Scholars LITERATURE

Journal of Clinical Oncology and Therapeutics

Short Communication

DOI: https://doi.org/10.47275/2690-5663-141
Volume 7 Issue 1

A Short Communication on Lung Metastasis in Breast Cancer: Clinical and Experimental Perspectives

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Abstract

Approximately 90% of all breast cancer-related deaths occur due to metastasis, which is the most common type of cancer in women worldwide. The spread of breast cancer is preferential to the lung, brain, bone, and liver, which is known as organ tropism. The lack of early prognostic/predictive methods to determine which organs are most likely to develop metastases has made current treatment methods for metastatic breast cancer ineffective. Most cancer patients die from distant metastases. Based on gene expression profiles, breast cancer can be classified into different subtypes, and different subtypes prefer to metastasize to different organs. Breast tumors that are luminal tend to metastasize to bone, whereas those that are basal-like are more likely to metastasize to the lungs. There is, however, still a need to investigate the mechanisms underlying this organ-specific pattern of metastasis. It is crucial to understand the mechanisms that drive breast cancer metastasis in order to identify novel biomarkers as well as therapeutic targets. 65% of patients who develop lung metastasis die as a result of this disease, which is associated with significant morbidity and mortality. The purpose of this review is to summarize current understanding of breast cancer metastasis to the lung and to discuss potential new treatment approaches for breast cancer metastasis to the lung.

Keywords: Breast cancer, Lung metastasis, Pre-metastatic niche, Exosomes, Tumor secreted factors, Targeted therapies

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Citation: Thota S, Priya RKS, Subhana A, Mittapally SR (2025) A Short Communication on Lung Metastasis in Breast Cancer: Clinical and Experimental Perspectives. J Clin Oncol Ther, Volume 7:1. 141. DOI: https://doi.org/10.47275/2690-5663-141

Received: November 29, 2024; **Accepted:** January 13, 2025; **Published:** January 17, 2025

Introduction

Approximately 785,423 women worldwide died from breast cancer in 2024, making it the most common malignancy in women. Because of lifestyle factors, breast cancer has historically been a higher burden in developed nations. A 'westernized' lifestyle and advances in health infrastructure have resulted in an increase in breast cancer incidence rates in developing nations. Approximately 2 in 10 women in western countries will develop breast cancer during their lifetime, and 1 in 29 will die from it [1]. Approximately 86% of breast cancer deaths are due to metastasis-related complications. Tumor cells are detached from their primary tumor and infiltrated into the blood stream during metastatic process. After arresting capillaries of distant organs, the circulating tumor cells (CTCs) extravasate into the parenchyma of the secondary organ, generating metastatic colonies [2].

Improved survival rates for breast cancer have been achieved by improving early detection and treatment. However, a substantial number of patients will relapse due to organ metastasis, especially those with triple-negative breast cancer (TNBC), which has the worst prognosis. It is possible for breast cancer cells to spread to distant sites, specifically the lungs, liver, bones, and brain [3]. Many patients die as a result of these macro proliferative masses. Recurring breast cancer patients with distant metastases have a survival rate of less than 20% after 5.2 years. It is most common for breast cancer to spread to the lungs, bones, and liver. It is estimated that about 60% of patients with metastatic breast cancer will suffer lung or bone metastases during their lifetime. The lungs are particularly susceptible to metastasizing from basal like breast cancer (BLBC). In these cases, survival is low, with the median survival only 21 months following lung metastasis treatment [4]. The presence of lung metastases was diagnosed in 65 - 75% of patients with metastatic breast cancer who died. Despite the availability of many treatment options for lung metastasis, such as chemotherapy, radiotherapy, and targeted therapy, the survival rate of breast cancer patients with lung metastasis remains low. The development of new therapeutic strategies depends on understanding and elucidating the underlying mechanisms. As a matter of fact, it has been shown that BLBC markers such as epidermal growth factor receptor (EGFR) and FOXC1 are associated with lung metastasis. There are many factors involved in determining which organ or organs are colonized by breast cancer, including the molecular variant. ER, PR, and HER2 receptors as well as the proliferation status determined by Ki67 can be used to subdivide breast cancer into four main clinical subtypes. All subtypes of breast cancer tend to metastasize to the bone, but TNBC has the highest incidence of lung metastases; at 35% compared with 25% for luminal A/B and 30% for HER^{2+}. It is unknown, however, when and by what mechanisms breast cancer molecular subtypes influence lung metastasis. This review summarizes current knowledge about molecular mechanisms driving breast cancer metastasis to the lungs. This article discusses the potential therapeutic approaches to improve the prognosis of breast cancer patients with lung metastases based on the large body of research surrounding this topic [5, 6].

Clinical features of metastasis in breast cancer

Currently, only 5 - 10% of patients with breast cancer have distant metastases at the time of diagnosis, thanks to improvements in early detection. Even after standard treatment, metastatic disease can recur. Metastatic breast cancer patients are more likely than non-metastatic breast cancer patients to undergo recurrence, and lung or bone metastases can occur in more than 60% of them. Metastatic breast cancer still kills half a million women worldwide annually, and 90% of those deaths are caused by metastases. Breast cancer most commonly metastasizes to the bone, liver, lung, and brain, which are associated with poor survival rates. Additionally, breast cancer subtypes differ in the preference of metastatic organs. Patients with luminal breast cancer tend to develop bone metastases, while those with TNBC are more likely to develop lung metastases. Compared to non-TNBC patients, TNBC patients can experience lung metastases at an incidence of up to 40%. Patients with lung relapse were more likely to be associated with luminal B and basal subtypes, whereas those with bone relapse were less likely to be associated with BLBC. It is striking that patients with luminal A breast cancer did not experience lung relapse, while those with BLBC and HER^{2+} breast cancer did. According to Hammer, et al. [7] hormone receptor-positive breast cancers had the best clinical outcomes, whereas HER^{2+} cancers and TNBC had the worst outcomes. Metastases to the liver are also more likely to develop in patients with the HER2+ subtype. Several surveillance, epidemiology, and end results (SEER) database analyses have shown that lung metastases are the most common presenting feature of patients with TNBC, especially BLBC. There was, however, no difference in the total probability of lung metastasis across all subtypes. Additionally, the study revealed that all breast cancers, regardless of subtype, metastasized more often to bone. Cancers of the luminal type are more likely to develop bone metastases [7]. Despite discrepancies between reports regarding the metastatic sites preferred by breast cancer subtypes, it is widely recognized that different subtypes show different behavior in regard to distant metastases. As well as having a poor prognosis, metastatic breast cancer that has spread to the lungs has extremely serious clinical presentations and consequences. Clinical symptoms such as pain, cough, hemoptysis, pleural effusion, and pulmonary dysfunction have a profound effect on quality of life and survival. Despite chemotherapy, targeted therapy, and endocrine therapy tailored to molecular receptor profiles, breast cancer patients with lung metastases have poor prognosis. To prevent breast cancer lung metastasis, early diagnosis is the only method currently available. In order to develop better treatment strategies, we must fully understand the mechanism of breast cancer lung metastasis (Figure 1).

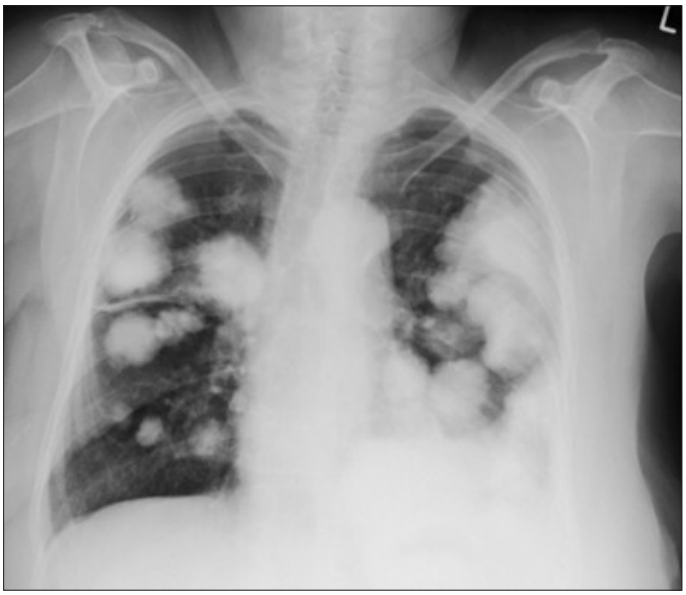

Figure 1: Multiple metastases in both lungs (Patient had a history of right mastectomy for breast cancer). (Source: Radiology-St. Vincent's University Hospital).

The Lung Metastatic Niche

There is very little success in completing the metastatic cascade and developing macro metastases at the secondary site due to the inefficiency of the metastasis process. There is clinical evidence that patterns of organ-specific metastasis are not random, but rather influenced by the microenvironment of the secondary organ. According to previous studies, cancer cells grow preferentially in the microenvironment of select organs only if the conditions at that site are conducive to growth. Our research group has demonstrated that breast cancer cells exhibit organ-specific proliferation and migration responses when exposed to organ-conditioned media from common sites of breast cancer metastasis (lymph node, lung, liver, bone, brain), supporting this theory. Metastatic behavior is supported by soluble components produced by certain organs. According to previous studies, organ-specific metastasis is regulated solely by physiological blood flow patterns in the early 1900s. Breast cancer cells enter the bloodstream through the lungs, which are the first major capillary beds they encounter. As tumor cells circulate throughout the lung, they may come into contact with as much as 100 square meters of surface vessels. The tumor cells are approximately five times larger than the exceedingly narrow pulmonary capillaries, providing a high likelihood of breast cancer cells arresting in these capillaries and then extravasating into lung tissue [8, 9]. Lung capillaries are composed of endothelial cells encapsulated by a basement membrane and adjacent alveoli. Tumors must express markers specific to the lung microenvironment in order to facilitate trans endothelial migration and extravasation. The ability of individual metastatic cells to successfully migrate from micro metastases to macro metastases and progress to macro metastases is extremely rare, despite the fact that extravasation may occur quite easily via these physical processes. Thus, these final events serve as a rate-limiting step in metastasis [10].

This "pre-metastatic niche" is hypothesized to be critical to the process of metastasis, and it consists of four phases: priming, licensing, initiation, and progression. When the primary tumor undergoes uncontrolled proliferation and becomes hypoxic, it secretes tumor-derived soluble factors and exosomes. Pre-mature metastatic niches are created by targeting the bone marrow for recruitment and remodeling the secondary organ. A constant secretion of factors from the primary tumor gradually recruits bone marrow-derived cells and immune regulatory/suppressive cells to the secondary site. The licensing process is facilitated by these processes, which create an immune-suppressed environment and an extracellular matrix (ECM) that facilitate cancer colonization. Upon entering this metastatic niche, cancer cells can remain dormant until the conditions at the secondary site can support the formation of micrometastases. As micrometastases progress to macrometastases, tumor secreted factors and other regulatory cells infiltrate the secondary site and control their growth [11].

Tumor-Derived Exosomes (TDE's)

Extracellular vesicles derived from tumors can be classified according to their size, including apoptotic bodies, microvesicles, and exosomes. As a result of fusion with the plasma membrane, exosomes are released from cells via the endosomal pathway. TDEs have been shown to modify the lung microenvironment through their effects on TDE's. Several studies have demonstrated that pre-treatment of mouse

models with TDEs derived from lung-seeking breast cancer cell lines can "educate" the lung, making it more susceptible to metastasis. The primary tumor's exosome can target the lungs by using integrins like ITGα6β1. In the lung, breast cancer-derived exosomes can deliver their cargo of RNA, DNA, and proteins to induce pro-metastatic changes. A number of factors, such as hypoxia, regulate exosome production and packaging, including environmental stimuli [12]. The production of breast cancer exosomes increases substantially in hypoxic conditions in a HIF-1α dependent manner. In addition, exosomes can impart properties such as chemotherapy resistance and increased invasiveness to recipient breast cancer cells (Figure 2).

Exosomes as clinical biomarkers

There are several factors secreted by tumors into the peripheral circulation that may be used as clinical markers of disease progression. The development of non-invasive blood-based biomarkers has thus received increased attention. As CTCs are sparsely concentrated in blood, many current methods have been aimed at enumerating and characterizing them, but this has proved to be challenging. The detection rate of CTCs in patients with early-stage breast cancer ranges between 23 and 37%, and there is no effective strategy to determine which organs might be affected by metastasis based on CTC analysis. The stability of TDE's in blood, their ability to be isolated from most bodily fluids (blood, urine, semen, milk) and their presence in circulation similar to soluble proteins may make them a compelling alternative. There is an inherent difficulty in distinguishing exosomes from normal or cancerous cells. It may be possible to identify metastasis sites by isolating breast cancer exosomes and analyzing their proteomic content by identifying the presence of specific organotropic integrins [13-16]. The combination of RNA analysis and proteomic data may also provide insight into how exosomes alter secondary sites, providing a targeted approach to circumventing metastatic potential. Early detection methods have great potential, but must be refined, validated in the clinical setting, and ideally coupled with new treatment approaches to become clinically useful.

Exosomes and stromal cells

In addition to interacting with immune cells, breast cancer-derived exosomes modulate the function of stromal cells in the lung microenvironment. A study showed that exosomes isolated from the MDA-MB-231 breast cancer cell line contained miR-122, and when applied to lung fibroblasts, these exosomes reduced glucose uptake by inhibiting pyruvate dehydrogenase. As a consequence, secreted exosomes from the primary tumor could reduce glucose uptake

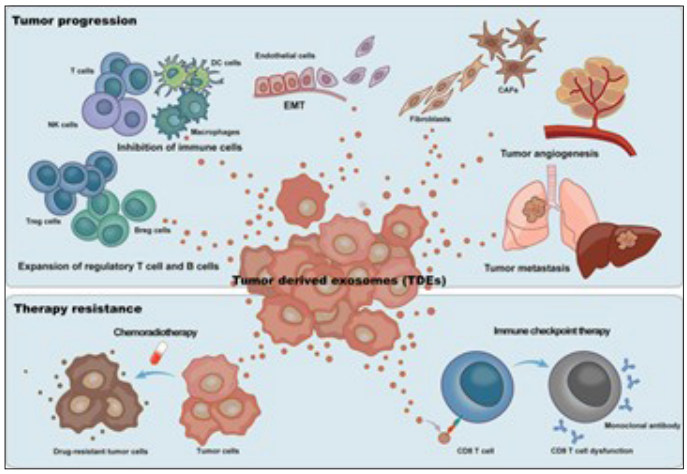

Figure 2: Tumor derived exosomes [12].

prior to colonization of the lung, allowing newly arrived cancer cells to proliferate more rapidly. The concept that breast cancer-derived exosomes play a crucial role in establishing a permissive niche in the lung necessary for metastatic colonization is supported by many other studies, and exosomes may be considered in clinical settings [17].

Exosomes and immune suppression

As a result of immune-suppression, the process of generating a pre-metastatic niche in the lung is highly related to ensuring that CD8+ T cells, natural killer cells (NKC) and patrolling monocytes are masked from the presence of tumor cells attempting to establish themselves as metastatic lesions. Interestingly, previous studies found that breast cancer-derived exosomes expressing PD-L1 are effectively protected from immune surveillance by blunting T-cell activation and killing activities. Tumor cells are capable of seeding and colonizing distant organ sites, such as the lungs, by suppressing the immune response. In spite of cancer cells' efforts to avoid circulating immune elements, there is evidence that chronic inflammation at pre-metastatic sites is associated with immune cell dysregulation. Also, although it is well established that myeloid-derived suppressor cells (MDSCs) facilitate tumor growth, their development during tumor growth remains a mystery. By releasing exosomes derived from breast cancer, Xiang and colleagues showed that bone marrow myeloid cells could be forced to differentiate into MDSCs. As a consequence, MDSCs expressing Cox2, IL-6, VEGF, and arginase-1 accumulate in the lungs, resulting in a pro-inflammatory, immunosuppressed environment that facilitates metastasis [18-21]. There has been no investigation of the relevance of this process to breast cancer lung metastasis.

Microenvironment factors

Metastatic cascades consist of numerous barriers that cancer cells must overcome in order to form distant metastases. When breast cancer cells spread beyond the primary tumor, they prefer to metastasize specific tissues, including bones, lungs, livers, and brains. There is a variety of communication between disseminated tumor cells and stromal cells in colonized tissues. A variety of factors contribute to the microenvironment that creates a tumor, including growth factors, immune cells, cytokines, chemokines, ECM, tumor-associated macrophages, cancer-associated fibroblasts (CAFs), and others yet to be determined. As well as organ-specific factors, the metastatic microenvironment can be influenced by stromal cell infiltration.

Transforming growth factor β (TGF-β)

Several studies have shown that abnormal expression of TGF-β promotes breast cancer progression by altering the microenvironment. Chen et al. [22] used the 4T1 syngeneic mouse model, we demonstrated that TGF-β modulates inflammatory cytokines and growth factors to create a lung pre-metastatic microenvironment. IN-1130, a novel TGFβ−1 receptor kinase inhibitor, suppressed lung metastases in the 4T1 breast cancer orthotopic xenograft mouse model. It appears that inhibiting TGF-β signaling alone or when combined with immunotherapy may be a promising treatment for breast cancer lung metastasis based on the findings of these studies [22].

ECM proteins

Tenascin-C (TNC), Periostin (POSTN) and Versican (VCAN) are ECM proteins that play a crucial role during the early stages of breast cancer colonization of a metastatic site such as the lung. BCSCs can also produce TNC, a protein normally produced by fibroblasts. BCSCs with aberrant expression of TNC promote lung colonization through metastasis-initiating effects. Also known as the Wnt ligand-binding factor, POSTN is derived from stroma. Several studies have shown that

it promotes lung metastasis development by spreading cancer stem cells [23]. Also, bone marrow-derived myeloid cells that invade the lung secrete VCAN within metastatic niches to promote lung metastasis. Metastatic growth may also be facilitated by ECM components because they provide an environment where disseminated tumor cells can interact. VCAM-1 (vascular cell adhesion molecule-1) occurs in breast cancer cells and interacts with fibronectin, as well as NKC and monocytes. Breast cancer cells expressing VCAM-1 prefer to grow in collagen and elastin-rich pulmonary parenchyma [24].

Tumor-Derived Secreted Factors (TDSFs)

TDSFs are other factors released by primary breast cancer tumors that are capable of priming or augmenting the lung microenvironment. In order for metastatic colonization to be successful, the ECM must be in good shape. VCAN, TNC, POSTN, and fibronectin are upregulated in pro-metastatic organs such as the lung. It is similar to exosome production in that the effect of primary tumor-secreted factors on the secondary site is influenced by both environmental stimuli and interactions with stromal cells. An increase in lysyl oxidase (LOX) expression occurs within the primary tumor as a result of hypoxia. There are numerous pro-metastatic processes associated with LOX, which is an amine oxidase that crosslinks collagen and elastin in the ECM. Under hypoxic conditions, Milano et al. [25] demonstrated that breast cancer primary tumors increase LOX expression, causing collagen crosslinking. As a result of this change in the ECM, CD11b+ myeloid cells can adhere, and upon binding produce MMP2, leading to collagen cleavage, which facilitates Bone marrow-derived dendritic cells (BMDCs) and cancer cell recruitment to the lung microenvironment. It is interesting to note that the status of the ECM determines the type of cells recruited to the lung, which can change the status of the ECM to create an environment favorable for the spread of metastatic disease.

Stromal-Derived Influences

Aside from hypoxia, the tumor microenvironment may also affect the primary tumor, including immune cells, endothelial cells, adipocytes, and other types of cells. Breast cancer cells may behave in a variety of ways due to a subset of activated stromal cells called CAFs. A CAF is composed of heterogeneous populations of specialized cells with a variety of origins marked by the expression of several markers, including SMA and PDGFR. Cancerous tissue is metastasized by CAFs through paracrine signaling and mechanical pressure. By binding to breast cancer cells, CAFs secrete IL-32, which activates p38 MAPK signaling, increasing the expression of EMT markers such as fibronectin, N-cadherin, and vimentin. In mice, CAFs were injected subcutaneously with BT549 breast cancer cells to determine their effect on metastasis. Lung stromal cells also play an important role in the process of influencing immune responses, apart from primary tumors. It is possible for breast primary tumors to up-regulate lung microenvironment S100A8 and S100A9. The primary tumor must influence several molecular and cellular processes in order to cause metastasis to the lung. In recent years, Lyden and colleagues have explored the interaction between BMDCs and the primary tumor. Mesenchymal stromal cells (MSCs) derived from bone marrow can differentiate into CAFs when co-cultured with tumor cells, according to studies. During the dormancy process, breast cancer cells also interact with bone marrow cells. Since dormant cancer cells remain in the mitotic arrest phase, drugs targeted at highly proliferating cells are unable to kill them. When they recur, they can spread to other organs as metastatic disease. The molecular mechanism behind this relationship between dormant breast cancer cells and the bone marrow is not fully understood [26]. MSCs may play a crucial role in facilitating this process. A trans well model will be used to simulate the interaction between MSCs and breast cancer cells in order to recapitulate this interaction.

Potential for Clinical Translation

Identifying and treating the key characteristics of the "seed" (lung-seeking cancer cells) as well as the "soil", which includes the lung microenvironment and the pre-metastatic niche, is essential to preventing breast cancer metastasis to the lung. Specifically, the lung pre-metastatic niche can play a significant role in determining the risk of a particular patient developing lung metastases. Pre-metastatic niche research has, however, largely been limited to mouse models, although this is increasingly moving towards clinical trials. Because S100A8 and S100A9 are crucial for the formation of pre-metastatic niches in the lung, we developed S100A9 specific single photon emission computed tomography whole body imaging that was tested in a pre-clinical breast cancer metastasis model. Previous authors also isolated exosomes from the breast cancer cell line 4175-LuT, which has a propensity to metastasize to the lung, using the knowledge that exosomes target specific organs. Female nude mice with tumor-naive exosomes were injected with the labeled exosomes. As a result of the tissue harvest, there was a high accumulation of exosomes in the lungs of the mice. Pre-metastatic niches can be identified using high resolution, non-invasive imaging such as SPECT using this method. A radiopharmaceutical was used by Xu et al. [27] to target VLA-4 on lung-localized BMDCs. To detect BMDCs in the pre-metastatic niche, PET was subsequently performed. Several preclinical studies indicate that colonization of the pre-metastatic niche can be prevented by attenuating the effects of the niche [27, 28]. In spite of these promising results, the clinical benefit of these approaches for patients with an increased risk of lung metastasis remains to be determined. A limited number of patient samples taken from metastatic lesions has hindered efforts to understand the complex underlying mechanisms that drive lung metastasis. It is possible, however, to obtain these samples through rapid autopsy programs. This field could be advanced by developing robust biobanks of matched primary tumors and metastatic lesions (from the lung and other organs). In addition to providing insights into the underlying mechanisms that drive metastasis to specific organs, profiling these samples could also uncover potential biomarkers that could help predict and/or prevent organ-specific metastases. In addition, further research should focus on determining how long the metastatic niche within the lung lasts after surgery, radiation, or chemotherapy. With personalized treatment regimens, it will be possible to prevent or reduce recurrence of metastatic disease in the lung even after cancer has been eradicated [29].

Therapeutic strategies

Early detection and improved treatments for breast cancer have significantly improved the overall survival rate of patients. It is estimated that less than 30% of women with metastatic breast cancer will survive more than five years. Metastatic breast cancer still has a low survival rate despite cytotoxic chemotherapy, endocrine therapy, and targeted therapies. As a result, systemic chemotherapy may not be as effective as it should be, and metastatic breast cancer may be more resistant to traditional treatments. As well as standard therapies, we need more targeted treatments that take advantage of the mechanisms of metastatic breast cancer. TNBC is currently treated only with cytotoxic chemotherapy. TNBC is enriched in breast cancer stem cells (BCSCs), which may make targeting CSC-associated pathways a valuable therapeutic strategy. Preclinical and clinical trials are being conducted to test inhibitors of Wnt and Hh signaling for the treatment of TNBC [30, 31].

Studies based on genomics continue to shed light on TNBC tumorigenesis and heterogeneity and could lead to the development of

TNBC-targeted therapies. Selumetinib, a MEK inhibitor, inhibits and prevents lung metastases of TNBC in xenograft models, suggesting that MAPK pathway could be a potential therapeutic target for TNBC lung metastasis prevention. Additionally, Cao et al. suppressed lung metastasis in breast cancer by using succinobucol (SCB), a VCAM-1 inhibitor [32]. Furthermore, Nakamura et al. suggested that Rho GEFs might be useful for treating breast cancer lung metastases. In recent years, immunotherapy has become one of the most popular treatment options for metastatic breast cancer [33]. It may be possible to increase the effectiveness of cancer treatments by combining cancer vaccines with standard treatments. The results of animal in vivo studies may provide some basic information for clinical treatment, but metastatic breast cancer remains a challenge for researchers. Is it possible to use markers to predict metastasis risk? Can drug resistance be screened? Research into the genetic, environmental, and immune pathways may lead to improved care in the future. There are still many problems to be solved.

Conclusions

Breast cancer continues to pose a significant burden to modern society. Developing a prevention strategy and understanding how it spreads requires further research. There are currently no effective strategies for early detection or eradication of metastatic lung cancer, which is associated with high patient morbidity and mortality. A complex network of interactions with the tumor microenvironment, lung stroma, immune cells, and BMDCs facilitates lung colonization, and crosstalk between these components is mediated by exosomes and tumor/stroma-derived factors. In the tumor microenvironment and secondary site, these secret elements vary according to environmental stimuli and interactions with stromal cells. As a result of these interactions, the lung microenvironment becomes a fertile niche for cancer cells to colonize. The CSCs and their signaling pathways, chemokines, and microenvironments are important regulators of breast cancer dissemination to the lungs. In recent years, we have gained a greater understanding of breast cancer progression. However, it is not entirely clear whether these regulators cooperate with one another or if some play a more dominant role in controlling breast cancer metastasis. In addition, developing biomarkers to predict and prognosticate lung metastasis at initial diagnosis remains a challenging task.

Although the therapeutic approaches described above are promising for preventing lung metastases, further research and development are needed. It is currently not possible to detect whether a patient is at an increased risk of lung metastasis based on clinically relevant biomarkers. Exosomes may be used as a predictor of organ-specific metastasis, if they are validated in patient samples. The validation of some markers and mechanisms identified in cell and mouse models is essential in clinical trials. It may be necessary to analyze matched primary breast cancer samples and lung metastasis samples for the purposes of establishing clinical relevance of research results from preclinical models. The development of therapeutic targets and biomarkers with the ultimate goal of preventing lung metastasis can be made possible by understanding the processes that lead to lung metastasis.

Acknowledgements

None.

Conflict of Interest

None.

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