

**Mini Review**

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Overexpression of HER2 Gene Responsible for Breast Cancer Progression and Metastasis

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Breast cancer is a common type of cancer that grows from breast tissue occurring both men and women, but it is much more common in women. Altered mechanisms of HER2 gene have been involved in the carcinogenesis and prognosis of breast cancer. HER2 gene overexpression is often observed in breast cancer and its upregulation contributes to tumor progression. HER2 gene amplification is a key factor in early malignant transformation. HER2 promotes cell motility in metastatic cells and cause metastasis in several organs. Metastatic forms of cancer are responsible for the deaths of most patients worldwide. Accurate HER2 gene expression analysis is important in determining appropriate patients for targeted therapies. So HER2 is the most significant oncogene that is liable for breast cancer.

Keywords: Breast cancer; HER2 gene; Oncogene overexpression; Metastasis

Introduction

Breast cancer usually occurs in women. Breast cancer is a set of different diseases, which can be divided into subtypes with diverse pathological and molecular features like other cancers. To understand the processes of breast cancer development, it is important to understand specific genes that are valuable in diagnosing malignancy degrees and individual breast cancers [1]. The metastatic form of breast carcinoma remains the main cause of death in most patients. Breast cancers are classified into five distinct subtypes, luminal A/B, HER2-positive (HER+), basal-like, claudin-low, and normal breast-like, based on the expression levels of estrogen and progesterone receptors (ER and PR), HER2, cytokeratins 5/6, and claudins 3/4/7 [2-5]. HER family of growth factors plays a vital role in breast growth and mammalian carcinogenesis. However, HER2 (Human Epidermal Growth Factor Receptor 2) has no ligand of its own, it forms heterodimers with ligand activated EGF receptor, HER3 and HER4 [6]. HER2 (also known as erbB-2 or neu), a proto-oncogene which is a member

of the type I family of tyrosine kinase growth factor receptors that are found in the cell membrane [7]. Alterations in the key mechanisms of the HER2 gene have been revealed in approximately 25% of human breast cancers which confers a more invasive tumor phenotype and associates with a poor prognosis in patients with this disease [8, 9]. In cancer cells, overexpression of HER-2 mediated unregulated cell proliferation, invasion, and metastases. The HER2 gene overexpression is reported in 20%–25% of invasive breast cancers. In case of survival rates are worse in patients whose tumors carry the HER-2 gene aberrant expression compared to normal patients [7]. HER2 is gene expression is higher in tumors, but it is found in very low levels in normal tissue. Amplification of HER2 oncogene was first identified by Slamon, in a study of 189 primary human breast cancer by southern analysis. In the following studies using tissue-derived DNA samples, HER2 overexpression was found at the protein level in human breast cancer cells. HER2 overexpression in breast tumorigenesis considered HER2 gene as a breast tumor-promoting factor with great importance [10].

Hence HER2 diagnosis has become a crucial part of the clinical evaluation of all patients with breast carcinomas. The American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) released guidelines for laboratory testing of HER2 status in breast cancer by immunohistochemistry (IHC) and fluorescent in situ hybridization (FISH) [11]. Analyzing combined primary tumor and remote metastatic lesions by IHC or FISH exhibit that, HER2 is located almost at 94% and 93% of the samples. Initial detection and cutting-edge treatment technology can decrease breast cancer mortality. Significantly, the upregulation of the HER2 level can be easily detected in human breast tissues that show early signs of transformation but have not yet fully matured. Detection of HER2 expression within breast lesions at various stages confirms cancer progression. Biopsy of benign breast shown the absence of HER2 protein expression. HER2 is found in the terminal duct lobular units (TDLUs)-known as lobules as well as in atypical ductal hyperplasia (ADH). Then, HER2 is overexpressed in highly ductal carcinoma in situ (DCIS), and in highly invasive breast cancer (IBC). Excessive expression of HER2 is present during the transition from hyperplasia to DCIS. However, the absence of overexpression in normal TDLUs and ADH, compared to the tendency to be relatively high in DCIS, increased levels of HER2 are considered an important factor in early malignant transformation. HER2 overexpression is sufficient enough to alter mammary development and induce malignant transformation. Increased expression of wild-type HER2, somatic mutations activated wild-type HER2, and temporal pattern of expression of activated HER2 induced mammary tumorigenesis. So, detection and treatment of high-risk pre-malignant disorder can prevent deadly invasive breast cancers. In breast carcinomas, HER2, p53, and estrogen receptor (ER) status are considered important prognostic factors. IBC is more likely to occur if the patient exhibits mild breast lesions with less HER2 aberrant gene expression or little elevated levels of p53 protein. Similarly, both HER2 gene aberrant expression and a long-term histopathologic diagnosis in benign breast biopsies of women may have substantial risks for subsequent IBC. In the development and progression of pre-malignant breast disease, HER2 can play a significant role by increasing cell proliferation and motility.

In invasive ductal carcinomas (IDCs), about 20% to 30% of enhanced HER2 gene expression was observed. The genomic features of the primary tumor help to predict the chances of metastasis already occurring in patients with clinically localized disease. Some signal controls such as HER 2 activations, provide a selective advantage during tumor initiation and may also encourage invasive and metastatic phenotype. The progression of breast cancer is related to its ability to invade and metastasize remotely, and a decrease in tumor cell adhesion is an important factor in this process. Thus, HER2 overexpression, loss of E-cadherin subsidizes mammary tumor initiation, progression, proliferation, and metastasis. Promoting cell motility in metastatic cells is an activity of HER2. Thus, HER2 overexpressing tumor cells can occupy the basement membrane, adapt to endothelial cells, extravasate, and transfer to normal organs. Although breast cancers metastasize to the bone marrow, lung, liver, and brain. HER2 overexpression in proliferating tumor cells found in the bone marrow which estimates poor clinical outcomes [12].

Metastasis can occur very early during the development of breast cancer and exists in a variety of places, including incomplete mutated phenotypes. It has recently appeared that breast tumor cells have cancer stem cell properties and are regulated by HER2. HER2 is responsible for the spread and survival of the primary tumor. HER2 overexpression increases the possibility of transformation [12]. The relationship between HER2 overexpression and human breast tumors, its extracellular accessibility, as well as involvement in tumor aggression, are all factors established that overexpressed HER2 gene is one of the leading causes of breast cancer progression and metastasis [10].

Acknowledgement

None.

Conflict of Interest

No conflict of interest.

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