Brain Metastases and Their Effect on Neuronal Signaling in Breast Cancer Patients

ABSTRACT

Background
Brain metastases are associated with increased aggressiveness of cancer. They significantly impair quality of life and lead to a poorer prognosis for patients.

Objective
This paper looks into how brain metastases in breast cancer patients affect neuronal signaling, specifically focusing on how neuronal pathways and signaling promote the growth of brain metastases.

Methods
PubMed was searched with terms like breast neoplasms, brain neoplasms, synaptic transmission, signal transduction, neurons, brain metastasis, signaling, and breast cancer. 5 studies were included in this review.

Results
The studies included in this review show that there are many factors that promote the growth of brain metastases in breast cancer patients, including NMDARs and TNC. The inhibition or impairment of some of these factors may be beneficial for therapeutic relief in patients.

Conclusion
The studies emphasize the impact of brain metastases on neuronal signaling, highlighting the need for continued research in order to develop more advanced treatments for patients.

INTRODUCTION

Breast cancer is the most common type of cancer diagnosed in women, and it has high potential to progress to advanced stages [1]. Breast cancer commonly forms beginning in the ductal epithelium, which lines the milk ducts, or in the breast lobes, where milk is produced [1]. Early detection plays a large role in improving patient outcomes, and breast cancer is commonly diagnosed through examination, imaging, and biopsy [1]. The most common symptoms of breast cancer include breast masses or abnormal amounts of nipple discharge [1]. Despite advancements in treatments, around 90% of patients eventually die from some form of distant metastasis [2].

Brain metastases significantly impair the prognosis for breast cancer patients [2]. Effectively treating brain metastases is incredibly difficult as the blood-brain-barrier's protective functions serve as an obstacle, restricting the penetration of many therapeutic agents [2]. Brain metastases occur in about 15-25% of patients battling stage IV breast cancer, making them a fairly common progression of breast cancer [3]. The conventional methods for treating cancer, such as surgery and chemotherapy, have proven to be unsuccessful for patients experiencing brain metastases largely due to the adaptability of the spreading tumor [3,4]. Brain metastases in breast cancer are challenging to treat as tumor cells uniquely adapt to the surrounding microenvironment in ways that enhance their growth potential [4]. Tumor and neuron signaling, together, are implicated in the progression of breast cancer brain metastases, [5]. Neuronal pathways play a role in the development of brain metastases in breast cancer patients, but these pathways have not been studied in detail [5].

The aim of this review is to piece together the findings from papers that discuss the effect of breast cancer brain metastases on neuronal signaling. More specifically, this review will detail the identified factors that play a role in the promotion of brain metastases in breast cancer patients through altered neuronal signaling and synaptic transmission. Through various experiments, the studies highlighted in this review shed light on possible solutions to counteract brain metastases in breast cancer patients.

METHODS

Articles were searched for via PubMed using the following keywords: breast neoplasms, brain neoplasms, synaptic transmission, signal transduction, neurons, brain metastasis, signaling, and breast cancer. These keywords were grouped together in a variety of combinations using Boolean operators, and papers were selected based on their relevance to the research question. Studies were excluded if published earlier than 2015 or if the study was a review article.

RESULTS

Table 1. Qualitative Synthesis of Studies Included in the Review

Study	**Aim**	**Key findings**	**Relevance to Research Question**
Mondal J, et al., 2025 [4]	This study aims to show how neuronal signaling was affected by metastatic breast cancer, ultimately promoting growth.	Drugs that modulate synaptic transmission can impair metastasis, and can be used therapeutically.	Displays how transmission and neuronal signaling promote the growth of brain metastasis in breast cancer patients.
Mendez-Santacruz LL, et al., 2025 [5]	This study aims to assess to what extent N-methyl-D-aspartate (NMDAR) receptors contribute to Inflammatory breast cancer's aggressiveness.	There was an increased NMDAR1 in IBC lines, showing that NMDAR plays a role in IBC growth. The results suggest that NMDARs are potential therapeutic targets for IBC.	Shows NMDAR contributions to IBC growth.
Hunt AL, et al., 2024 [6]	This study aims to uncover microenvironmental factors that explain why younger breast cancer patients develop more aggressive brain metastases.	The protein TNC was elevated in younger patients, and their neuronal signaling pathways were altered.	Shows how age correlates to brain metastasis in breast cancer patients.
Foo SL, et al., 2022 [7]	This study aims to find a mechanistic signaling axis between cancer cells and microglia that facilitate brain metastasis.	Microglia activation was observed. Metastatic cancer cells produce ANXA1 to aid microglial migration. ANXA1 inhibition can be therapeutic for breast cancer patients.	Displays how microglia affect metastatic breast cancer by promoting growth.
Zeng Q, et	The aim of this study is to	Pathways in mice were able	Offers a possible solution to

al.,2019 [8]	show how NMDAR signaling promotes brain metastasis in breast cancer patients.	to be slowed down. The study concluded that cancer cells can co-operate with neuronal signaling through NMDARs in order to thrive.	slowing down brain metastasis in breast cancer patients.

The studies included in this review show the relationship between brain metastases and neuronal signaling in breast cancer patients. More specifically, the various factors that lead to the growth of brain metastasis are highlighted in these studies. These factors alter neuronal signaling and pathways, exploiting them to contribute to metastatic growth. Table 1 displays the aim of each study, along with its key findings and relevance to this paper. The third study in the table shows how a younger age can increase the frequency and severity of factors that cause brain metastases in breast cancer patients [6]. In particular, the study found the protein TNC to be elevated in young mice [6]. The elevation of TNC contributes to the growth of breast cancer brain metastases, especially in younger patients [6].

The fourth study in the table discusses the connection between the microglia and cancer cells with regards to brain metastases [7]. As the microglia and a mutant form of ANXA1 were assessed in infected mice, the study found that metastatic 4T1 mammary cancer cells make ANXA1 to promote microglial migration, enhancing overall tumor cell migration [7]. This shows how the breast cancer cells act as a stimulant for microglia, exploiting the microglia to support growth [7].

The studies listed second and fifth in the table both discuss how NMDARs affect brain metastases specifically in breast cancer patients. The second study primarily focuses on NMDARs' effect in inflammatory breast cancer (IBC) [5]. The study displays that NMDA receptors, which play a role in neuronal signaling, contribute to the aggressive phenotype of IBC [5]. The results suggest that NMDAR is a biomarker and therapeutic target in cells affected with IBC [5]. The fifth study similarly finds that metastatic cancer cells can co-operate neuronal signaling through NMDARs in order to thrive in the brain [8]. Ultimately, NMDARs contribute to the rapid growth of brain metastasis, especially in breast cancer patients [8,5]. The fifth study also suggests that NMDAR inhibition can slow pathways and metastasis, as observed in the mice model [8].

The first study in the table was able to conclude that drugs that modulate synaptic transmission can impair metastasis, demonstrating their therapeutic benefit while also highlighting that synaptic transmission plays a role in promoting the growth of brain metastases in breast cancer patients [4]. As AMPA and GABA receptor units were increased for breast cancer patients with brain metastasis, both receptors and their respective neurotransmitters are thought to be

implicated in the metastatic process [4]. Ultimately, neuronal signaling pathways are altered, aiding in the growth and migration of brain metastases [4].

Together, these studies show that there are many factors that contribute to the alteration of neuronal signaling pathways. These alterations eventually promote the growth of brain metastases, leading to a more aggressive cancer for patients to battle.

DISCUSSION

This review contains findings from studies that discuss how neuronal signaling and neuronal pathways are affected by the growth of brain metastases in breast cancer patients. Together, these studies highlight different factors contributing to the growth of brain metastasis, offering new targets for therapeutic interventions.

Mechanisms & Parallels

Studies have shown that the inhibition of NMDARs may allow for therapeutic relief for breast cancer patients with brain metastases [8]. In the study by Mendez-Santacruz LL, et al., IBC cell lines and non-IBC controls were cultured to assess NMDAR mRNA and protein expression [5]. Immunochemistry and confocal microscopy were used to localize NMDARs [5]. Ultimately, the results showed that NMDAR1 was located in IBC lines [5]. Given the association between NMDARs and the aggressive nature of IBC, it is likely that NMDARs play a role in the pathogenesis of brain metastasis, secondary to IBC. This is likely as NMDARs play a role in neuronal signaling, and breast cancer cells exploit neuronal signaling in order to grow [8]. The hypothesis that NMDARs are factors contributing to the growth of brain metastases in breast cancer patients was tested when researchers injected mice with breast cancer cells and analyzed the NMDARs [8]. They also used confocal microscopy to confirm the contact between neurons and cancer cells [8]. Along with this, immunofluorescence staining confirmed neuron-tumor interface [8]. They also analyzed human tissues [8]. As a possible therapeutic intervention, mice models were used to test NMDAR inhibition [8]. With this experiment, they were able to slow pathways and metastasis in mice [8]. Ultimately, the study showed that metastatic cancer cells can co-operate neuronal signaling through NMDARs in order to thrive in the brain [8]. Together, these two studies explore how NMDARs are a factor promoting the growth and aggression of brain metastases in breast cancer patients and may offer a potential target for therapeutic intervention.

In Foo SL, et al.'s study, researchers found that silencing ANXA1, a protein involved in microglial activation, may be therapeutic for patients, as ANXA1 promotes the growth of brain metastases [7]. This is similar to how NMDARs can be inhibited for therapeutic purposes. In this study, mice were injected with breast cancer cells via the carotid artery [7]. Researchers noted

how active microglia were usually close to tumors, hypothesizing that these cells must play a role in tumor progression [7]. Growth and movement of the microglia were also evaluated [7]. Along with this, ANXA1 was examined using CRISPR [7]. Signaling pathways were assessed with western blotting [7]. Ultimately metastatic 4T1 mammary cancer cells were found to produce ANXA1 to promote microglial migration [7].

Another factor that was found to promote the growth of brain metastases in breast cancer patients was the protein TNC. TNC is a positive regulator of tumor cell migration, resulting in its elevated levels to be a contributor to the increased brain metastases in younger breast cancer patients [6]. TNC is found to be a factor contributing to the metastatic nature of breast cancer [6]. In this study by Hunt AL, et al., they used quantitative mass spectrometry to identify proteins that lead to breast cancer brain metastases [6]. They harvested tumor metastases and uninvolved tissue through laser microdissection [6]. The results showed alteration in signaling pathways, including neuronal signaling, highlighting the idea that TNC and other microenvironmental factors contribute to the increased brain metastasis in younger breast cancer patients [6]. Interestingly, TNC was also elevated in young mice, suggesting that breast cancer metastases may be more prevalent in younger patients due to elevations in this protein [6].

Lastly, the study by Mondal J, et al. discusses how brain metastases affect neuronal signaling, altering pathways to promote the growth of brain metastases in breast cancer patients [1]. They used RNA - sequencing on parental and brain metastatic derivatives to identify an increase in AMPA and GABA receptor units for patients with brain metastases [4]. Researchers realized that this was a specific adaptation necessary for metastasis, offering a potential therapeutic target that could be subsequently tested [4]. The researchers used preexisting drugs to target breast cancer that had metastasised to the brain [4]. They were able to conclude the drugs that modulate synaptic transmission can impair metastatic potential and be used therapeutically [4].

Relevance

Breast cancer is the most common cancer among women [1]. With its rapid growth potential, brain metastasis are unfortunately fairly common. Understanding factors that promote the growth of brain metastases and how these factors affect pathways in the nervous system can allow for the opportunity to slow the spread of brain metastases in breast cancer patients.

Future Directions

Studies relating to neuronal signaling pathways and brain metastases in breast cancer patients are fairly new. As such, more research is needed to be done in order to fully assess how the growth of brain metastases and neuronal signaling are correlated. These future studies should focus on identifying effective targets for therapeutic intervention to slow down brain metastases in breast cancer patients, improving the quality and length of patients' lives.

REFERENCES

1. Menon G, Alkabban FM, Ferguson T. Breast Cancer. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; February 25, 2024.
2. Nie Y, Ying B, Lu Z, Sun T, Sun G. Predicting survival and prognosis of postoperative breast cancer brain metastasis: a population-based retrospective analysis. *Chin Med J (Engl)*. 2023;136(14):1699-1707. doi:10.1097/CM9.0000000000002674
3. Balinda HU, Kelly WJ, Kaklamani VG, et al. Sacituzumab Govitecan in patients with breast cancer brain metastases and recurrent glioblastoma: a phase 0 window-of-opportunity trial. *Nat Commun*. 2024;15(1):6707. Published 2024 Aug 7. doi:10.1038/s41467-024-50558-9
4. Mondal J, Nylund P, Malgulwar PB, Johnson WE, Huse JT. Synaptic transmission promotes brain metastatic outgrowth in breast cancer. *JCI Insight*. 2025;10(19):e193119. Published 2025 Sep 2. doi:10.1172/jci.insight.193119
5. Mendez-Santacruz LL, Bittman-Soto XS, Molina-Nieves A, Maldonado-Vlaar CS, Peterson-Peguero E. Pharmacological inhibition of NMDA receptors reduces migration and viability in triple-negative inflammatory breast cancer cell lines. *Discov Oncol*. 2025;16(1):1764. Published 2025 Sep 29. doi:10.1007/s12672-025-03604-x
6. Hunt AL, Khan I, Wu AML, et al. The murine metastatic microenvironment of experimental brain metastases of breast cancer differs by host age in vivo: a proteomic study. *Clin Exp Metastasis*. 2024;41(3):229-249. doi:10.1007/s10585-023-10233-7
7. Foo SL, Sachaphibulkij K, Lee CLY, et al. Breast cancer metastasis to brain results in recruitment and activation of microglia through annexin-A1/formyl peptide receptor signaling. *Breast Cancer Res*. 2022;24(1):25. Published 2022 Apr 5. doi:10.1186/s13058-022-01514-2
8. Zeng Q, Michael IP, Zhang P, et al. Synaptic proximity enables NMDAR signalling to promote brain metastasis. *Nature*. 2019;573(7775):526-531. doi:10.1038/s41586-019-1576-6