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Monoamine neurotransmitters in breast cancer: Progression, immunomodulation, and therapeutic strategies

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Abstract

Monoamine neurotransmitters, including serotonin, dopamine, histamine, and adrenaline/noradrenaline (Epinephrine/Norepinephrine), are key neuromodulators in the nervous system that influence complex behavioral and cognitive functions. They also affect peripheral tissues and inflammation, playing a crucial role in the biology of various malignancies, including breast cancer, the most common cancer among women worldwide. These neurotransmitters are essential for mammary gland development and are linked to depression, a major breast cancer risk factor. Elevated levels of circulating proinflammatory cytokines in depression may mediate neuroendocrine, neural, and immune pathways, affecting the metabolism of monoamine neurotransmitters. In the tumor microenvironment, serotonin and norepinephrine generally exhibit pro-tumorigenic effects, while dopamine has shown promising anti-tumor activity by enhancing immune responses. Histamine also shows potential in anti-tumor immunity, although its effects on breast cancer progression remain inconclusive. Research into the relationship between these neurotransmitters and breast cancer cell growth highlights their significant role in breast cancer biology and their potential in improving treatment outcomes. This review explores the role of monoamine neurotransmitters in breast cancer progression, their immunomodulatory functions, and the therapeutic potential of targeting these neurotransmitters. By analyzing these complex relationships, we aim to illuminate novel therapeutic strategies that could enhance the clinical management of breast cancer.

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Highlights

What is current knowledge?

- Monoamine neurotransmitters modulate behavior and cognition in the nervous system.
- Monoamine neurotransmitters are linked to mammary gland development and depression, a breast cancer risk factor.
- Monoamine neurotransmitters influence immune responses and cancer progression in tumors.

What is new here?

- This article details how monoamine neurotransmitters affect breast cancer progression.
- The role of monoamine neurotransmitters as immunomodulators linking neurological and cancer pathways is explored.
- The potential of targeting these neurotransmitters to improve treatment outcomes is highlighted.

Introduction

Monoamine neurotransmitters, such as serotonin, dopamine, histamine, and adrenaline/noradrenaline (Epinephrine/Norepinephrine), function as neuromodulators in the nervous system, affecting complex behaviors, cognitive processes like learning and memory, and essential homeostatic functions such as sleep and feeding. In addition to their neural roles, these neurotransmitters significantly impact peripheral tissues, influencing inflammation, the tumor microenvironment, and other pathways that contribute to the initiation and progression of various cancers (1-5).

Breast cancer (BC) is the most prevalent cancer and has the highest mortality rate among women worldwide (6). Despite advancements in early detection and treatment, breast cancer remains a significant threat to society and public health providers due to its potential for metastasis and the complexity of its molecular characteristics (7). Monoamine neurotransmitters significantly influence breast cancer biology (Table 1 and Figure 1). These neurotransmitters are crucial for mammary gland development (8). Additionally, they are implicated in the development of depression, a significant risk factor for breast cancer progression. Patients with breast cancer also face a heightened risk of depression, which accelerates cancer progression by affecting the metabolism of monoamine neurotransmitters in the brain and amino acids in the blood. Changes in gut microbiota may impact neurotransmitter synthesis. Furthermore, the inflammatory environment associated with depression can lead to immune dysfunction, further promoting tumor growth (9).

Exploring the connection between these neurotransmitters and breast cancer cell growth has revealed their crucial role in breast cancer biology and their potential significance in enhancing breast cancer treatment (Table 2) (5,10).This review discusses the influence of monoamine neurotransmitters on breast cancer progression, their role as immunomodulators, and the therapeutic potential of various drug classes that modulate these neurotransmitters, including monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), antihistamines, beta-blockers, and phenothiazines.

Role of monoamine neurotransmitters in breast cancer

Serotonin

Serotonin (5-HT) is recognized as a growth factor in various cancers, including breast cancer. Research predominantly indicates that serotonin promotes growth, angiogenesis, and metastasis in breast cancer (11-16). Serotonin's autocrine and paracrine functions are essential for maintaining homeostasis in mammary gland development and cancer progression (17). However, the role of serotonin in breast cancer is complex and concentration-dependent. At low levels, serotonin can act as a tumor suppressor in non-transformed cells and early-stage cancers by inhibiting growth and reducing blood supply through decreased THP-1 expression. As the tumor progresses, genetic and epigenetic changes in serotonin signaling lead to resistance to its suppressive effects. This transition allows for increased serotonin production and altered receptor expression, promoting breast cancer progression. Consequently, while low doses of serotonin inhibit tumor growth, elevated levels and modified 5-HT receptor signaling can contribute to malignant transformation. Overall, this model illustrates the shift in serotonin's role from protective in early stages to potentially tumor-promoting in advanced disease (13,14,17).

Serotonin promotes angiogenesis in multiple ways: it stimulates the proliferation, invasion, and migration of endothelial cells and regulates macrophage-mediated angiogenesis. Additionally, it influences blood vessel formation (18,19). Moreover, serotonin disrupts the interaction between osteoblasts and osteoclasts in breast cancer cells, suggesting that high levels of gut-derived serotonin may boost breast cancer bone metastasis (20).

Epinephrine and norepinephrine

Stress-related activation of adrenergic receptors plays a significant role in cancer progression (21). Psychological and pharmacological inhibition of excessive adrenergic and inflammatory stress signaling can be beneficial in cancer treatment (22). Breast cancer tissues exhibit an overexpression of β-adrenergic receptors (23), with β2-adrenoceptor (β2AR) activation facilitating tumor proliferation and angiogenesis through the upregulation of vascular endothelial growth factor, metalloproteinase-2, and metalloproteinase-9. This molecular pathway significantly promotes the angiogenic and metastatic progression of breast cancer (24).

Additionally, β2AR signaling contributes to tumorigenesis by inducing DNA damage and inhibiting p53-mediated apoptotic pathways (25). In cases of metastatic breast cancer, the skeleton is a common site of metastasis. Activation of β2AR in osteoblasts has been shown to enhance bone vascular density, creating a more favorable microenvironment for the colonization and growth of cancer

cells (26-28). These findings underscore the critical role of epinephrine and norepinephrine signaling in breast cancer progression and metastasis.

Dopamine

Dopamine plays an important role in lactation and mammary gland development, with its receptors expressed in mammary epithelial cells. The dopaminergic system has a multifaceted role in the development and progression of breast cancer, influencing various aspects such as cell proliferation, apoptosis, migration, invasion, and angiogenesis (29-34). Factors such as tumor type, receptor expression, and dosage affect dopamine's impact on cancer growth. In breast cancer research, dopamine has demonstrated a significant reduction in angiogenesis, showcasing an inhibitory effect on tumor growth. While it did not reduce the proliferation and invasion of breast and colon cancer cells, the activation of some dopamine signaling pathways induces growth arrest in vitro, resulting in tumor shrinkage and diminished bone metastasis (35,36).

Dopamine signaling interacts with pathways such as estrogen and human epidermal growth factor receptor 2 (HER2), influencing tumor growth and progression (37). Overall, the link between the dopaminergic system and breast cancer underscores the complexity of tumor biology and highlights the potential of targeting dopaminergic pathways for novel therapeutic strategies in breast cancer treatment (38-41).

Histamine

Studies have presented conflicting evidence on how histamine affects breast cancer. On one hand, histamine has been shown to promote tumor cell proliferation and metastasis in various human cell lines, including breast cancer, lymphoma, ovarian cancer, colorectal cancer, and melanoma (42). This proliferative effect is further supported by studies demonstrating increased proliferation of mammary tumor cells in female rats treated with histamine (43), as well as in breast cancer cell lines (44,45).

Conversely, other studies highlight histamine's potential anti-tumor effects. In nude mice, histamine administration significantly reduced tumor cell proliferation, increased tumor apoptosis, and improved median survival (46). Additionally, the treatment of tumor-bearing mice with histamine resulted in reduced tumor growth, increased apoptosis, and a higher presence of tumor-infiltrating lymphocytes (47). These findings suggest that while histamine can enhance tumor proliferation in certain contexts, it may also inhibit proliferation and promote apoptosis in others, indicating a complex and context-dependent role in breast cancer progression.

Role of monoamine neurotransmitters as immunomodulators in breast cancer

Inflammation is an important factor in the pathophysiology of both depression and cancer. Cancer patients have a higher rate of depression within the first five years of diagnosis, and chronic depression is linked to increased cancer risk and reduced survival. Elevated levels of circulating proinflammatory cytokines in depression may mediate neuroendocrine, neural, and immune pathways, influencing monoamine neurotransmitter metabolism. Inflammation is a significant cancer risk factor, with 20% of cancers caused by chronic inflammation; however, an anti-inflammatory microenvironment also promotes tumor immune evasion (48-51).

Monoamine neurotransmitters impact immune response modulation and breast cancer in complex ways. Histamine and dopamine generally boost immune responses, potentially enhancing anti-tumor immunity, while serotonin and stress-related adrenaline/noradrenaline can both promote and inhibit immune functions, often contributing to a pro-tumorigenic effect. These interactions highlight the complex roles of monoamine neurotransmitters in modulating immune responses and cancer progression.

Among the inflammatory mediators, histamine can also be produced by tumor cells (e.g., breast tumor cells) and can induce chronic inflammation and the growth of certain tumors by recruiting inflammatory cells. Histamine influences tumor pathophysiology, treatment efficacy, and patient survival (42,47,52-54). Similarly, epinephrine and norepinephrine, triggered by stress, can lead to the release of pro-inflammatory complexes from neutrophils, which can activate dormant cancer cells (55).

In contrast to epinephrine and norepinephrine, histamine has been shown to promote anti-tumor immunity, increasing T CD4+ and natural killer (NK) cell infiltration in the tumor microenvironment (56). Additionally, histamine inhibits regulatory T cell (Treg) function (57). These cells typically suppress cytotoxic T cell activity, thereby promoting tumor development (58). Furthermore, histamine enhances B-cell-related immune responses and anti-tumor immunity (59).

Similar to histamine, dopamine generally exerts a stimulatory effect on immune cells. It stimulates cytotoxic T cells and down-regulates Treg function, contributing to an antitumor action (60-62). Dopamine also enhances macrophage activity (63), shifting tumor-associated macrophages (TAMs) from the M2 to the M1 phenotype (64), and inhibits myeloid-derived suppressor cells, thereby boosting anti-tumor immunity (65). Activation of D1-like receptors increases NK cell cytotoxicity (66), further supporting dopamine's antitumor role. Conversely, more recent studies have also demonstrated an inhibitory effect of dopamine on immune cells; one study showed that activation of D2-like receptors suppresses NK cell function (66). Additionally, inhibition of dopamine receptor D3 signaling in dendritic cells enhances antigen cross-presentation to CD8+ T-cells, favoring anti-tumor immunity (67).

Earlier studies reported that serotonin promotes NK cells and T cell anti-tumor activity (68-70). However, the effect of serotonin on immune cells is significantly influenced by factors such as the specific cell type and the subtype of the 5-HT receptor involved. Consequently, it is challenging to definitively categorize serotonin as having a purely pro- or anti-tumorigenic role (71). Most studies indicate that serotonin influences immune signaling, promotes the growth of breast cancer cells (5), and may contribute to a pro-tumorigenic effect by facilitating tumor immune evasion through the creation of an anti-inflammatory microenvironment (11).

More recent research has demonstrated that signaling through serotonin receptors facilitates the differentiation of anti-inflammatory M2 macrophages, which subsequently contribute to tumor progression. Serotonin also has an inhibitory effect on cytokine secretion, including TNF-α and IL-12, by monocyte-derived M2 macrophages (19,72). Additionally, serotonin signaling plays a role in the differentiation of anti-inflammatory dendritic cells (DCs), potentially influencing T cell polarization toward a regulatory phenotype (73). Serotonin influences cytokine secretion by DCs, increasing the release of IL-1β and IL-8 while decreasing the secretion of IL-12 and TNF-α from DCs (74). These findings underscore the complex regulatory role of serotonin in the tumor microenvironment.

Therapeutic potential of modulating monoamine neurotransmitter pathways

MAOI

Monoamine oxidase enzymes moderate levels of monoamine neurotransmitters in the central nervous system and peripheral organs. Monoamine oxidase A (MAO-A) is involved in the degradation of serotonin, dopamine, epinephrine, and norepinephrine, while monoamine oxidase B is involved in the degradation of histamine (75,76). The expression level of intratumoral MAO-A is negatively correlated with patient survival in multiple breast cancer cohorts (77). Disruption in neuroendocrine-immune interactions in female rats with mammary tumors can be reversed by deprenyl, a monoamine oxidase inhibitor, which enhances catecholaminergic activity and readjusts immunological responses (78).

MAO-A expression was significantly downregulated in clinical hepatocellular carcinoma samples, correlating with cancer vasoinvasion, metastasis, and poor prognosis, suggesting that increasing MAO-A expression or activity may be a novel treatment approach for hepatocellular carcinoma (79). Treatment with MAOIs such as phenelzine, clorgyline, moclobemide, and pirlindole inhibited tumor progression in preclinical models by reprogramming TAMs and suppressing tumor growth. Additionally, combining MAOI and anti-PD-1 treatments resulted in synergistic tumor suppression (80). These results highlight the potential of MAOIs as a promising therapeutic strategy in cancer treatment.

Selective Serotonin Reuptake Inhibitors (SSRIs)

SSRIs are commonly used medications for treating a range of conditions, such as depression and anxiety. Studies on cells and mouse models have shown that SSRIs, particularly sertraline, can reduce breast tumor-initiating cell activity and tumor growth and enhance tumor cell death when combined with drugs used in chemotherapy such as docetaxel (81-83). However, population-based cohort studies have indicated that SSRI use is associated with an increased breast cancer mortality risk. One study of 23,669 patients revealed a 27% increase in mortality risk with SSRI use, and a 54% rise in mortality for those using SSRIs for three years or longer (84). Another analysis of 7,000 patients found that SSRI use before or after a breast cancer diagnosis was linked to a significantly higher mortality rate (85).

Antihistamines

Antihistamines, functioning as histamine receptor antagonists, play a significant role in modulating the effects of histamine in tumor cells, thereby influencing breast cancer treatment outcomes. While some studies suggest that antihistamines may increase tumor cell numbers, potentially leading to negative outcomes for breast cancer patients (44), several research findings support their beneficial effects, demonstrating that antihistamines can enhance treatment efficacy and improve the survival rates of breast cancer patients (53,86). Additionally, antihistamines have been found to induce autophagy and apoptosis (87), inhibit cell proliferation, activate the mitochondrial apoptosis pathway, and reduce tumor growth in breast cancer cells (88). Furthermore, they have been shown to decrease the proliferation rate of various breast cancer cell lines (89).

Beta-blockers

The literature on the effects of beta-blockers in breast cancer has yielded a diverse range of results. A meta-analysis of six studies, encompassing over 18,000 breast cancer patients, found no benefit of beta-blockers on overall survival, cancer-specific survival, or recurrence (90). Similarly, another more recent meta-analysis of 17 studies reported no significant association between beta-blocker use and breast cancer recurrence (91).

Some studies suggest potential benefits of beta-blockers for breast cancer in certain subgroups. A systematic review and meta-analysis indicated that beta-blocker use was associated with longer recurrence-free survival in patients with early-stage breast cancer, with a more pronounced effect observed in those with triple-negative disease (92). Conversely, a study found that existing beta-blocker use at the time of anti-HER2 therapy was associated with worse overall survival among patients with advanced HER2-positive breast cancer (93). Additionally, a

meta-analysis of nearly 15,000 breast cancer patients in New Zealand revealed a short-term increased risk of death among patients who took beta-blockers post-diagnosis, but a protective effect with long-term use (94).

Phenothiazines

Phenothiazines, a class of anti-psychotic medications that antagonize dopamine receptors, have been shown to reduce invasion and proliferation while increasing apoptosis of triple-negative breast cancer cells (95). Additionally, administering phenothiazines to mice with triple-negative breast cancer xenografts resulted in reduced tumor growth and metastasis (96). In vitro experiments have shown that trifluoperazine, a phenothiazine used to treat disorders such as depression and anxiety, induces cell cycle arrest and apoptosis in various cancer cell lines, including triple-negative breast cancer. It also suppressed the growth of subcutaneous xenograft tumors and brain metastases without causing detectable side effects, leading to prolonged survival in mice with brain metastases (97).

Table 1. Role of monoamine neurotransmitters in breast cancer progression and cancer immunity

Monoamine neurotransmitter	Role in breast cancer progression	Role as immunomodulator in breast cancer
Serotonin	• Facilitating tumor proliferation, promoting metastasis and angiogenesis (11-16). • Suppressing tumor growth in non-transformed cells and early-stage cancers (13,14,17).	• Promoting NK cells and T cell anti-tumor activity (68-70). • Facilitating tumor immune evasion (11), facilitating the differentiation of anti-inflammatory M2 macrophages (19,72). • Promoting differentiation of anti-inflammatory DCs, influencing T cell polarization toward a regulatory phenotype (73).
Epinephrine and norepinephrine	Facilitating tumor proliferation, promoting metastasis and angiogenesis (24,26-28)	Facilitating release of pro-inflammatory complexes from neutrophils, which can activate dormant cancer cells (55).
Dopamine	No effect on proliferation; reduced angiogenesis and metastasis (35,36).	• Stimulating cytotoxic T cells and down-regulating Treg function (60-62). • Shifting TAMs from the M2 to the M1 phenotype (64), and inhibiting myeloid-derived suppressor cells (65). • Increasing NK cell cytotoxicity (66).
Histamine	• Promoting tumor cell proliferation and metastasis (42,43,45). • Reducing tumor growth (46,47)	• Promoting anti-tumor immunity, increasing T CD4+ and NK cell infiltration in the tumor microenvironment (56). • Inhibiting Treg function (57). • Enhancing B-cell-related immune responses and anti-tumor immunity (59).

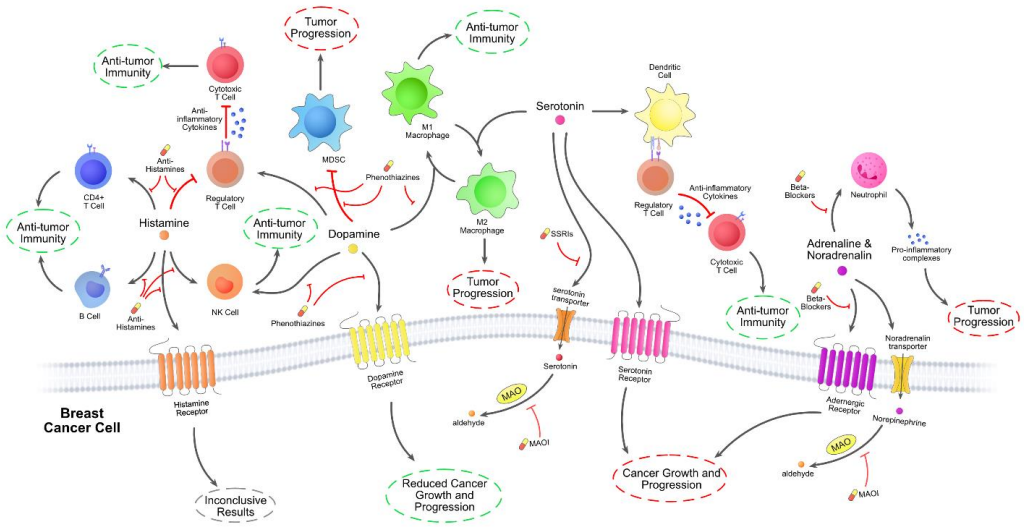

Figure.1: Role of monoamine neurotransmitters in breast cancer growth, progression and cancer immunity

Table 2. Treatment outcomes of monoamine neurotransmitter modulating drug classes

Monoamine neurotransmitter modulating drug class	Treatment outcomes
MAOI	Inhibited tumor progression in preclinical models by reprogramming TAMs in mouse and human (80).
SSRIs	Increased breast cancer mortality (84,85).
Antihistamines	Improved the survival rates of breast cancer patients (53,86).
Beta-blockers	• No benefit on overall survival (90,91). • Potential benefits for triple-negative breast cancer (92). • Worse overall survival among patients with advanced HER2-positive breast cancer (93). • Short-term increased risk of death among patients who took beta-blockers post-diagnosis, but a protective effect with long-term use (94).
Phenothiazines	• Reduced tumor growth and metastasis (96). • Prolonged survival in mice with brain metastases (97).

Conclusion

The complex role of monoamine neurotransmitters in breast cancer progression, angiogenesis, and metastasis is influenced by various factors, leading to varied outcomes. Serotonin, epinephrine, and norepinephrine generally exhibit pro-tumorigenic effects by modulating tumor cells, the tumor microenvironment, and immune cells. Conversely, dopamine has shown promising anti-tumorigenic activity, enhancing immune responses and potentially boosting anti-tumor immunity. Although histamine also shows potential in enhancing anti-tumor immunity, its effects on breast cancer progression remain inconclusive due to conflicting evidence.

The impact of drugs that modulate monoamine neurotransmitters on breast cancer progression is equally complex. Beta-blockers have produced mixed results, with their effects on cancer progression remaining controversial. SSRIs, such as sertraline, have been associated with a significantly higher mortality rate in population-based cohort studies, requiring careful consideration for breast cancer patients who may also suffer from depression, as this malignancy considerably elevates their risk of developing depression. In contrast, MAOIs, antihistamines, and phenothiazines have demonstrated promising inhibitory effects on tumor progression. These findings underscore the complex role of these drugs in breast cancer treatment, highlighting their therapeutic significance.

These insights not only call for further research but also open exciting avenues for improved breast cancer treatments. The multifaceted impact of these drugs in managing cancer and comorbid conditions underscores the need for careful prescription to optimize patient outcomes.

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Ethical statement

This narrative review did not involve any new studies of human or animal subjects performed by any authors.

Conflicts of interest

The authors declare no conflict of interest.

Author contributions

Idea and conceptualization, Homa Davoodi. All authors have read and agreed to the published version of the manuscript.

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