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REVIEW ARTICLE

Molecular pathways of common breast cancer metastases and the distinguishing features of triple-negative breast cancer

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ABSTRACT

Breast cancer is the most common type of female cancer in Turkey, and metastasis is the most important cause of death, as in other solid organ cancers. Triple-negative tumors constitute 15-20% of breast cancer patients. Within three years after the development of the primary tumor, the tumor spreads to other organs. Breast cancer tends to spread to distant organs, such as bone, liver, brain, lung, and adrenal gland, either through regional lymph nodes or vascular channels. This condition, defined as the tendency to metastasize to specific organs, is called organotropism. Triple-negative breast cancer is a heterogeneous breast cancer subtype showing organotropism for the brain and the lungs. Identifying the molecular changes that may cause tropism for various regions and organs in non-metastatic tumors at the time of diagnosis is vital to developing targeted therapies and achieving longer overall and disease-free survival. In this review, we aimed to summarize the pathogenesis of breast cancer metastasis, the molecular changes involved in the metastatic process, and organotropism, as well as to emphasize the distinguishing features of triple-negative breast cancer in terms of metastatic organotropism.

Keywords: Breast cancer, triple-negative breast cancer, metastasis, molecular pathway, organotropism

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INTRODUCTION

Breast cancer is the most common type of female cancer in Turkey (1). Among all breast cancer subtypes, triple-negative breast cancer (TNBC) is a very heterogeneous subtype and constitutes 15-20% of breast carcinomas (2). These tumors are characterized by negativity for hormone receptors and HER2 gene amplification. Metastasis is the most important cause of death for cancer patients, including breast cancer (3). TNBCs, which are particularly predisposed to lung and brain metastases, have a lower risk for bone metastasis and differ from other breast cancer subtypes in terms of organotropism (4-6). In general, breast cancer has an aggressive clinical course in 10-15% of patients in whom the tumor spreads to other organs within three years after the development of the primary tumor (5). Metastasis, cancer's most distinguishing and challenging feature, significantly impedes treatment success (6). Although the metastatic process and associated molecular mechanisms are not fully understood, molecular studies have led to increased knowledge of the biology of metastasis and the emergence of new therapeutic targets. Metastatic breast cancer, irrespective of its subtype, tends to spread to regional lymph nodes and distant organs, such as bone, liver, brain, lungs, and adrenal glands (7). In metastatic breast cancer patients who respond less to chemotherapy, the 5-year survival rate is approximately 20% (8). It is crucial to understand metastatic organotropism, the steps of metastasis, and the molecular pathways involved in these processes to predict and prevent breast cancer metastasis and to develop more effective treatments, especially in metastatic TNBC cases where treatment options are limited.

Metastatic process in breast cancer

Metastasis is defined as the spread of cancer cells to adjacent tissues or distant organs. The heterogeneous nature of breast cancer and its distinct metastatic mechanisms make it difficult to treat (9). In general, breast cancer metastasis develops by the following processes, which are also valid for other solid organ cancers (10);

- Separation of neoplastic cells from the extracellular matrix (ECM), initiation of invasion and migration by crossing the basement membrane: The metastatic process begins with the separation of adjacent cells from each other and the basement membrane, as a result of disruption of the connection of cancer cells to ECM through cellular adhesion proteins, such as integrins. Neoplastic cells invade the surrounding tissues with proteolytic enzymes that degrade ECM.

- Intravasation: Cancer cells attach to the vessel walls, invade, and enter the lumens of lymph or blood vessels (Figure 1).

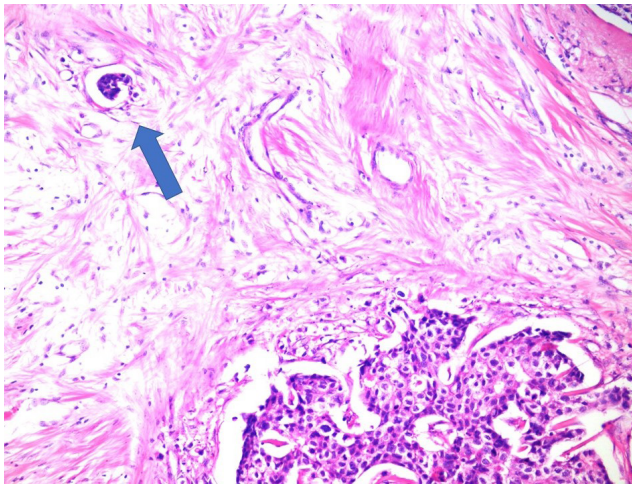

Figure 1. Lymphatic space invasion around invasive breast carcinoma (arrow, H&E, x200).

- Spread of tumor cells to other organs via blood or lymphatic circulation: Cancer cells must develop resistance to anoikis (a form of programmed cell death) to survive in circulation.

- Arrest, adhesion, and extravasation at sites of metastasis: Cancer cells, whose cell cycle stops before being extravasated at the site of metastasis, adhere to the capillary walls in target organs.

-Metastatic tumorigenesis: Since metastasis is a complex and multistep process, metastatic cells need the ability to survive, invade, and form new tumors in different conditions. In addition, cancer cells must be able to evade the immune system and apoptosis to survive. Cancer cells that gain these features can form a metastatic mass (Figure 2).

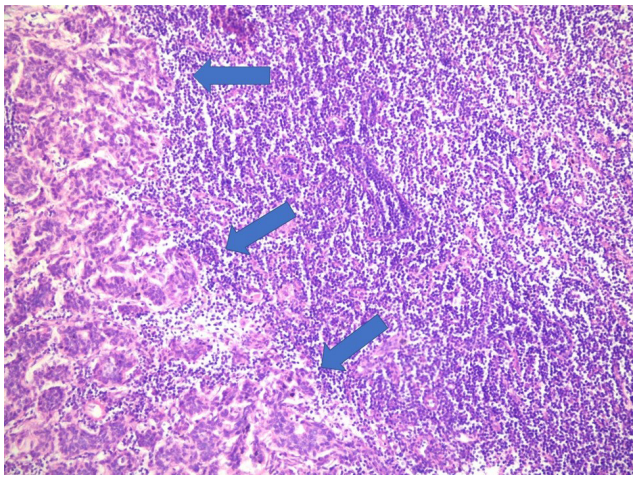

Figure 2. Invasive breast carcinoma metastasis in axillary lymph node (arrows, H&E, x200).

Molecular mechanisms involved in breast cancer metastasis

Critical proteins in cancer cell motility and survival are integrins. Cancer cells bind to the ECM through these heterodimeric proteins, which consist of α and $\alpha\beta$ subunits (11). It has been reported that integrin $\alpha 2\beta 1$ expression decreases in poorly differentiated breast cancer cells (12). Specific integrins, such as integrin $\alpha 3\beta 1$, are associated with matrix metalloproteinase (MMP)-9 activity. This relationship provides the ability to invade, metastasize, and reduce ECM components for neoplastic cells (13). E-cadherin has also been shown to play an essential role in cell-to-cell adhesion and cancer metastasis (14). It has been shown that a decrease in E-cadherin level in breast cancer is associated with increased metastatic potential, and mutation in the E-cadherin gene (CDH1) causes increased ability for invasion in lobular breast carcinoma (15). In addition, decreased expression of E-cadherin is a crucial indicator of epithelial-to-mesenchymal transition (EMT), a cellular process that plays a critical role in cancer progression and metastasis (16).

It has been found that epithelial markers, such as E-cadherin, occludin, and cytokeratin, show loss of expression. In contrast, the expression of mesenchymal markers, such as vimentin and N-cadherin, increases in the EMT process (3). The transcription factor-associated proteins, which are expressed by genes such as TWIST, SNAIL, SLUG, ZEB1, and ZEB2, increase EMT by suppressing E-cadherin expression in cancer cells (17).

TGFβ gene has also been shown to act as an EMT inducer (18). TGFβ is a tumor suppressor gene in the early stages of carcinogenesis. However, exposure of cancer cells to TGFβ protein in later stages causes the transformation of epithelial phenotype into mesenchymal-like phenotype and increases the metastatic potential (19). The TGFβ pathway has two types of signaling: SMAD-dependent and SMAD-independent signaling. It has been shown that SMAD2 and SMAD3 are up-regulated in the mammary epithelium, and EMT is induced due to SMAD-dependent signaling (20). TGFβ signaling may also occur via non-SMAD signaling pathways, such as the PI3K/AKT pathway. Both SMAD-dependent and SMAD-independent pathways have been shown to control transcription factors that mediate EMT, including TWIST, SNAIL, and SLUG (21).

Concerning tumor metastasis, angiogenesis has been investigated extensively, and it has been shown both in clinical and experimental studies that breast cancer is an angiogenesis-dependent cancer (22). Factors that increase angiogenesis have been identified, among which vascular endothelial growth factor (VEGF) shows the most effective activity (23). VEGF gene induces endothelial cell proliferation, aids in new vessel formation, and controls vascular permeability. In the process of new blood vessel formation, VEGF activates receptors VEGFR1 and VEGFR2 in endothelial cells, stimulating endothelial cell motility, vascular permeability, cell survival, and proliferation (24). The increase in vascular permeability, which VEGF causes, facilitates the metastatic spread of cancer cells (25). The activity of VEGF in inducing angiogenesis has been demonstrated and is recognized as a factor that increases the aggressiveness of breast cancer. In addition, VEGF signaling is also known to have several non-angiogenic functions. It is suggested that the VEGF pathway increases cell survival and migration by avoiding apoptosis through AKT and ERK signals in breast carcinoma cells (26).

Organotropism in breast cancer metastasis

Primary tumors tend to metastasize to specific sites and organs. The tendency to spread to particular organs is a nonrandom process known as metastatic organotropism (27). In recent years, the mechanism of metastatic organotropism has been defined. Organotropism is determined partially by cancer cell-specific pathways. Genetic mechanisms that mediate organ-specific metastasis and autonomous mechanisms have also been identified in organ tropism. For example, chemoattractants in metastatic organs can recognize cognate chemokine receptors expressed in cancer

cells (28). Organotropism is regulated by many factors, such as subtypes of related cancer, molecular characteristics of cancer cells, host immune system, microenvironment, and interactions with local cells (7).

The host microenvironment can be modified to create a pre-metastatic niche (PMN), a supportive environment for metastatic tumor growth before a tumor spreads to that area. PMN is regulated by factors and exosomes secreted from the tumor cell, aggregation of cells that do not belong to this region, and host cells (29). In addition, tumor cells can interact with the ECM of the host tissue to facilitate metastasis to specific sites. This theory, known as the "seed and soil" theory, has been proposed by Steven Paget to describe site-specific metastasis. According to this theory, the ability of tumor cells to initiate growth largely depends on the communication between metastatic tumor cells and the host microenvironment (30).

There are many factors affecting organotropism in breast cancer metastasis. These include histologic and molecular subtypes of breast cancer, genetic alterations, gene expression features, micro-RNAs, exosomes, stem cell-like molecular features, circulating tumor cells, circulating cancer stem cells, and the immune system (7).

Bone metastasis

Bone is a region where 70% of breast carcinomas metastasize, and metastases frequently occur as osteolytic type (7). Although all molecular subtypes of breast cancer are prone to bone metastases, luminal tumors (>80%) develop bone metastases at a higher rate (31). The group with the lowest risk for bone metastasis is TNBC, which significantly overlaps with the molecular basal-like subtype (32).

Among molecular changes that contribute to the tendency of breast cancer to form bone metastases, integrin complexes play significant roles, such as tumor cell adhesion and osteolytic tumor growth (7). With the effect of the TGFβ-SMAD4-IL11 signaling pathway and HIF1α, both VEGF activation and CXC chemokine receptor 4 (CXCR4) activation occur, which causes a predisposition for the development of bone metastasis (33). Growth factors such as IGF1, PGE2, PDGF, and FGF2, interleukins such as IL1 and IL-6, PTHrP, OPN, Heparanase, RANKL-RANK pathway, and Src-dependent pathways are also associated with the development of bone metastasis (7).

Liver metastasis

The most common site of metastasis for all solid organ cancers is the liver. It is also the second most common site (30%) where breast cancer metastasizes (34). Metastatic masses formed in the liver by breast cancer are larger and more numerous than lung cancer. This suggests that the liver has a favorable microenvironment for breast cancer metastasis (35).

Liver metastasis was found to be associated with ER expression, high Ki-67 proliferation index, and luminal B subtype (34). It has also been shown that the beta-catenin-independent WNT signaling pathway plays a role in the development of liver metastases in breast cancer patients (35). In addition, the downregulation of ECM genes is an essential factor for liver metastasis of breast carcinoma. The other molecular pathways include CXCR4/CXCL12 chemokine and chemokine receptor interaction, integrin complexes such as IL-6, α2β1 and α5β1, N-cadherin, HIF-regulated LOX, OPN, VEGF, and TWIST genes (7).

Brain metastasis

Brain metastases develop in 10-30% of breast cancer patients (36). Younger age, poorly differentiated tumors, HER2-enriched subtype, and luminal B subtype are associated with an increased risk of brain metastasis. Still, the subtype that most commonly metastasizes to the brain is TNBC.

Molecular changes that play a role in the tendency of breast cancer to form brain metastases include the effect of ST6 N-Acetylgalactosaminide alpha-2,6-sialyltransferase (the protein product of ST6GALNAC5 gene) in crossing the blood-brain barrier and expression of cancer stem cell markers, Nestin, CD133, and CD44 in tumor cells. Cytokines, such as MMP-1 and MMP-9, are also crucial as they act in transendothelial migration. In addition, growth factors VEGF and HBEGF, CXCR4 chemokine and its receptor, CK5, IL-8, Ang-2, COX2, and L1CAM are associated with developing brain metastasis (7).

Lung metastasis

Considering the molecular subtypes of breast cancer, basal-like tumors that make up the majority of TNBCs, as well as luminal B tumors, have a more aggressive clinical course and a higher rate of metastasis to the lung (38). Similarly, when histological subtypes are considered, infiltrating ductal carcinoma with a triple-negative phenotype is associated with a higher risk for lung metastasis (39).

One of the molecular changes suggested to be responsible for the tendency of breast cancer to metastasize to the lung is the attachment of tumor cells to the lung capillaries via MMP-1, MMP-2, and COX2 as a result of the effects of TGFβ, EGFR, EREG, and VEGF gene products and their receptors (7). Lung-derived bone morphogenetic proteins (BMP) are known as the source of the lung's antimetastatic signal. GALNT and Coco, which are BMP inhibitors, neutralize these signals and allow metastatic breast cancer cells to colonize in the lung (40).

Regional lymph node metastasis

Lymph node metastasis is a predictive factor for distant organ metastasis and is a poor prognostic feature (41). Among breast cancer subtypes, luminal and HER2-enriched subtypes show a higher correlation with lymph node metastasis (42). The presence of lymphovascular invasion and a high Ki-67 proliferation index are essential indicators of the metastatic potential of neoplastic cells.

It has been shown that four members of the kallikrein (KLK) family (KLK10, KLK11, KLK12, and KLK13) are up-regulated, and the B cell receptor signaling pathway is down-regulated in breast cancer cases with lymph node metastasis (43).

The distinctive molecular features of triple-negative breast carcinomas

The heterogeneity of TNBC has been explored by Lehmann et al. (4), who subdivided these tumors into four molecular subtypes: basal-like 1 (BL1), basal-like 2 (BL2), mesenchymal (M), and luminal androgen receptor (LAR). Among these subtypes, BL1 represents the majority of TNBCs, having TP53 mutations in more than 90% of cases and a high frequency of homologous recombination DNA repair deficiency (HRD) related mutations. The BL2 subtype also shows a high mutation rate in TP53 and HRD-associated signatures. BL1 and BL2 subtypes constitute most tumors with germline and somatic BRCA1 mutations. On the other hand, the mesenchymal subtype is characterized by activation of the PI3K pathway and the LAR subtype is characterized by mutations in PIK3CA, AKT1, NF1, GATA3, and CDH1 genes (44).

CONCLUSION

Metastatic tumors show mutational similarities with their primary site and may contain different mutations. This phenomenon indicates that new mutations can develop during the metastatic process (45). In terms of targeted therapy, detecting mutations in metastatic tumors is considered as a more rational approach. Although it is known that the probability of pathological complete response after neoadjuvant therapy is high in TNBCs, the probability of brain and lung metastases within three years after the diagnosis is higher than in other subtypes (5, 6). Nevertheless, the identification of molecular changes that can cause tropism to develop for various regions and organs in non-metastatic tumors at the time of diagnosis will help us to develop targeted therapies and achieve longer survival for breast cancer patients.

Declarations

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