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REVIEW

HER-3 molecular classification, expression of PD-L1 and clinical importance in breast cancer

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ABSTRACT
Receptors of the large HER family play an important role in breast cancer, which is undergoing a gradual development in connection with biological development, both in the field of diagnostics and therapy. Dimerization of HER-2 with other HER members, such as HER-3, is the biggest driver of tumor cell growth and survival. Numerous studies show that HER-3 gene overexpression correlates with poor prognosis. However, other studies have shown HER-3 overexpression to be a positive prognostic factor. HER-3 may confer resistance to certain EGFR or HER-2 receptor therapeutics. An interesting fact, however, is that HER-3 expression can serve as a marker in immunotherapy for triple-negative breast cancer (TNBC). It is thought to be involved not only in cell survival and proliferation, but also in the regulation of PD-L1 expression. In breast cancer, PD-L1 expression is heterogeneous and is generally associated with the presence of tumor-infiltrating lymphocytes and a number of factors with poor prognosis such as young age, hormone receptor negativity, and high HER-2 expression and proliferation index. Our results showed amplification of HER-3 (CERB3) in 2 out of a sample of 20 patients with TNBC, and 13 of 20 HER-2-positive patients. PD-L1 expression was demonstrated in 3 out of 13 HER-3-positive patients and 2 out of 2 HER-3-positive TNBC patients. There was a strong correlation between positive HER-3 and PD-L1 TNBC expression ($p = < 0.001$). Thus, the view of the HER-3 receptor will be much more complex, and the overexpression of this receptor appears to have both negative and positive prognostic and clinical impacts *(Tab. 1, Ref. 17)*. Text in PDF *www.elis.sk*
KEY WORDS: breast cancer, HER family, overexpression, HER-3, HER-2, PD-L1, TNBC.

Epidemiology and etiology of breast cancer

Although the treatment of breast cancer, especially in the early stages, is very successful, breast cancer remains the most common cancer cause of death in women. Breast cancer often affects women of childbearing age, with almost 43 % of patients under the age of 60. However, breast cancer is most common in the age group of 60–65 years. Breast cancer can be diagnosed as a sporadic or hereditary disease. In the case of the sporadic form, which we find in most women with breast cancer, it arises due to the accumulation of somatic mutations in the cells of the breast. Tumor transformation of mammary epithelia is caused by deregulation of critical signal-transduction pathways (cell division, apoptosis and genomic DNA repair) based on proto-oncogene activation and tumor suppressor gene inactivation, which is caused by genetic disorders accompanied by epigenetic changes. These failures result in the emergence of a malignantly transformed cell *in situ*, which, due to genomic instability caused by DNA repair disorders, can produce a number of genetically unstable daughter cells tolerating genomic defects affecting other regulatory mechanisms (1). Molecularly, the view of breast cancer has changed significantly over the last decade. Based on gene expression profiles, the basic ("intrinsic") types of breast cancer have been characterized as follows: luminal A, luminal B, human epidermal growth factor receptor 2 (HER-2)-positive and basal like, and normal breast-like tissue, which is a taxonomic term that is widely used in breast cancer research. According to the latest findings, it is clear that estrogen receptor (ER)-positive and negative breast cancers are two completely different diseases that have different precursors, dissemination pathways, clinical behavior and response to treatment. This means that the genetic profile of ER-positive low-grade invasive carcinoma will be completely different from ER-negative high-grade breast cancer. Tumor grading is related to the degree of genetic instability of the tumor. In 2012, the complete genetic profile of the most representative group of breast cancers was described. Interestingly, the widest spectrum of gene mutations was found in ER-positive luminal carcinomas (1).

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Biological and cellular aspects of the human epidermal growth factor receptor 2 family

Advances in molecular biology have led to the identification of several potential markers with prognostic and therapeutic significances. HER-2 testing for targeted therapy is now the basic algorithm in the treatment of this disease. The aim of the current research is to determine the frequency and prognostic significance of overexpression of other members of the HER family, namely HER-3 and HER-4, in invasive breast cancers. The large HER family of receptors plays an important role in breast cancer. HER-2 positivity in breast cancer was initially an unfavorable prognostic factor. This changed with the introduction of modern monoclonal antibody therapy. From the molecular point of view, the therapeutic goal is to achieve heterodimerization of HER-2 and HER-3 receptors. This is because dimerization of HER-2 with other members of the HER family is the biggest driver of tumor cell growth and survival. The human epidermal growth factor family of receptors includes four homologous members. The activation of these receptors affects essential tumorigenic processes and plays a crucial role in the pathogenesis of breast cancer. Recently, attention has been focused on HER-3. Spontaneous homodimerization and activation of the human epidermal growth factor receptor HER-2 is generally thought to occur in HER2/neu gene amplification breast cancer cells (2). However, another potential mechanism of HER-2 phosphorylation is HER-3 transactivation, where HER-3 can be phosphorylated by HER-2. Phosphorylated HER-3 can then bind to the phosphatidylinositol-3-OH kinase (PI [3] K)/ kt pathway directly, whereas HER-2 does not. The formation of HER-2 / HER-3 heterodimers thus forms the most mitogenic and transforming receptor complex within the HER family of transmembrane receptor tyrosine kinases (RTKs) (3). A therapeutic milestone was passed by adding the monoclonal antibody pertuzumab to standard therapy with trastuzumab and docetaxel. Pertuzumab binds to the same target as trastuzumab but at a different binding site, thus inhibiting HER-2 and HER-3 receptor heterodimerization. Thus, this combined approach improves the blockade of the HER-2 signaling pathway by disrupting HER-3 and HER-2 receptor dimerization (1).

Tab. 1. The results of the immunochemical staining and cytogenetics analysis status of the breast cancer patients.

Sample of HER-2 positive	HER-2/neu gene	HER-2	ERBB3 gene	HER-3	PD-L1
1	positive	positive			
2	positive	positive	positive	positive	
3	positive	positive	positive	positive	positive
4	positive	positive	positive	positive	
5	positive	positive	positive	positive	positive
6	positive	positive	positive	positive	
7	positive	positive	positive	positive	
8	positive	positive			
9	positive	positive	positive	positive	
10	positive	positive	positive	positive	
11	positive	positive	positive	positive	
12	positive	positive	positive	positive	
13	positive	positive			
14	positive	positive			
15	positive	positive	positive	positive	
16	positive	positive	positive	positive	positive
17	positive	positive			
18	positive	positive	positive	positive	
19	positive	positive			
20	positive	positive			

Sample of TNBC	HER-2/neu gene	HER-2	ERBB3 gene	HER-3	PD-L1
1	negative	negative			
2	negative	negative			
3	negative	negative			positive
4	negative	negative			
5	negative	negative			positive
6	negative	negative			
7	negative	negative	positive	positive	positive
8	negative	negative			
9	negative	negative			
10	negative	negative			
11	negative	negative			
12	negative	negative			
13	negative	negative			
14	negative	negative	positive	positive	positive
15	negative	negative			
16	negative	negative			
17	negative	negative			
18	negative	negative			positive
19	negative	negative			
20	negative	negative			

Significance of HER-3 and other members of this family in invasive breast cancer

Among the members of the HER family, EGFR and HER-2 are the most studied. However, data on the significance of changes in other members, namely HER-3 and HER-4, are lacking. Dimerization of HER-2 and HER-3 receptors may be crucial for the

growth and progression of breast cancer. In addition, HER-3 may provide a pathway for resistance to EGFR or HER-2 receptor-targeted drugs. Although a number of studies have shown that HER-3 overexpression is associated with poor prognosis in breast cancer patients, other studies have shown that HER-3 overexpression may also be a positive prognostic factor. Existing studies suggest that HER-4 signaling promotes differentiation and growth inhibition of breast cancer cells (4). HER-4 is more consistently associated with a favorable prognosis in breast cancer. HER-4 has several biological activities and many of its functions are mediated by its intracellular domain. In addition, a loss of HER-4 expression may be a marker of tamoxifen resistance. Due to the functional interdependence between HER receptors, it is possible that the effect on cell proliferation and tumor growth depends on receptor trans-signaling. Therefore, elucidation of how and to what extent these different signaling pathways are involved in breast carcinogenesis may lead to further therapeutic options (5). The ErbB3/HER3 domain appears as a molecular target for various types of cancer. HER-3 is overexpressed and activated in a number of cancers with acquired resistance to other HER family therapeutic interventions, such as tyrosine kinase inhibitors and antibody therapies. The regulation of HER-3 expression and signaling involves many proteins that interact with HER-3. These proteins include PI3K, SHC, E3 ubiquitin ligase, NEDD4 and Nrdp1. In addition, the recent identification of a number of HER-3 oncogenic mutations in colon and gastric cancers clarifies the role of HER-3 in disease development. Despite strong evidence for the role for HER-3 in cancer, the current understanding of HER-3 expression and activation requires further research.

HER-3 expression in triple-negative breast cancer

The HER-3 expression is expected to be a possible prognostic marker in TNBC (6). A large study (7) was performed on samples from 100 cases (40 fibroadenomas and 60 invasive ductal carcinomas (IDC)) that were not otherwise specified. All patients underwent modified radical mastectomy. All samples were assayed for HER-2/neu, ER and PR expression by immunohistochemistry (IHC) and quantitative determination of HER-3 mRNA expression by real-time PCR. A significantly higher level of HER-3 mRNA was demonstrated in cancer cases when compared to fibroadenomas. Among the malignant cases, HER-3 mRNA levels were significantly associated with advanced T stage, grade, number of positive lymph nodes, tumor size, and *in situ* component cases. In addition, HER-3 mRNA levels had the highest values in the Her-2/neu positive group, followed by triple negative cases with the lowest levels in the luminal group ($p < 0.05$). HER-3 is upregulated in IDC, especially in those tumors that have poor prognostic features. As the study shows, HER-3 mRNA levels may identify a subset of patients with a poor prognosis, who could undergo further evaluation of the effectiveness of HER-3 anticancer therapy. In another study, the aim was to evaluate the prognostic significance of HER-3 expression in invasive breast cancer. The study included 950 cases of invasive breast cancer with long-term clinical follow-up data (median 109.7 months). The expressions of ER, PR, HER-2, EGFR and HER-3 were characterized immunohistochemically. Each case was classified as one of four subtypes by IHC, based on hormone receptor (HR) and HER-2 expression. In the TNBC subtype, the HER-3 (+) group showed a worse survival (DFS, $p = 0.010$) and overall survival (OS, $p = 0.015$) as compared to the HER-3 (–) group. In the HER-2 subtype, the HER-3 (+) group also showed a worse DFS ($P = 0.022$) and OS ($p = 0.077$) as compared to the HER-3 (–) group. However, there was no difference in patients with HR-positive breast cancer. The HER-3 expression was associated with poor DFS in TNBC and HER-2 subtypes and a shorter OS in the TNBC subtype. The HER-3 overexpression has been shown to be an important prognostic marker of hormone receptor-negative breast cancer and further studies are needed to elucidate the role of HER-3-targeted therapy (8).

Significance of HER-3 expression in connection with immunotherapy

The use of HER-3 expression as a possible marker of immunotherapy in TNBC appears to be very interesting. The HER-3 receptor is thought to be involved not only in cell survival, but also in regulation of PD-L1 expression. It is thought that the HER-3 receptor expression regulates PD-L1 expression and could therefore be a potential target for immunotherapy, and a predictive marker in TNBC.

PD-L1 expression

Breast cancers, both TNBC and HER-2-negative breast cancers, respond to therapy by blocking immune checkpoints due to their high immunogenicity. In breast cancer, the PD-L1 expression is heterogeneous and is generally associated with the presence of tumor-infiltrating lymphocytes and a number of other poor prognostic factors such as young age, hormone receptor negativity, high HER-2 expression and high proliferation indices (9). The research in immune control blockade is currently focused in two directions. These are to identify the correct biomarkers of immune control blockade and to combine therapies with antibodies against PD-1/PD-L1 blockade to achieve optimal clinical results (10). These inhibitors, which affect the interaction between PD-1 and PD-L1, are used in a large group of cancers, and their use is associated with improved treatment outcomes. PD-1 is activated by the ligand PD-L1, which leads to suppression of the immune response and is a very common mechanism of attenuation of the anti-tumor immune response. By influencing the interaction between PD-1 and PD-L1 by using checkpoint inhibitors, anti-tumor immunity is restored by T-lymphocytes. Activated T cells in secondary lymphoid organs/tumor tissue upregulate the expression of the co-inhibitory cell surface receptor PD-1. Binding of PD-1 to its ligands, PD-L1 or PD-L2, found on the surface of several immune cells as well as tumor cells, inhibits downstream signaling from the TCR, thereby reducing T cell activity. Targeting PD-1 or PD-L1 with antibodies can revive depleted T cells at the tumor site, increase their activity, which in turn will allow T cell-mediated tumor cell killing (11).

Aim of the study

The aim of the study was to monitor the amplification of ERBB3 and HER-2/neu gene and IHC HER-2 and HER-3 receptor expressions in a cohort of 40 patients (20 HER-2-positive patients and 20 TNBC patients) using cytogenetic methods. At the same time, the study aims to monitor PD-L1 expression and assess its correlation with the HER-3 receptor in both HER-2-positive and TNBC patients.

Patient selection

A total of 40 patients with breast cancer were included in the study: 20 with HER-2 amplification and 20 with TNBC. The patients with HER-2 amplification had a median age of 49.4 years (14 were postmenopausal (46.7 %) and 16 were premenopausal (53.3 %)). Histologically, 18 patients had the HER-2 subtype (without hormone receptor positivity) and two patients had the luminal B subtype (hormone receptor-positive). No patients had evidence of distal metastases (6 were in stage I, 13 were in stage II and 1 was in stage III).

The patients with TNBC had a median age of 33.6/33.2 years (10/10 no relapse/relapse). No patients had evidence of distal metastases (2/2 in stage I, 5/5 in stage II and 3/3 in stage III). Median follow-up (months) 59.8/23.3; median time to relapse (months) NR/15.9; median overall survival (months) NR/30.2.

Methods

Processing of the tissue

All specimens were immediately fixed in 10 % formalin and then embedded in paraffin. Histological slides were then created and stained with hematoxylin and eosin and evaluated under an Olympus BX53 microscope (Tokyo, Japan).

Immunohistochemistry

Immunohistochemical examinations were performed using monoclonal rabbit antibodies against the HER-2 protein (clone 4B5, prediluted, Ventana anti-HER2/neu), HER-3 (clone HER-3/c-erbB-3RMab) and PD-L1 (Anti-PD-L1, Clone28-8, Dako). Automated HER-2, HER-3 and PD-L1 staining was conducted by the immunostainer BenchMark Ultra following the manufacturer's instructions, with an ultraView Universal DAB Detection kit and bluing reagent as a visualization reagent and chromogen. All materials were obtained from Roche Diagnostics GmbH, Mannheim, Germany.

Fluorescence in situ hybridization (FISH). Sections (thickness of 2-3 μm) of paraffin-embedded tissues were processed for FISH using materials as follows: ZytoLight SPEC HER2/CEN 17 Dual Color probe and ERBB3 gene amplification ZytoLight SPEC ERBB3/CEN12 Dual Color Probe (ZytoVision GmbH, Bremerhaven, Germany). The assay procedures involving materials precisely followed the manufacturer's instructions.

Results

The results of the immunochemical staining and cytogenetics analysis status of the breast cancer patients are summarized in Table 1. Expression of CERB3/HER-3 was demonstrated in 2 of the 20 TNBC patients, and 13 of the 20 HER-2-positive patients. The expression of PD-L1 was demonstrated in 3 of the 20 HER-2 -positive patients and 5 of the 20 TNBC patients. In the case of HER-2-positive carcinomas, the expression of HER-3 correlated in 100 % with that of PD-L1. There was a strong correlation between positive expressions of HER-3 and PD-L1 ($p \leq 0.001$). In the case of TNBC, the PD-L1 expression was detected in 5 cases, of which 2 cases also showed HER-3 expression.

Discussion

Many solid tumors, including breast cancer, show an increase in the activation of several growth factor receptors, specifically of epidermal growth factor receptor (EGFR) and its members which promote proliferation, inhibit apoptosis, and induce metastasis. The inhibition of EGFR (its members) is expected to be an effective therapeutic strategy in triple-negative breast cancer (12, 13). One of the members is the HER-3 receptor, which still has a lack of biomarkers in breast cancer associated with HER-3 expression and therefore represents a major challenge for the clinical development of HER-3-targeted antibodies. Therefore, a better understanding of HER-3 regulation should improve HER-3 therapeutic target strategies in cancer treatment (14), which was the goal of our study. This topic has been addressed in a number of studies. In one, the HER family receptor expression was monitored in a cohort of 4,046 patients diagnosed with invasive breast cancer with median 12.5 years of follow-up (15). The analysis was performed in formalin-fixed and paraffin-embedded tissues. The expressions of HER-1, HER-2, HER-3 and HER-4 were tested immunohistochemically and HER-2 was further confirmed by fluorescence *in situ* hybridization using amplification probes, as in our study. In this study, HER-3 overexpression was found in 10 % of tumors and was a significant marker of shorter survival. In our case, HER-3 expression was found in 37.5 % of tumors. Although we attribute this discrepancy to a small cohort of patients compared to the study, we believe that the expression will be higher in the population. This study further demonstrated that the HER-3 status is an important prognostic indicator of survival in patients with invasive breast cancer. Based on our results, the assessment of HER-3 expression levels may identify a subset of patients with poor disease prognosis that could benefit from HER-3 -targeted therapeutics.

The members of the human epidermal growth factor (HER) receptor family are important in the process of tumorigenesis when their signaling functions are deregulated. Trans-signaling is a key feature of HER family signaling, and activation of the PI3K/Akt pathway, so critical in cancer, is driven predominantly by phosphorylation in the transmembrane inactive HER-3 kinase. Because HER-3 is an inactive kinase, it is not a direct target of kinase inhibitors and is not currently readily available therapeutically. How-

ever, HER-3 plays an important role in cancer and in mediating resistance to EGFR and HER-2 inhibitors (2), or the tumor-specific HER-3 expression may cause resistance to PD-1 inhibitor (16) in patients with solid tumors. However, another issue is the case of TNBC, where HER-3 receptor expression is thought to regulate PD-L1 expression and would therefore be a potential target for immunotherapy and a predictive marker in TNBC. However, our study detected an increase in HER-3 expression in only 2/20 tumors (HER-2 expression was HER-3-positive in 13/20 tumors). As for PD-L1, our study showed its expression in 3/20 HER-2-positive patients and in 5/20 TNBC patients. In the case of HER-2-positive cancers, the HER-3 expression correlated 100% with that of PD-L1. In the case of TNBC, the PD-L1 expression was detected in 5/20 tumors, which is more than in HER-2 positive tumors, but only 2 cases showed the HER-3 expression. This is evidenced by a number of studies that describe an increase in the expression of PD-L1 in TNBC as compared to HER-2-positive cancers, which makes immunogenicity more important in TNBC (17).

Thus, our results indicate that PD-L1 expression does not have to be directly dependent on HER-3 expression. Another study also showed that TNBC overexpresses PD-L1 on the surface of cancer cells, although the role of PD-L1 as a biomarker is still unclear (18). Thus, the question is to what extent the expression is predictive of response to treatment. The variability in PD-L1 expression assessment methodology, in different numerical positivity thresholds, and in analysis performed on different tissue types, which include archived, fresh, primary, and metastatic samples, will also play an important role, which is why our aim was to base our study on standard paraffin blocks for tissue archiving. A higher immune response to tumor-associated antigens is generally associated with the presence of tumor-infiltrating lymphocytes (TILs), which has been shown to be higher in TNBCs as compared to HR-positive breast cancers (18). TNBC is generally characterized by genomic instability and high rate of genetic mutations, which implies a higher production of neoantigens and increased immunogenicity. Therefore, it is considered to therapeutically target TNBC with monoclonal antibodies that block the PD-1/PD-L1 axis (11).

Conclusion

The role of the HER-3 receptor in breast cancer is much more complex than previously thought. An overexpression of this receptor appears to have both negative and positive prognostic significances. Although further studies are needed, the results suggest that molecular characteristics play an important role in breast carcinogenesis and that ERBB-3 amplification and HER-3 expression appear to be suitable biological markers of therapy and prognosis. Attention should be paid to the whole signaling pathway, including the activation of the immune system in the context of immunotherapy, where our results confirm the findings of large studies showing that increased PD-L1 expression is found in TNBC to a greater extent than in HER-2-positive cancers. However, as our results further demonstrate, HER-3 expression is detected at the same time, which could have a negative impact on the use of checkpoint inhibitors, especially in TNBC.

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