Breast Cancer Netastasis: Mechanish, Biomarkers and Therapuetic Strategies

Pattan. Heena Azme, Devarampati. Swathi, Pannem. Supriya Valla, Malli. Spandana
Dept of Pharmacy, St.Ann's College of Pharmacy

INTRODUCTION

Breast cancer is one of the most common cancers diagnosed in women worldwide, accounting for a significant number of cancer-related deaths. While early-stage breast cancer is often treatable with surgery, chemotherapy, and radiation, metastatic breast cancer (MBC) remains a major challenge in oncology. Metastasis, the spread of cancer cells from the primary tumour to distant organs, is the leading cause of mortality in breast cancer patients. The molecular mechanisms underlying metastasis are complex and multifactorial, involving genetic mutations, cellular changes, and interactions with the tumour microenvironment. This review aims to explore the mechanisms of breast cancer metastasis, the biomarkers used for its detection and prognosis, and the therapeutic strategies being developed to target metastatic disease.

Mechanism of Breast Cancer Metastasis:

Breast cancer metastasis involves a series of steps, each essential for cancer cells to leave the primary tumour, invade surrounding tissues, and colonize distant organs.

1. Local Invasion: Metastasis begins when cancer cells break away from the primary tumour and invade surrounding tissues. Several factors contribute to this process:

Loss of Cell Adhesion: Cancer cells reduce their expression of E-cadherin, a protein responsible for keeping cells attached to each other. This allows them to detach and move independently.

Epithelial-to-Mesenchymal Transition (EMT): The cells undergo changes that make them more mobile and invasive, acquiring mesenchymal traits like increased motility and resistance to apoptosis (programmed cell death).

Degradation of the Extracellular Matrix (ECM): Cancer cells release enzymes such as matrix metalloproteinases (MMPs) that break down the ECM, enabling them to move through tissues

2. Intravasation: Once cancer cells invade surrounding tissues, they enter nearby blood vessels (hematogenous spread) or lymphatic vessels (lymphatic spread). This step is facilitated by:

Interaction with Endothelial Cells: Cancer cells manipulate blood vessel walls to make them more permeable, allowing easy entry.

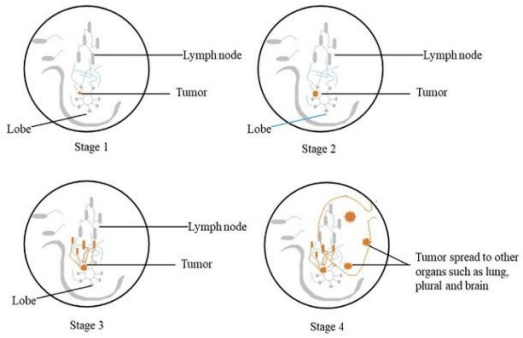
Support from Tumour Micro environment: Immune cells, fibroblasts, and cytokines help cancer cells survive and navigate into circulation.

3. Survival in Circulation

The bloodstream is a hostile environment for cancer cells due to immune system attacks and mechanical stress. To survive:

Platelet Shielding: Cancer cells can coat themselves with platelets, forming protective clusters that shield them from immune detection.

Resistance to Shear Forces: Cancer cells must withstand physical stress caused by blood flow. Some achieve this by altering their shape and cytoskeletal structure



4. Extravasation: Cancer cells must exit circulation to reach distant organs. This step involves:

Adhesion to Vessel Walls: Tumor cells express surface molecules like integrins that help them stick to the blood vessel lining in target organs.

Transmigration: The cancer cells squeeze between endothelial cells to exit the blood vessel and enter the surrounding tissue

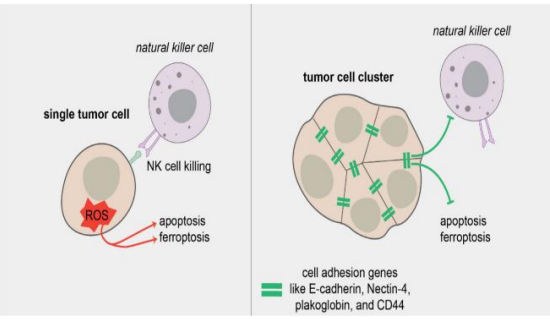
5. Colonization and Tumour Growth:

After reaching a new organ, cancer cells must adapt to the new environment and start growing. However, this is one of the most challenging steps, as they need to:

Overcome Immune Attacks: Some metastatic cells enter a dormant state to evade immune surveillance.

Create a Supportive Microenvironment: They recruit nearby cells and blood vessels (angiogenesis) to supply nutrients and oxygen, enabling tumour growth.

Modify the Organ Niche: Cancer cells release factors that make the new environment favourable for their survival and expansion



Biomarkers in Metastatic Breast Cancer:

Biomarkers are essential for diagnosing and predicting the progression of metastatic breast cancer. These include:

Diagnostic Biomarkers: Circulating tumour cells (CTCs) and cell-free DNA (cfDNA) are biomarkers that can be detected in the bloodstream, providing non-invasive methods to identify metastatic spread. Additionally, microRNAs, small non-coding RNA molecules, have shown potential as biomarkers for early detection of metastasis.

Prognostic Biomarkers: Oestrogen receptor (ER), progesterone receptor (PR), and HER2 expression on cancer cells provide critical information on the likelihood of metastasis. For example, HER2-positive breast cancer is more likely to metastasize, particularly to the brain and liver.

Emerging Biomarkers: Liquid biopsy, which involves analysing blood samples for genetic mutations and other biomarkers, has become an area of intense research. This method provides real-time information about tumour dynamics and can be used to monitor treatment response and detect early signs of metastasis.

Therapeutic Strategies for Metastatic Breast Cancer

Treatment of metastatic breast cancer is complex and involves a combination of modalities.

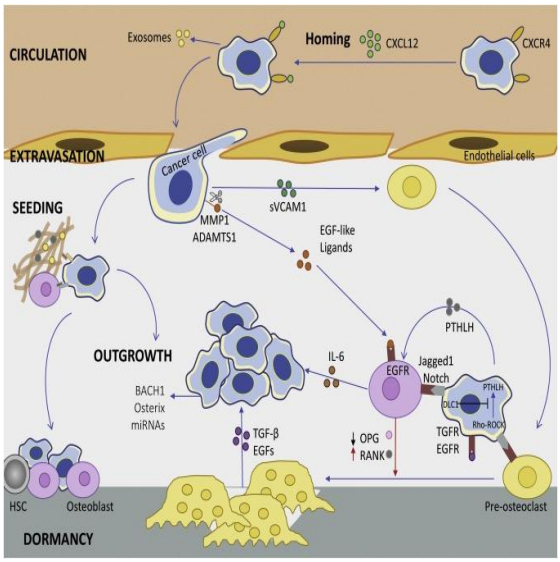
Chemotherapy: Chemotherapy has been a cornerstone of treatment for metastatic breast cancer. Drugs like anthracyclines and taxanes are used to target rapidly dividing cancer cells. However, chemotherapy often leads to side effects and resistance, limiting its long-term efficacy.

Targeted Therapies: Targeted therapies, such as HER2 inhibitors (e.g., trastuzumab) and CDK4/6 inhibitors (e.g., palbociclib), are designed to block specific molecules that drive cancer progression. These therapies have shown promise in managing metastatic disease, particularly in HER2-positive and hormone receptor-positive subtypes.

Immunotherapy: Immunotherapy aims to activate the immune system to recognize and kill metastatic cancer cells. Immune checkpoint inhibitors, such as pembrolizumab, are being explored in clinical trials for their ability to enhance immune responses against metastatic breast cancer cells.

Radiation Therapy: Radiation is often used in cases where metastatic breast cancer has spread to the bones or brain. Targeted radiation can shrink tumors and provide symptom relief, though it is not a curative option for widespread metastasis.

Combination Therapies: Combining chemotherapy, targeted therapies, and immunotherapies is a growing trend in the treatment of metastatic breast cancer, providing more effective outcomes by targeting multiple pathways involved in metastasis.



Challenges in Treating Metastatic Breast Cancer:

Despite advancements, treating metastatic breast cancer remains a significant challenge:

Drug Resistance: One of the major issues is the development of resistance to treatments. Tumor cells can evolve and acquire mutations that make them less susceptible to chemotherapy or targeted therapies. Overcoming drug resistance is critical to improving outcomes.

Tumour Heterogeneity: Breast cancer is a heterogeneous disease, meaning that even within a single patient, the metastatic cells may have different genetic profiles and characteristics. This diversity complicates treatment, as therapies that work on one subset of cells may be ineffective against others.

Clinical Trials and Research: Ongoing clinical trials are exploring novel treatments and strategies to overcome the challenges of metastatic breast cancer. These include investigating new biomarkers, combination therapies, and exploring the potential of cancer vaccines.

FUTURE DIRECTIONS AND CONCLUSION

The future of metastatic breast cancer treatment is promising, with many new therapies in development. Advances in personalized medicine, where treatment is tailored to the genetic profile of the tumor, are likely to improve outcomes. Additionally, immunotherapies, including CAR-T cell therapy, are becoming more important in the fight against metastatic disease. Better understanding of metastasis will also lead to improved diagnostic techniques, allowing for earlier detection and better monitoring of treatment efficacy.

In conclusion, while metastatic breast cancer remains a major challenge, significant progress is being made in understanding its mechanisms, identifying biomarkers, and developing new therapeutic strategies. Continued research is crucial to improving patient outcomes and ultimately finding a cure for metastatic breast cancer.

REFERENCES

[1]. Lambert, A. W., & Weinberg, R. A. (2009). Links between tumorigenesis and metastasis: A critical overview. *The Journal of Clinical Investigation*, 119(4), 809-818. doi:10.1172/JCI38025

[2]. Gupta, G. P., & Massagué, J. (2006). Cancer metastasis: Building a framework. *Nature*, 446(7131), 153-157. doi:10.1038/nature05795

[3]. Cristofanilli, M., & Hayes, D. F. (2011). Circulating tumor cells: A novel prognostic factor in metastatic breast cancer. *Breast Cancer Research*, 13(4), 229. doi:10.1186/bcr3011

[4]. Agostini, M., et al. (2020). Circulating biomarkers in metastatic breast cancer: A systematic review and meta-analysis. *Critical Reviews in Oncology/Haematology*, 145, 102852. doi:10.1016/j.critrevonc.2019.102852

[5]. Neve, R. M., et al. (2006). Targeted therapies for metastatic breast cancer. *Oncologist*, 11(7), 701-709. doi:10.1634/theoncologist.11-7-701

[6]. Linder, A., & Boudou, M. (2020). Immunotherapy in metastatic breast cancer: Current landscape and future directions. *Cancers*, 12(12), 3729. doi:10.3390/cancers12123729

[7]. O'Shaughnessy, J. (2005). Chemotherapy for metastatic breast cancer: Current treatment options. *Cancer Chemotherapy and Pharmacology*, 56(S1), 61-69. doi:10.1007/s00280-005-0926-1

[8]. Gucalp, A., & Traina, T. A. (2019). Challenges in the treatment of metastatic breast cancer: The role of drug resistance. *Seminars in Oncology*, 46(5), 509-518. doi:10.1053/j.seminoncol.2019.07.003

[9]. Pusztai, L., et al. (2016). Overcoming resistance to targeted therapies in breast cancer. *Breast Cancer Research and Treatment*, 159(3), 373-383. doi:10.1007/s10549-016-3985-4

[10]. Hegde, P. S., & Chen, D. S. (2020). Immune checkpoint blockade: The therapeutic landscape and future directions. *Nature Reviews Drug Discovery*, 19(10), 563-586. doi:10.1038/s41573-020-00088-2

[11]. Tolaney, S. M., & Bardia, A. (2018). Emerging therapies in the treatment of metastatic breast cancer: A focus on immunotherapy. *Journal of Clinical Oncology*, 36(23), 2221-2229. doi:10.1200/JCO.18.00842