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Organ Specificity Nature of Breast Cancer Metastasis

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Abstract

Breast Cancer (BC) continues to be a prevalent malignancy affecting women worldwide. BC exhibits diverse patterns of metastasis, displaying a preference for various organs. This variability leads to differences in patient prognosis and responses to treatment. The primary sites of metastasis in BC are the bone, lung, liver, and brain. The molecular mechanisms underlying the organ-specificity of BC metastasis are still a subject of ongoing investigation. In recent years, the emergence of novel genomic techniques has revolutionized our understanding of breast cancer metastasis and provided a promising foundation for the development of more effective therapeutic strategies.

Keywords: Breast cancer; Organ-specific markers of metastasis; Progression

Introduction

Breast cancer stands as the most frequently diagnosed malignancy among women globally, projected to represent approximately a quarter of all new female cancer cases in the near future. While the incidence remains high, advances in early detection and improved therapeutic strategies have contributed to a gradual decline in mortality rates in developed countries. Nevertheless, approximately 10% of women still receive a diagnosis of primary disseminated breast cancer, and the 5-year survival rate for these patients is only 25% .

It's essential to note that it's the development of metastases in breast cancer, rather than the primary tumor itself, that accounts for over 90% of cancer-related deaths. Recent studies indicate that patients with metastatic breast cancer experience bone metastases in up to 60% to 75% of cases, lung metastases in up to 32% to37%, liver metastases in up to 32% to 35%, and brain metastases in up to 10% of instances. Metastases to the gastrointestinal tract in breast cancer occur with a frequency ranging from 4% to 8%, while metastases to the adrenal glands are rare.

The identification of ovarian metastases poses a contentious issue concerning the organ-specificity of distant metastasis in breast cancer. The reported incidence of ovarian metastases in breast cancer patients varies from 3% to 47% and is primarily ascertained through post-mortem examinations and preventive or therapeutic oophorectomies. Furthermore, it has been observed that breast cancer patients are 3 to 7 times more likely to develop primary ovarian cancer rather than ovarian metastases. Additionally, metastatic ovarian lesions in breast cancer can sometimes exhibit clinical and histological characteristics that closely resemble those of primary ovarian cancer. In some cases, they even lose the typical expression levels of Estrogen Receptor (ER) and Progesterone Receptor (PR).

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Consequently, the organ-specific heterogeneity of breast cancer metastasis results in varying treatment responses and patient prognoses. For instance, the 5-year overall survival rate in the presence of bone metastases is 22.8%, whereas in the case of lung metastasis, it stands at 19%, and for liver metastasis, it drops to 13% . Ovarian metastasis in patients with breast cancer is associated with a median OS ranging from 16 to 38 months, and a 5-year survival rate varying from 6% to 26% . However, the presence of brain metastasis in breast cancer patients is linked to the shortest life expectancy.

Metastatic breast cancer

Irrespective of the tumor type, the process of tumor cell dissemination precedes the initial stages of the metastasis cascade. This dissemination process encompasses the initial facets of invasion and metastasis, enabling malignant tumor cells to acquire the properties required for them to exit the primary site and journey to distant tissues. One of the pivotal premises driving scientific exploration into the organ-specificity of tumor metastasis, particularly in the context of breast cancer, is the notion that the characteristics of the primary tumor cells and their subsequent spread determine distinct metastatic properties, organotropism, and responses to therapy. In vitro studies reveal that metastatic tumor cells often migrate individually. However, in vivo observations suggest that the dissemination of metastatic tumor cells within the body frequently occurs in clusters, with groups of tumor cells moving collectively.

The immediate process of tumor metastasis is a complex and sequential progression involving multiple stages: local invasion with the exit from the adjacent tissues of the primary tumor, infiltration into blood or lymphatic vessels (intravasation), survival within the bloodstream as Circulating Tumor Cells (CTCs), departure of CTCs from the circulatory system (extravasation), adaptation to the microenvironment as disseminated tumor cells, transformation into cells instigating metastasis, culminating in the formation of macrometastases.

Metastatic cancer encompasses a diverse array of cells with varying genetic and phenotypic characteristics, leading to differences in progression, metastasis, and resistance to drugs. Numerous genes govern invasive potential, with the notion that a specific genetic signature responsible for metastasis can be identified within primary breast tumor cells . Specific mutations may contribute to invasion and metastasis. Clinical genomics studies have demonstrated that TP53, CDKN2A, PTEN, PIK3CA, and RB1 are the most prevalent genes that undergo somatic alterations in metastasis .

Characterizing biomarkers in uncommon patterns of breast cancer metastasis

The research conducted by Kutasovic J.R. in 2018 provided an extensive account of the clinical, pathological, and molecular characteristics of breast cancer metastases to gynecological organs. The study encompassed data from 54 female patients diagnosed with breast cancer and experiencing metastasis to gynecological tissues between 1982 and 2015. In total, these 54 patients presented with 258 metastatic foci, averaging approximately five metastases per patient (ranging from 1 to 11). The gynecological organs most frequently involved were the ovaries (46 out of 54, 85.1%), fallopian tubes (29 out of 54, 53.7%), and the uterus (20 out of 54, 37%). Regrettably, the median survival of these patients was a mere 1.95 years.

Genomic characteristics of organ-specific metastasis in breast cancer

Understanding the intricacies of gene activity involved in metastasis has been a pivotal objective over the past few decades. Alongside the advancements in high-throughput technologies in experimental and clinical oncology, there has been a surge in the identification of novel prognostic gene markers (gene signatures or differentially expressed genes) capable of predicting the risk of metastasis in breast cancer patients. This section compiles current insights into the exploration of the genomic profile, encompassing expression characteristics, active signaling pathways, and Copy Number Alterations (CNA), in the context of organ-specific metastasis in breast cancer.

In 2017, a comprehensive meta-analysis was conducted to investigate the expression patterns of potential marker genes associated with metastatic breast cancer. This analysis collated relative gene expression data from 12 studies encompassing primary breast cancer and metastatic breast cancer, extracted from the Genevestigator database (Nebion). The results of this meta-analysis were cross-referenced with literature data concerning putative markers of metastatic breast cancer, verifying the consistency of their reported differential expression.

The findings from this study suggest that VCAM1 appears to be a promising candidate as a marker for metastatic breast cancer. However, it necessitates validation through gene expression analysis in metastatic tissue samples, ensuring immune cell contamination is effectively avoided. Elevated expression of the FZD3 gene was observed in metastatic tumors compared to primary tumors, a trend substantiated by existing literature. Significant differences in gene expression, particularly DEPDC1, NUSAP1, FOXM1, and MUC1, between metastatic tissues and primary breast tumors, may serve as prognostic markers for metastatic progression. Notably, COX2 gene expression was significantly diminished in metastatic tissue compared to both primary tumors and normal tissue, making it a valuable marker for differential diagnosis in metastatic cancer. RRM2 gene expression exhibited a decrease during the progression of metastatic breast cancer, suggesting its utility as a marker for monitoring progression. This investigation also identified MMP1, VCAM1, FZD3, VEGFC, FOXM1, and MUC1 genes as potential markers for breast cancer occurrence due to their significant differential expression in breast neoplasms compared to normal tissue .

In the same year, an intriguing study aimed at the comprehensive identification of molecular biomarkers in breast cancer metastases to the brain was published. This research involved a comparison of expression profiles among three cases of breast cancer with brain metastasis, 16 cases of non-metastatic breast cancer, and 16 cases of primary brain tumors. The analysis identified distinctive overexpression of genes encoding BCL3, BNIP3, BNIP3P1, BRIP1, CASP14, CDC25A, DMBT1, IDH2, E2F1, MYCN, RAD51, RAD54L, and VDR in metastatic breast cancer with brain metastases when compared to non-metastatic breast cancer and brain tumors. Network analysis highlighted key pathways such as Akt, ERK1/2, NFkB, and Ras at the predicted stage of activation in metastatic breast cancer. Genes with reduced expression that were common to metastatic breast cancer and brain tumors included JUN, MMP3, TFF1, and HAS2, which are markers of cell line invasion, among others . In 2019, research focused on identifying alternative pathways between primary breast cancer and liver-metastatic breast cancer using microarray analysis data. Gene expression microarray data was extracted from the GEO database, comprising 153 samples from the primary breast cancer group and 43 samples from the liver metastasis breast cancer group. Due to an imbalance in sample numbers between the primary cancer and metastatic cancer groups, a bootstrap analysis was carried out, randomly selecting 43 samples from each group to create a balanced analysis set, with a total of 10 repetitionsThe Breast International Group (BIG) has conducted genomic and transcriptomic analyses of primary breast cancer and its associated metastases. The AURORA study's primary objective is to investigate the processes underlying the metastatic recurrence of breast cancer by performing multi-omic profiling of paired primary tumors and early metastases. This research involved data from 381 breast cancer patients. It uncovered the driver roles of somatic GATA1 and MEN1 mutations. Metastases were found to be enriched with mutations in ESR1, PTEN, CDH1, PIK3CA, and RB1, as well as amplifications in MDM4 and MYC and a deletion in ARID1A. Clonality changes were observed in the ERBB2 and RB1 driver genes .

In 2021, a study exploring the role of TFF1 in the risk of breast cancer metastasizing to the bone was published. This retrospective analysis involved 90 surgically resected breast cancer specimens. TFF1 was identified as a closely correlated marker of bone metastases for ER+ breast cancer primary tumors. To substantiate this observation, the study delved into the function of TFF1 during ER+ breast cancer oncogenesis and its metastasis to the bone, utilizing an MCF7 model with both enhanced and inhibited TFF1 function. The study revealed that TFF1 expression in primary tumors can modulate the growth of ER+ breast cancer .

Furthermore, in 2021, a study investigating the gene expression profile of metastatic breast cancer in relation to the target organ was published. This retrospective study encompassed 184 metastatic tumor samples from 176 breast cancer patients.

Conclusions

The progression of metastatic disease presents a significant therapeutic hurdle, characterized by the presence of unpredictable tumor heterogeneity, which exists not only between patients but also within each individual tumor. This complexity poses a substantial challenge in the quest for a rational therapeutic strategy. The wealth of information gathered on the genomics of breast cancer in the past decade has notably enhanced our comprehension of intratumoral heterogeneity, which is increasingly recognized as a key driver of cancer progression. However, it's important to acknowledge that the knowledge and understanding of metastatic breast cancer lags behind that of primary cancer.

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