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Breast Cancer progression to other organs

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***Abstract*---**Breast cancer has become very common among women and is the major cause of morbidity. The progression of breast cancer and the formation of secondary tumors in other organs is of major concern. Relapse and recurrence of breast cancer worsen the situation. Multiple genes get altered facilitating metastasis of cancer and downregulation/upregulation of many genes causes variations in molecular expression leading to progression in breast cancer cells. Mainly subtypes of breast cancer are distinct in the expression of hormone receptors (HR) and other proteins like ER, PR, HER2. Breast cancer can invade distant organs commonly in the bone, brain, lung, liver, and also the local region like the chest wall, and lymph nodes. Understanding the mechanism of cancer progression and molecules involved in breast cancer will help in developing therapies to prevent metastasis and find cures for breast cancer. In this review, the biomolecules such as ER, PR, HER2, etc. and the genes involved in breast cancer during its progression, and the mechanisms involved in metastasis have been discussed.

***Keywords*---**metastasis, estrogen receptor (ER), progesterone receptor (PR), HER2, breast cell.

Introduction

Breast cancer occurs when breast cells grow and divide uncontrollably, forming a mass of tissue. These breast cancer cells can further be mutated and can migrate into other organs. According to WHO records, 2.3 million women were diagnosed with breast cancer, and 68,5,000 died in the year 2020. In the last 5 years, around 7.8 million women are alive who were detected with breast cancer, making it the world's most widespread cancer. Breast cancer has become very common among women and a major reason for death (2, 9). The cause of death in cancer is not the primary tumor, its invasion, and formation of a secondary tumor. As proposed by the English surgeon Stephen Paget in 1889, tumor spreading

depends upon the cancer cell type (the seeds) and invading organs (the soil) (4, 22). Recurrence of breast cancer can invade distant organs commonly in the bone, brain, lung, liver, and also the local region like the chest wall, and lymph nodes (2).

The progress of cancer is a complicated and sequential process of changes, in this way cells gradually start to migrate toward other organs, which is referred to as metastasis (2). Cancer cell metastasis involves the primary tumor cells migrating and reaching other organs leading to the form of a secondary tumor. And the secondary tumor is believed to be the main cause of death. During the progress, additional mutations are generated overtime the period causing the accumulation of mutations in various genes beginning metastasis of cancer cells. Cancer cell gains the various ability of detachment from neighboring cells, mobility, intravasation, invading other tissues, escape mechanism from immune surveillance, and adapts to the microenvironment (17, 22). While the spread of cancer cells several genes get altered, such as activation, inactivation, amplification of genes, and several epigenetic and genetic mutations in somatic cells take place (2, 17).

Various theories have been supposed about the cause of cancer progression, such as epithelial-to-mesenchymal transition (EMT), and stem cell mutations (18, 22). Stroma cells and the microenvironment plays important role in the progression of cancer (17). Various signaling pathways and extracellular matrix are involved in development and metastasis (18, 22).

Subtypes of breast cancer invading organs

Breast cancer subtypes are classified on the bases of gene expression profiling, mainly distinct hormone receptors (HR) and other proteins involved or not involved in each cancer. Major molecular subtypes of breast cancer have been identified, they are triple-negative or basal-like breast, luminal A, luminal B, and human epidermal growth factor receptor 2 (HER2)-enriched breast cancer as per record (33,40).

Luminal A

Luminal A breast cancer is categorized by the high expression of estrogen and progesterone. Luminal A is the most common breast cancer, with almost 40% of cases of all breast cancer worldwide (78). These tumors have diverse mutations at the genetic and transcriptional levels (77). These tumors are HER-2 negative, estrogen receptor (ER) positive, and Erb-B2 receptor tyrosine kinase 2 (ERBB2) negative, high expression of progesterone receptor (PR), low Ki-67, and also regulated gene associated with ER activation (77, 78, 79).

Luminal B

Luminal B breast cancers are characterized by a lower expression of estrogen receptor (ER), and progesterone receptor (PR). In breast cancer, 15%-20% comprises Luminal-B and aggressive phenotype (78, 80). These tumors are ER-positive, have lower PR expression, are HER2-negative, and have a higher level of

Ki67 (78). Research suggests that the luminal-B subtype shows amplified fibroblast growth factor receptor 1 (FGFR1) gene and may contribute to poor prognosis (40).

HER2-enriched

HER2-enriched tumors are characterized by HER2 positive, high expression of ERBB2, and low expression of the luminal-related gene. HER2 accounts for 12%–20% of all types of breast cancers (40, 77). The HER2 and ERBB2, encode a transmembrane tyrosine kinase receptor that binds to its extracellular signal and helps in the initiation of the cascade that causes cell proliferation, differentiation, and survival (77).

Basal Like

Basal-like tumors are ER, PR- negative, and also lack high expression of HER2. The basal-like subtype comprises from 8% to 37% of all breast cancers. Basal-like tumor cells express high levels of myoepithelial markers and they are ER, PR, and HER2 negative. Basal-like cancer cell commonly shows mutations in the tumor protein 53 (TP53) gene (40).

Metastasis of breast cancer to other organs

Previous studies have reported that if cancer metastasizes, different types of tumors show distinct preferences among organs. Organotropism of breast cancer depends upon the subtypes as they show dissimilar tropism. The common targets for breast cancer are bone, lung, liver, and brain (3, 9).

Breast Cancer Liver Metastasis (BCLM)

The common site of metastasis in breast cancer is the Liver. Patient Survival from breast cancer depends upon metastasis and early identification. Metastasis is not a random event; it depends upon the microenvironment. Thus, in the case of liver metastasis, hepatic microenvironment, sinusoidal structure, and also breast cancer subtype plays a vital role in cancer progression (33). *Koo et al.* (81) concluded that according to the metastatic site, breast cancer cell shows different Immunohistochemical phenotypes properties. Also identified, is that ER+, PR+, and HER-2 show a relationship with organ specificity during metastasis. They found that ER-positive, PR-positive, and HER-2-negative were majorly present in the liver metastasis (81). For the seeding of breast cancer cells in the liver, a significant increase in HER2 phosphorylation has been observed (82).

In T1 breast cancer liver metastatic (4TLM), expression of 869 genes upregulation whereas 1,661 genes downregulation were observed. Along with these multiple tight junctions, adhering junctions, and protein expression were either downregulated or missing. The expression of junction proteins like claudin 4, claudin 7, and γ-catenin was found to be downregulated. For 4TLM colonization and growth in the liver, Claudin 2 is crucial as it increases their ability to adhesion to the extracellular matrix by increasing the expression of cell surface molecules $\alpha_2\beta_1$- and $\alpha_5\beta_1$-integrin complexes in breast cancer cells (41, 83)

The study suggests, that POU1F1 transcription factor (Pit-1), C-X-C chemokine receptor type 4 (CXCR4), and C-X-C motif chemokine 12 (CXCL12) aid in the chemotactic movement of cancer cells during metastasis. Pit-1 expression was found to be connected with CXCR4 and CXCL12 expression in a positive manner, in primary tumors of the breast and involved in specific metastasis to the liver (84). In the HER2 type, the risk of liver metastasis is shown to be increased by CXCL12 and CRCR4 through integrin-dependent signaling, as HER2 can upregulate CXCR4 expression. Fibroblast growth factor 13 (FGF13) could promote liver metastasis in triple-negative breast cancer (33, 34). Chemokines expression on the cell surface of breast cancer liver-metastatic cells that recruit immune cells in the secondary tumor site (84). g-catenin is involved in the establishment of liver metastases. g-catenin is involved in linking E-cadherin and actin cytoskeleton and also affects cell differentiation. Loss of g-catenin expression is seen in 4TLM cells (41).

Studies suggest that E-selectin also plays an important role in the progression of breast cancer liver metastasis (BCLM), and induction of E-selectin via tumor necrosis factor-alpha (TNF-alfa) increases its production and also increases the potential of breast cancer to colonize in the liver (33, 85). The tumor microenvironment releases chemokine (C-C motif) ligand 5 (CCL5), which can increase the chance of spreading breast cancer to the liver (33). In the liver, the seeding of breast cancer cells could be eased by E-cadherin. It facilitated the adhesion of breast cancer cells to hepatocytes (33). It was found that the high expression level of CD44 in that cancer cell metastasized to the liver (48). CD44 surface molecule overexpressed on Cancer stem cells (CSCs), CD44 is a cell surface adhesion receptor supposed to be involved in metastasis, invasion, adhesion, and also in apoptotic resistance. Thus, metastasis of breast cancer cells towards the liver also depends upon the Cancer stem cells (CSCs). CD44 expressed by CSCs is believed to have the potential to modulate adhesion, invasion, apoptosis resistance, and metastasis processes. it seems that cell adhesion molecules play vital roles in BCLM (33, 48)

Breast Cancer Lung Metastasis

Basal-like breast cancer (BLBC) is highly prone to metastasize to the lung. 60–70% of Metastatic breast cancer death cases are considered because of lung metastasis. Various studies suggest that the risk of lung metastasis shown higher in the luminal B and basal subtypes classes. Whereas the absence of lung relapse was observed in the luminal A subtype. Cancer stem cells play a vital role in breast cancer lung metastasis, a CD44 present in CSCs may consider having the ability to promote metastasis. *Yae et. al.* (91) found that the lung colonization potential of CD44vC 4T1 mouse mammary tumor cells is much higher than that of CD44v cells due to the increased activity of the cystine transporter xCT induced by CD44v (91).

Yae et. al. (91) found the potential of CD44vC 4T1 mouse mammary tumor cells is very high for lung metastasis. Alternate splicing of CD44 mRNA14 is regulated by epithelial splicing regulatory protein 1 (ESRP1) highly expressed in CD44v+ 4T1 cells, embryonic stem (ES) cells, and induced pluripotent stem (iPS). CD44v+ stem-like cells dominantly inhabit and enlarge within the lung (52, 91). CD44v+

lung metastases formed by 4T1 cells showed high levels of reduced glutathione (GSH). GSH plays a vital role in maintaining Intracellular redox homeostasis. As the activity of GSH-related enzymes like γ-glutamyl cysteine ligase (GCL) and γ-glutamyl-transpeptidase (GGT) is found to be high, and so GSH in some tumor cells is high (61). Signifies that CD44v provides resistance from reactive oxygen species resistance to cancer cells by elevating GSH synthesis (52).

CCL2 can cause overexpression of toll-like receptor 4 (TLR4) ligands in the lung, which can increase the cancer cell survival in the target organ. The TLR4-dependent innate immune system plays a critical role in pre-metastatic finding place in the lung for growth (62). Gong et al. found that radiation therapy causes pulmonary injury and that induces CXCL12-CXCR4 overexpression. CXCL12-CXCR4 overexpression leads to an increased number of metastatic nodules in the lungs (49).

Studies demonstrated that in breast cancer metastasis, the abnormal activation of the Notch signaling pathway contributes to metastasis by primarily modulating EMT and angiogenesis (48). In addition, BCSCs that spread from primary sites to distant microenvironments establish lung niches that are associated with Notch (48). A study found knockdown of notch-1 inhibits the formation of EMT-induced metastatic lung nodules, in salivary adenoid cystic carcinoma cells. The regulator mechanism of Notch signaling is not clear in breast cancer metastasis (49). Vascular cell adhesion molecule-1 (VCAM-1) is involved in the process of metastasis. Studies have shown that VCAM-1 is abnormally expressed in breast cancer cells and interacts with its α4β1integrin ligand. Binding between VCAM-1 and α4β1integrin seems to be involved in the metastasis of breast cancer cells, such as lung metastasis. It also interacts with fibronectin and is expressed in NK cells, monocytes, and other immune cells. It has been founded that the pulmonary parenchyma which contains collagen and elastin fibers acts as a suitable soil for the seeding of VCAM-1-expressing breast cancer (49, 87).

BLBC markers such as EGFR and FOXC1 have also seemed to regulate lung metastasis. The pathogenesis of human basal-like breast cancer (BLBC) is not well understood and patients with BLBC have a poor prognosis. The expression of the epidermal growth factor receptor (EGFR) and nuclear factor-κB (NF-κB) is well-known to be upregulated in BLBC. The forkhead box C1 (FOXC1) transcription factor, an important prognostic biomarker specific for BLBC, is induced by epidermal growth factor (EGF) and is critical for EGF effects in breast cancer cells. How FOXC1 is transcriptionally activated in BLBC is not clear (88).

Breast Cancer Bone metastasis (BCBM)

Almost 50% of metastasis and 70% of reoccurrences of breast cancer cells invade to bone (65). Evidence supports breast cancer cells' progress in bone by degrading bone cells through activating osteoclast. Thus, breast cancer cells can team up with osteoclasts and play a vital role to cause osteolytic bone metastases (89). Metastasis of cancer cells to bone results in degradation of bone cells, accompanying pain and loss of function. Breast cancer cells also distraught normal remodeling of bone, that bone formation, and bone resorption are no longer coupled. Study shows that osteoclast activity increases possibly due to

increased osteoclast genesis. It is also considered that osteoblast is involved in imbalance (65, 90).

During metastasis of breast cancer cells, the incidence of apoptosis in osteoblast cells increases, it has been observed in hFOB 1.19 (human osteoblast cell line). Apoptosis leads by various pathways such as TUNNEL, and caspase activity (90). As soon as, breast cancer cells from the primary site reach the bone adapts microenvironment of bone marrow. Inhabitant metastatic breast cancer cells secrete an excess of osteolytic factors (64). RANKL pathway plays a vital role in the process of osteolysis. In osteoblast, parathyroid hormone-related protein (PTHrP) upregulates the RANKL expression whereas down-regulates osteoprotegerin (OPG) expression (90). NIH-PA ability of RANKL-dependent and independent activation of osteoclast formation and bone resorption. Monocytes/macrophage lineage-derived cell or direct osteoclast activation takes place by tumor for bone reabsorption can be independent of RANKL. The activation of bone resorption and the osteoclastogenesis process encourage RANKL in presence of colony-stimulating factor 1 (CSF1) (64).

IL11, CTGF, CXCR4, and MMP-1 are overexpressed genes in bone metastatic populations and show different activity. IL11 induces osteoclast formation from precursor cells in the bone marrow. Osteoclasts cause bone resorption in osteolytic bone metastases. Few studies say overexpressing of IL11 only is not sufficient to enhance bone metastasis formation, and founds that along with IL11, osteopontin (OPN) is also overexpressed continuously in metastatic cells. So, might be that IL11 collaborates with osteopontin (OPN) during the bone metastasis process. Osteopontin (OPN) is consistently overexpressed in highly metastatic cells (65).

In addition, these inhabitant stromal cells in the bone marrow can support the differentiation, proliferation, and survival of cancer cells. In various myeloma, the production of osteolytic cytokines is observed to be increased in those stromal cells which express vascular cell adhesion molecule (VCAM-1) T cells that express RANKL and secrete TNF-α, which are known to be mediators of bone resorption, which can be triggered by metastatic tumor cells. Tumor-derived parathyroid hormone-related protein (PTHrP) and IL-8 are considered to activate transient T cells, which increases bone resorption (64). In 1970s research it was reported that prostaglandins could resorb fetal bone in tissue culture and aspirin, and indomethacin which are inhibitors of a COX-1 and COX-2 respectively can prevent osteolysis in tissue culture. Monocytes can be induced to transform into mature osteoclasts in osteolysis by triggering PGE2 signaling through the EP4 (66).

Breast Cancer Brain Metastasis

In the case of metastatic breast cancer patients with HER2-positive tumors, the occurrence of brain metastases ranges from 26% to 48% (68). To invade the brain cell, breast cancer cells first need to attach to the endothelial cells of the brain, and then they can cross the Blood-brain barrier (BBB). Blood-brain barrier constitutes the endothelium and the surrounding cells. Anatomically, BBB is an inimitable structure, which makes a physical barrier formed by brain

microvascular endothelial cells, tight junctions and adhering junctions between the brain endothelial cells, and perivascular elements including pericytes, astrocytes, oligodendrocytes, and the basement membrane (70, 73). It makes a complex structure that makes a physical barrier for cells and molecules, that strictly regulates the flow of ions, nutrients, and cells into the brain according to their molecular weight and charge. Also regulates the diffusion and maintains homeostasis in brain parenchyma by highly selective transport mechanisms facilitating flux of solutes and molecules and a metabolic barrier is also present, which contains very specific enzymes (73).

A widely accepted theory for brain metastasis is that tumor cells attach to the endothelium layer triggering the withdrawal of the endothelium due to which vascular basement membrane gets exposed to the tumor cell (70). The Brain microvascular endothelial cells (BMEC) forming the BBB are different from the systemic endothelial cells (68). Controlling the brain fluid environment by establishing an active permeability barrier and transport system (70, 73).

COX-2, EGFR ligand, ANGPTL4, and LTBP1 are known to encourage disruption of the endothelial layer and enhance the change of metastasis to the brain. Studies say if COX-2 and EGFR ligand HB-EGF are expressed it increases the extravasation of cancer cells across the capillaries (70). The α2,6-sialyltransferase (ST6GA LNAC5) also found to be specific in brain metastasis, allows the cell to cell interaction between cancer cells to brain endothelial cells (70, 74). A ligand Heparin-binding EGF (HBEGF) of EGFR was identified specifically in brain metastasis, and HBEGF was shown to raise the migration and invasiveness of cancer cells. Cyclooxygenase-2 (COX2) enzyme was also found in brain metastasis, nuclear EGFR upregulates COX2. COX2 synthesizes prostaglandins and plays a vital role in permeabilizing the BBB in response to inflammation (74). Tumor growth is preceded by the development of new blood vessels, which provide a pathway for metastasis and nutrients essential for growth. Vascular endothelial growth factor A (VEGF) is a key angiogenic mediator that stimulates endothelial cell proliferation and regulates vascular permeability. breast cancer patients that have tumor cells secreting high levels of VEGF may have a higher risk of developing breast cancer metastasis to the brain (70, 92).

Kodack et. al. (75) developed a mouse model using an orthotopic xenograft of BT474 cells of HER2-amplified breast cancer brain metastasis. They found that the HER2 inhibitor and an anti–VEGF receptor-2 (VEGFR2) antibody in combination effectively slow down the growth of tumors in the brain (75). The vascular endothelial growth factor (VEGF) shows a potential role in angiogenesis in breast cancer metastasis to the brain, considered a major angiogenic factor (69). Bohn at. el. (76) has observed that in lesions Ang-2 expression increased and vascular permeability has increased. Ang-2 is up-regulated due to the cyclooxygenase-2 (COX-2) enzyme, which induces its expression. In a healthy brain, Ang-2 is hardly present but VEGF has been revealed to induce Ang-2 expression in the brain, which leads to resulting in both brain vasculature remodeling and changing the properties of the endothelium. Disturbance in the Vascular system happens in hypoxia which induces the formation of HIF-1 (76).

Conclusion

Metastasis remains the major obstacle to finding a cure for breast cancer. Worldwide researchers are working on the abstract outline of breast cancer metastasis by analyzing molecular basis related to metastasis, roots, and progression of it, thus trying to establish a deeper knowledge of the area. Subtypes of breast cancer display diverse molecules, they differ in their disease progression, metastatic spread, and response to therapy. Elucidation of molecules that are associated with those signaling pathways that facilitate the stages of the invasion of breast cancer cells can be targeted to block the migration of tumor cells into other organs. The findings mentioned in this review paper are considered to be positive in designing novel therapies, customizing treatments, and developing new drugs to battle breast cancer in the future.

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Conflict of Interest

We wish to confirm that there are no known conflicts of interest associated with this publication.

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