Notch, and Wnt signaling pathways are vital for maintaining the characteristics, self-renewal, and differentiation of BCSCs[5]. However, dysregulated BCSCs exhibit enhanced self-renewal, differentiation capabilities, and the capacity to initiate tumor growth, leading to uncontrolled proliferation and transformation into breast cancer cells. Among these signaling pathways, the Wnt signaling pathway is highly conserved and predominantly associated with the proliferation and metastasis of breast cancer. It also has significant functions in regulating the immune microenvironment, maintaining stemness, and shaping the phenotypes of breast cancer[6,7]. Research has indicated that sustained activation of β-catenin in the canonical Wnt signaling pathway can transform glandular epithelial progenitor cells, enabling them to acquire tumorigenic capabilities. When Wnt is present, it interacts with the seven-transmembrane Frizzled receptor, leading to the phosphorylation of the co-receptor LRP5/6. This process recruits Dvl protein and Axin, which inhibits β-catenin phosphorylation. Consequently, β-catenin accumulates and translocates into the nucleus, where it binds TCF/LEF transcription factors. This interaction activates the transcription of various Wnt target genes, including *MYC*, *CYCLIN D1*, *TCF1*, *PPARγ*, *AXIN2*, *CD22*, and *COX2*[6,8,9]. Ultimately, the increased activity of the Wnt/β-catenin signaling transduction can enhance the tumorigenic potential of BCSCs[10]. Cancer cells preferentially invade healthy tissues along paths of least resistance, leading to secondary tissue remodeling and disruption. The tissue structures that guide or inhibit invasion vary in structure and molecular composition between organs[11]. The formation of blood vessels around tumors is a critical step in facilitating further growth and metastasis of solid tumors [12,13], which may increase the chances of tumor cells entering the bloodstream. Several possible regulatory mechanisms have been proposed regarding the regulation of angiogenesis around breast cancer. Studies have found that the RNA-binding protein TARBP2 can promote the generation of blood vessels around breast cancer tumors by selectively inhibiting the expression of anti-angiogenic genes, including *THBS1/2, TIMP1, and SERPINF1*[12]. In addition to the role of TARBP2, nestin is highly expressed in breast cancer cells and proliferative tumor blood vessels.

3. The role of neural regulation in the development of breast cancer: interactions between neurotransmitters, neurons, and immune cells

3.1. The key role of neural regulation in shaping the breast cancer microenvironment: a novel perspective on neurological interactions with tumor cells

The tumor microenvironment (TME) significantly influences tumor development, progression, and metastasis owing to its structured composition. Typically, TME comprises extracellular matrix, fibroblasts, adipocytes, immune-inflammatory cells, as well as neural, blood, and lymphatic vascular networks. The nervous system creates a microenvironment conducive to cancer

cell growth and division by releasing specific growth factors and neurotransmitters[14]. During cancer development, the nerve density in tumors is approximately twice as high as in healthy tissues. Importantly, Increased nerve penetration in tumors is associated with malignancy and often corresponds to an unfavorable prognosis. Additional investigation has uncovered the role of the nervous system in angiogenesis associated with tumors[15].

In recent years, researchers have discovered that the CNS, particularly the hypothalamus, has been found to participate in regulating the progression of peripheral cancer cells. Among these mechanisms, the hypothalamic-pituitary-adrenal (HPA) axis serves as a bridge connecting the CNS and the hormonal system, widely acknowledged for its involvement in stress response regulation[16]. Stimulation of the HPA axis may play a role in the onset and advancement of breast cancer. The hypothalamus secretes corticotropin-releasing hormone, which prompts the anterior pituitary gland to release adrenocorticotropic hormone. This, in turn, stimulates the adrenal cortex to produce and release glucocorticoids such as cortisol. Cortisol, upon binding to its cytoplasmic receptor GR, promotes the breakdown metabolism of proteins, fats, and carbohydrates, initiating a series of physiological responses to stress signals. Studies indicate that excessive secretion of cortisol can facilitate the onset of breast cancer. Cortisol activates aromatase, promoting the conversion of adrenaline in stromal cells to estrogens, thereby stimulating the occurrence and proliferation of breast cancer cells[17]. Glucocorticoids also reduce immune reactions by inhibiting the synthesis, release, and promotion of cytokines, thereby fostering the development and metastasis of breast cancer. Excessive secretion of glucocorticoids[18,19] leads to decreased activity of natural killer cells, phagocytic function, and the generation of inflammatory cytokines, including interleukin-2, interferon, and tumor necrosis factor (TNF), by Th1 cells is accompanied by a decrease in the functioning of cytotoxic T cells., thereby inhibiting the occurrence of immune responses[20]. Additionally, certain research suggest that glucocorticoids can promote the settlement of tumor cells dependent on glucocorticoid receptors (GR), thereby promoting breast cancer metastasis. In breast cancer metastasis, GR activity is enhanced, most likely due to increased glucocorticoids during breast cancer progression.

Research has also suggested that the central nervous system may impact the advancement of breast cancer by engaging directly with tumors via neural pathways[21]. Research has revealed a greater prevalence of anxiety disorders in breast cancer patients, linked to heightened activity in the amygdala. The amygdala processes inputs from the cerebral cortex and internal amygdala, modulating anxiety through projections to brainstem nuclei such as the lateral paragigantocellular nucleus (LPGi). Furthermore, the central medial amygdala (CeM) activates corticotropin-releasing hormone (CRH) neurons, which can modulate anxiety levels by regulating physiological and behavioral responses. Sympathetic nerve fibers newly innervate breast tumors and form multiple synaptic interactions with CeM^{CRH} neurons and $LPGi^{CA}$ neurons. Activation of CeM^{CRH} neurons has been shown to elevate the activity of nearby sympathetic nerves within breast tumors, suggesting a direct association between CeMCRH neurons and sympathetic nerve fibers distributed in the stroma of breast tumors., thereby directly activating sympathetic nerve fibers. Moreover, activation of CeM^{CRH} neurons leads to a significant decrease in infiltrating CD45+ leukocytes, CD4+ T cells, and CD8+ T cells, suppressing anti-tumor immunity and promoting the development of breast cancer.

The PNS, consisting of motor, sensory, and autonomic elements, it provides nerve supply to organs and tissues across the entire body. This results in the release of neurotransmitters and trophic signals that control tissue growth, stability, and renewal. The progression of breast cancer is heavily influenced by PNS. Specifically, the sympathetic nervous system promotes breast cancer growth, while the parasympathetic nervous system acts to inhibit it [22]. This highlights the intricate regulatory functions of various neural categories in distinct tumors, along with the influence of the nervous system on the immune microenvironment within tumors.

Overstimulation of the sympathetic nervous system contributes to breast cancer advancement. The sympathetic nervous system innervates primary and secondary immune organs, regulating immune cells and suppressing anti-tumor immunity, thus supporting breast cancer progression. The sympathetic nervous system has the ability to suppress the body's natural immune response by encouraging M2 polarization of tumor-associated macrophages (TAMs) and reducing NK cell activity. Additionally, it can impede dendritic cell (DC) maturation and inhibit the cytotoxic effects of T lymphocytes in order to dampen adaptive immunity. In addition, the sympathetic nervous system's activity has the potential to enhance the number and function of immunosuppressive regulatory T lymphocytes and myeloid-derived suppressor cells. It can also elevate the expression of immune checkpoint proteins such as PD-1, PD-L1, and FOXP3, thereby contributing to the establishment of an immunosuppressive tumor microenvironment (TME)[23].

In addition to regulating immune cells, sympathetic nerve fibers have the ability to release catecholamine neurotransmitters, exerting a direct influence on the α and β receptors present in tumor cells. This, in turn, promoting the survival, growth, infiltration, movement, and spread of breast cancer cells[23].Catecholamine hormones trigger the cAMP-PKA signaling pathway, which enhances tumor angiogenesis and induces the upregulation of vascular endothelial growth factor (VEGF) in breast cancer cells.VEGF has the potential to stimulate the development of lymphatic vessels in and around tumors, hence providing pathways for tumor evasion. Moreover, excessive activity of catecholamines may promote breast cancer metastasis[20]. Particularly, the actions of norepinephrine (NE) and epinephrine (E) can influence the TME, affect tumor cell proliferation, invasion, and metastasis Additionally, these actions can also alter the activity and distribution of immune cells, thereby affecting immune surveillance and suppression of tumors. In the end,

this may lead to the advancement and spread of breast cancer.

In contrast to the sympathetic nervous system, inhibiting the parasympathetic nervous system speeds up breast cancer advancement. Evidence indicates that the parasympathetic nervous system's ability to hinder breast cancer progression may result from its effects on breast cancer cells and aspects of the tumor microenvironment, such as immune cells. Studies have indicated that inhibition of vagal nerve activity reshapes the tumor immune microenvironment of breast cancer. This leads to the recruitment of tumor-associated myeloid cells and an increase in pro-tumorigenic macrophages (CD163, M2 macrophages), while decreasing the infiltration of anti-tumor macrophages (CD11c, M1 macrophages) in the microenvironment. This transition changes the immune microenvironment from being in an activated immune state to being in a suppressive immune state, thereby inhibiting immune system function and promoting tumor development[24-26].

The above content indicates that the nervous system has the ability to directly impact tumor cells, hence influencing their growth, proliferation, and metastasis. Additionally, it can indirectly effect tumor progression by influencing the immune system to regulate anti-tumor immunity.

3.2. The involvement of the nervous system at various stages of breast cancer progression

3.2.1 The regulatory role of the nervous system in the growth process of breast cancer cells

The progression of breast cancer is heavily influenced by peripheral nerves, particularly the autonomic nervous system. Locally, sympathetic nerves release neurotransmitters, including E and NE, which directly act on breast cancer cells via adrenergic receptors (ARs). Overactivation of α2-ARs particularly promotes breast cancer progression. Conversely, the parasympathetic nervous system inhibits breast cancer progression. Studies indicate that parasympathetic nerves release acetylcholine (ACh), which primarily inhibits tumor progression by binding to M1-AChR receptors on breast cancer cells[24]. Additionally, sympathetic, parasympathetic, and sensory nerves modulate breast cancer progression by influencing tumor immunity. The sympathetic nervous system regulates the immune system in multiple ways, promoting breast cancer progression by modulating anti-tumor immunity. Sympathetic nerve activity inhibits innate immunity by polarizing M2 macrophages within tumor-associated macrophages (TAMs), suppressing natural killer (NK) cell activity, impairing dendritic cell (DC) maturation, and restricting cytotoxicity of T cells[23]. Activation of the parasympathetic nervous system contrasts with the sympathetic nervous system by promoting anti-tumor immunity, which inhibits breast cancer progression[23]. Tumor-specific stimulation of parasympathetic nerves has been demonstrated to reduce the expression of immune checkpoint molecules PD-1 and PD-L1 in an immunocompetent breast cancer model. This implies that activating these nerves may suppress breast cancer advancement via the activation of adaptive immunity[24]. Sensory nerves, in addition to autonomic nerves such as sympathetic and parasympathetic nerves, impact breast cancer progression by modulating tumor immunity. Capsaicin-sensitive sensory nerves release substance P, which enhances the cytotoxic effects of lymphokine-activated killer cells and NK cells, thereby boosting anti-tumor immune responses and inhibiting breast cancer progression[27]. Furthermore, research has demonstrated that inactivating sensory nerve fibers and vagal nerves can promote tumor growth and dissemination [28].

In addition to these connections between neurogenic pathways and breast cancer, a range of neuroactive molecules also play pivotal regulatory roles in disease progression. Specifically, neurotrophic factors like nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) play critical roles in multiple facets of breast cancer development, including initiation, proliferation, and anti-apoptotic processes. Research has revealed that NGF induction leads to critical complex formation involving CD44v3 and Tropomyosin kinase A (TrkA), which is pivotal for tumor development and metastasis in breast cancer cells [29]. Furthermore, NGF has also been demonstrated to enhance VEGF expression across various tissues and cells, suggesting its role as a significant stimulatory factor in breast cancer angiogenesis alongside VEGF, facilitating invasive processes[30]. Beyond NGF, BDNF also serves as a critical neurotrophic factor crucial for CNS development. Recent studies have demonstrated that BDNF promotes breast cancer cell growth via tyrosine kinase receptors TrkA, TrkB, and death receptor $p75^{NTR}$[23,31]. Moreover, several microRNAs have been identified to modulate the BDNF/TrkB signaling pathway.

3.2.2 The nervous system's role in regulating brain metastasis mechanisms in breast cancer

Reports suggest that 20-30% of breast cancer patients may experience cancer cell metastasis after initial tumor diagnosis and treatment, with about 90% of cancer-related deaths linked to this progression[32]. Breast cancer demonstrates a propensity for metastasis to multiple organs, including bones, lungs, liver, and brain, reflecting its metastatic heterogeneity[33]. Among these cases, around 15-30% of patients with MBC may experience brain metastasis[34]. Brain metastasis in breast cancer progresses through several stages: initial detachment of tumor cells from the primary tumor, local invasion, migration through the local stroma into blood vessels and lymphatics[33,35]. Epithelial-to-mesenchymal transition (EMT) is a crucial process in initiating metastasis, marked by the loss of epithelial markers, transformation into mesenchymal-like cells, and gaining migratory and invasive abilities[33,35,36]. Neurons can release substances that promote tumor proliferation, migration, and invasion, such as NTN4[37], NTF4[38], and AMPH-1[39]. Upregulation or downregulation of these substances can promote the EMT process in primary tumor cells. NTN4, a secreted protein

in the NTN family of neuronal guidance factors, plays a pivotal role in tumor occurrence, migration, and invasion. Studies indicate that loss of NTN4 function upregulates EMT-associated biomarkers such as vimentin and N-cadherin, boosting breast cancer cell migration and invasion[37]. NTF4, a neurotrophic factor, promotes the EMT process by activating the PRKDC/AKT pathway, enhancing phosphorylation of GSK-3β, stabilizing the negative transcription factor SNAIL, and reducing E-cadherin transcription[38]. Additionally, NTF4 facilitates E-cadherin degradation through the lysosomal pathway. Amphiphysin 1 (AMPH-1), abundant in nerve terminals, inhibits apoptosis and supports cell cycle progression in breast cancer cells. This aberrant EMT pathway activation ultimately drives metastasis[39].

After acquiring invasive capabilities, breast cancer cells undergo a crucial event in brain metastasis, which involves their migration across the blood-brain barrier (BBB)[40]. The BBB, formed by endothelial cells that express specific membrane transport proteins, tightly controls the brain's environment, limiting the passage of most foreign substances[35]. Downregulation or loss of tight junction proteins like claudin-5, ZO-1, and occludin between endothelial cells compromises blood-brain barrier integrity, resulting in leakage[40]. Among these, claudin-5, a major claudin in the BBB, primarily regulates barrier permeability and cell motility. However, certain breast cancer cells with metastatic potential can breach the BBB through specific mechanisms to colonize brain tissue. Molecules like CXCL12 and VEGF participate in disrupting the BBB. Studies have shown that VEGF, by binding to VEGFR2, activates the STAT3 and PI3K pathways, inducing angiogenesis or reducing endothelial integrity, enhancing tumor cell migration through endothelial cells, thereby promoting brain metastasis.

Once breast cancer cells successfully breach the BBB, they initiate the process of metastatic colonization. However, a considerable proportion of cancer cells, upon successful extravasation, are eliminated by the body's anti-tumor immune mechanisms, while a minority enter a dormant state, posing a risk for cancer recurrence in the future. A small subset of cancer cells undergo vascular co-option, promoting micro-metastasis formation by reprogramming their metabolism to better suit the new microenvironment. The period of vascular co-option is considered a critical early stage breast cancer cells to colonize brain tissue after extravasation. Research indicates that an anti-plasminogen activator (PA) serpin originating from cancer cells prevents the destruction of axon pathfinding molecule L1CAM by fibrinolysin, aiding invading cancer cells in finding shared vessels[41]. However, there is limited research on the neural regulation of vascular co-option, and investigations in this area hold promise for providing effective therapeutic targets to block breast cancer metastasis to distant tissues. During the process of breast cancer cell colonization in brain tissue, metastatic breast cancer cells adapt to the neural microenvironment and establish colonies through interactions with neuronal cells. The neural-specific splicing regulator SRRM4 mediates the splicing of REST to REST4, which is crucial for neuron development, maturation, and maintenance. When breast cancer cells encounter the neuronal microenvironment, there is an upregulation and nuclear localization of SRRM4/REST4, accompanied by a decrease in REST. Moreover, breast cancer cells exhibiting elevated SRRM4/REST4 activity show improved colonization of brain tissue due to increased expression of CNS-specific mediators essential for neurotransmission and synaptic response. This indicates that breast cancer cells effectively adapt to the CNS metastasis microenvironment by utilizing neural developmental pathways[42].

4. The mechanism by which the breast cancer microenvironment and immune response affect the nervous system

4.1. Regulation of neural structure and function by the breast cancer microenvironment

Lately, there has been growing focus on how TME regulates processes like neurogenesis, axonogenesis, and neural reprogramming. In breast cancer, tumor cells guide nerves into the TME and induce nerve branching, resulting in significant neural infiltration, a process known as tumor neurogenesis[23,43]. Subsequently, they release factors such as lymphangiogenesis and angiogenesis, stimulating nearby nerve growth and recruiting new nerve axons into the tumor tissue. This phenomenon, termed neoneurogenesis, promotes perineural invasion[15,23,44]. Among these factors, NGF secreted by cancer cells is thought to enhance cancer growth and metastasis by promoting neural cell infiltration into TME[44,45]. Research indicates that NGF secreted by breast cancer cells could potentially aid neural infiltration into tumors and trigger synaptic and axonal development through the generation and secretion of NGF and various other neurotrophic factors[46]. Additionally, VEGF can also promote the growth of neural axons in breast cancer tumors[47]. VEGF can bind to one of its receptors, VEGFR-2, to activate it, thereby upregulating the activity of the VEGF-A/VEGFR2/ARP2/3 pathway, which further activates downstream PI3K/Akt, ERK, and p38 signaling pathways, ultimately inducing axonal growth[47,48]. Interestingly, VEGF and NGF may not act independently, as there may be some interaction between them, collectively participating in the midst of neural infiltration in breast cancer[49]. In summary, substances secreted by breast cancer cells upregulate the expression of markers associated with axonogenesis and neural growth mRNA and trigger the expression of proteins associated with actin and microtubule structures, extending axonal growth cones and promoting neurite growth, ultimately inducing the formation of neuronal synapses, axonal elongation, and the growth of axonal branches[48,50].

4.2. The impact of breast cancer cells on glial cells

Glial cells are a type of non-neuronal cells found in the nervous system. They have multiple functions, including

providing support and protection to neurons, regulating ion and chemical environments, providing energy and nutritional support, and participating in immune and inflammatory responses[51,52]. They constitute the fundamental components of neural tissue along with neuronal cells. Among them, there are two types of glial cells, namely astrocytes and microglia, which interact with invasive cancer cells during the process of brain metastasis in breast cancer[53,54].

Astrocytes play a critical role in various homeostatic and supportive functions, being a type of glial cell closely connected to neurons and blood vessels[51]. In the normal adult brain, astrocytes lack proliferative capacity; however, under pathological conditions, they may become activated and undergo morphological and molecular changes, becoming reactive astrocytes, leading to the formation of glial scars or gliosis[54,55]. Brain metastasis of breast cancer triggers the local activation of astrocytes into reactive forms, which in turn enhance breast cancer cell migration to and colonization within brain tissue[54]. Shumakovich *et al.* demonstrated bidirectional crosstalk between breast cancer cells and astrocytes by co-culturing them, showing that breast cancer cells can induce alterations in astrocytic behavior[56]. Protocadherin 7 expressed by breast cancer cells promotes the formation of gap junctions with astrocytes, facilitated by connexin 43, allowing breast cancer cells to transfer the second messenger cGAMP to astrocytes. This interaction activates the STING pathway, leading to the production of interferon-α (IFNα), TNF, and other inflammatory cytokines. These cytokines act as paracrine signals that subsequently activate the STAT1 and NF-κB pathways in brain metastatic cancer cells, promoting breast cancer growth and resistance to chemotherapy[57]. Mészáros *et al.* also demonstrated that soluble factors released by TNBC cells undergoing brain metastasis induce the secretion of NLRP3 inflammasome-dependent IL-1β in surrounding astrocytes, thereby promoting TNBC cell proliferation within the brain[58]. Additionally, breast cancer cell-secreted extracellular vesicles (EVs) can be engulfed by astrocytes, thereby modulating astrocytic behavior.

Microglia are brain parenchymal macrophages crucial to brain metastasis, involved in immune responses and CNS homeostasis maintenance[59]. Microglia, like astrocytes, typically remain in a resting state but can transform into two distinct phenotypes upon activation: the M1 phenotype, which demonstrates anti-tumor properties, and the M2 phenotype, which promotes tumor growth. Specifically, M2 microglia have been shown to facilitate breast cancer cell invasion and colonization in brain tissue by creating a tumor-immune suppressive environment[54,59]. Certain tumor-derived soluble factors can polarize microglia into tumor-supportive and immune-suppressive cells, thereby facilitating tumor persistence and progression. The loss of XIST in breast cancer cells boosts the secretion of exosomal miRNA-503, leading to the polarization of microglia from the M1 to the M2 phenotype. This shift upregulates immune suppressive factors in microglia and suppresses T cell proliferation[60].

5. Neural regulation and breast cancer therapy: mechanistic insights and future prospects

While there has been notable advancement in cancer research and treatment in the last thirty years, resulting in a reduction of over 40% in breast cancer mortality rates in many high-income nations, 685,000 women still lost their lives to this illness in 2020. Predictions indicate that by 2040, the global occurrence of breast cancer will increase from 2.3 million cases in 2020 to surpassing 3 million cases, with fatalities reaching 1 million[61].

As a diverse illness, breast cancer exhibits considerable differences in treatment approaches due to its various molecular subtypes. The most prevalent subtype is hormone receptor-positive breast cancer, which constitutes around 70% of all cases of this disease. The growth, survival, and progression of these tumors rely on the expression of HR, mainly the ER, and its ligand estrogen. The predominant treatment approach for this subtype involves endocrine therapy, typically lasting 5 to 10 years. Endocrine therapy utilizes pharmaceutical agents to lower estrogen levels in the body, thereby inhibiting the growth of tumor cells. Medications used for endocrine therapy in breast cancer patients can be categorized based on how they work. These groups consist of drugs known as selective estrogen receptor downregulators, aromatase inhibitors, and gonadotropin-releasing hormone analogs, and progestins. There are a total of 44 hormonal agents in these categories. Furthermore, 12 specific therapies are employed in conjunction with endocrine therapy, such as CDK4/6 inhibitors, mTOR inhibitors, and histone deacetylase (HDAC) inhibitors. This type of breast cancer has a high cure rate and favorable prognosis.

HER2-positive breast cancer makes up around 20% to 25% of all cases of breast cancer. This particular type is known for its heightened malignancy, rapid advancement, increased likelihood of recurrence and spread to other parts of the body, as well as a less favorable prognosis. Nevertheless, due to the emergence and progression of therapies targeting HER2, the survival rates for individuals with HER2-positive breast cancer have notably improved. These treatments can be categorized into three main groups: monoclonal antibodies, small molecule tyrosine kinase inhibitors, and antibody-drug conjugates. The process of anti-HER2 targeted therapy encompasses neoadjuvant therapy, adjuvant therapy, and salvage therapy for advanced stages. Comprehensive systemic treatment, various treatment options, such as surgical procedures, chemotherapy, targeted therapy, endocrine therapy, and radiotherapy, provide the opportunity for achieving a cure in patients with HER2-positive breast cancer.

TNBC is considered to be among the most difficult subtypes of breast cancer, known for its tendency for early recurrence and metastasis, as well as rapid progression of the disease, lack of effective therapeutic targets, and significant tumor heterogeneity. Currently, chemotherapy continues to be the primary systemic treatment for this particular subtype. With the advancement of precision medicine and the emergence of new technologies, cancer

immunotherapy has shown promising efficacy by enhancing the immune system's anticancer response. Therapies involving immune checkpoint inhibitors, such as PD-1 and PD-L1 monoclonal antibodies, have exhibited effective management of recurrent and metastatic triple-negative breast cancer. Additionally, two PARP inhibitors can treat HER2-negative MBC patients carrying BRCA1/2 gene mutations[62]. However, the molecular nature and treatment strategies of triple-negative breast cancer still require further investigation to improve the current outcomes of cancer therapy.

Currently, targeted neurotherapy is becoming a research hotspot in breast cancer treatment. Targeted neurotherapy aims to influence tumor growth, metastasis, and treatment response by intervening in the nervous system. This therapeutic approach may include drugs or other interventions targeting neurons, neurotransmitters, or neurotransmitter receptors surrounding the tumor. Its purpose is to modulate the activity of the nervous system, affecting the TME, immune responses, and tumor cells themselves, thereby enhancing treatment efficacy or reducing treatment-related side effects. Current therapeutic strategies include the development of drugs capable of blocking NGF and its receptors. For instance, it has been found that NGF released by breast cancer cells is a driving factor in tumor neurogenesis[63], further stimulating cancer cell growth and metastasis[64]. Moreover, NGF can bind to the neurotrophic tyrosine kinase receptor A (TrkA) on nociceptive sensory neuron surfaces, activating cytoplasmic ERK, PLC/PKC, and other signaling pathways, lowering neuronal action potential thresholds, increasing neuronal excitability, and thus sensitizing pain[65]. Therefore, selective inhibition of NGF may help suppress breast cancer growth and metastasis while blocking pain signals originating from the breast from entering the spinal cord and brain. Anti-NGF monoclonal antibodies are thus considered promising next-generation analgesics in the pain field, offering superior features such as long-lasting safety, non-addictiveness, and non-resistance. Utilizing nerve blockade techniques or surgical methods to sever physical connections between tumors and the nervous system is another approach. For instance, bupivacaine nanoparticles can aggregate around cancerous tissue's nerve cells, locally anesthetizing nerves and interrupting communication between nerve cells and cancer cells. Targeting neurons in the TME with bupivacaine nanoparticles can inhibit nerve sprouting and cancer cell signaling, thereby suppressing tumor growth and metastasis[66]. Additionally, repurposing existing neuropharmacological agents is a viable strategy. For example, β-adrenergic receptor blockers can be used to treat TNBC[67]. Beta-adrenergic receptor blockers inhibit sympathetic nervous system neurotransmitter signaling through beta-adrenergic receptors (β-AR), thereby improving the effectiveness of anthracycline chemotherapy in reducing TNBC tumor metastasis and recurrence[68].

Apart from the tumor itself, which poses a threat to the patient's health, anti-tumor treatments and tumor-related complications may also adversely affect the prognosis. With the transition from the conventional medical model to the bio-psycho-social medical approach, psychological elements have increasingly gained significance in understanding the causes and outcomes of breast cancer. Extended psychological stress is acknowledged as a potential factor contributing to the progression of breast cancer[20,69,70]. At the same time, as a physical and mental illness, breast cancer can bring negative emotions such as panic, anxiety, and depression to patients, and the physical changes caused by treatment can exacerbate these negative emotions[71]. Research has indicated that feelings of depression frequently arise as a complication for individuals diagnosed with breast cancer.[72]. Suppression of the immune response by depression may contribute to the onset and progression of breast cancer[18] and promoting excessive secretion of estrogen[73]. It can also reduce patients' enthusiasm, self-management level, and control over their own behavior, leading to a decrease in patients' self-management ability to follow the treatment plan, a decrease in compliance with medical care, The progress of treatment can be affected, ultimately resulting in a negative prognosis and higher mortality rates for breast cancer. Patients who experience depression before or after being diagnosed with cancer have a reduced chance of survival. In comparison to patients without depression, those with depression face a significantly elevated risk of mortality. Therefore, early detection and continuous treatment of depression are key to improving patient survival[74]. The above conclusions provide a theoretical basis for psychotherapy as an adjunct to tumor immunotherapy, indicating that psychotherapy is expected to become a potential adjunct to tumor treatment. Hence, the identification of depression in breast cancer patients and the provision of suitable behavioral and pharmaceutical interventions, as well as timely psychological interventions, play a vital role in the care of individuals with breast cancer. This suggests that clinical doctors need to use a variety of methods to provide psychological interventions to patients in addition to using chemotherapy, endocrine therapy, and other methods to treat breast cancer, to enhance the efficacy of breast cancer treatment and enhance patients' quality of life more effectively.

6. Conclusion and Prospect

Recent advancements in neuroscience research have enhanced our understanding of how the nervous system influences the onset and progression of breast cancer. However, the field of cancer neuroscience is still in its infancy, with limited exploration of the complex mechanisms underlying the interaction between the nervous system and breast cancer. This article provides a concise overview of the regulatory mechanisms through which the nervous system impacts the microenvironment of breast cancer. It also explores the effects of breast cancer cells on neuronal production, structure, and function.

A thorough comprehension of the interaction between the neurological system and breast cancer is essential to understand the development and spread of the disease, as

well as to devise effective therapeutic strategies. This article outlines various treatment approaches for different molecular subtypes of breast cancer and proposes that neurotherapy may hold a key role in breast cancer management. To further our understanding of breast cancer and other malignancies, it is imperative to increase research funding in cancer neuroscience. This will aid in the development of more effective, less recurrent, and less harmful treatment options.

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