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HER2 Expression and PI3K-Akt Pathway Alterations in Gastric Cancer

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Key Words

HER2 · Gastric cancer · PI3K · Akt · Phosphate and tensin homolog · *PIK3CA* · Trastuzumab

Abstract

The anti-HER2 antibody trastuzumab has led to an era of personalized therapy in gastric cancer (GC). As a result, HER2 expression has become a major concern in GC. HER2 overexpression is seen in 7–34% of GC cases. Trastuzumab is an antibody that targets the HER2 extracellular domain and induces antibody-dependent cellular cytotoxicity and inhibition of the HER2 downstream signals. Mechanisms of resistance to trastuzumab have been reported in breast cancer. There are various mechanisms underlying trastuzumab resistance, such as alterations of HER2 structure or surroundings, dysregulation of HER2 downstream signal effectors and interaction of HER2 with other membrane receptors. The PI3K-Akt pathway is one of the main downstream signaling pathways of HER2. It is well known that *PIK3CA* mutations and phosphate and tensin homolog (PTEN) inactivation cause over-activation of the downstream signal without an upstream signal activation. Frequencies of *PIK3CA* mutations and PTEN inactivation have been reported to be 4–25 and 16–77%, respectively. However, little is known about the association between HER2 expression and PI3K-Akt pathway alterations in GC. We have found that HER2 overexpression was significantly correlated with pAkt expression in GC tissues. Furthermore, pAkt expression was correlated with poor prognosis. These results suggest that the PI3K-Akt pathway plays an important role in HER2-positive GC. Moreover, *PIK3CA* mutations and/or PTEN inactivation might affect the effectiveness of HER2-targeting therapy. Hence, it is necessary to clarify not only HER2 alterations but also PI3K-Akt pathway alterations for HER2-targeting therapy in GC. This review will introduce recent investigations and consider the current status of HER2-targeted therapy for treatment of GC.

Significance of HER2 Expression in Gastric Cancer

Gastric cancer (GC) is one of the most common cancers and the second leading cause of cancer-related death in the world [1]. Trastuzumab is the first molecular target drug in GC and it brought about an era of personalized therapy. Trastuzumab, a monoclonal antibody that targets the HER2 extracellular domain, inhibits HER2 downstream signal activation and induces antibody-dependent

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cellular cytotoxicity. Trastuzumab has shown a survival advantage in patients with breast cancer with HER2 overexpression.

In the ToGA study, standard chemotherapy regimens (capecitabine plus cisplatin or fluorouracil plus cisplatin) with trastuzumab resulted in longer survival times than those without trastuzumab in patients with HER2-positive GC [2]. Median overall survival periods were 13.8 months in patients assigned to a trastuzumab plus chemotherapy group and 11.1 months in patients assigned to a chemotherapy alone group (hazard ratio 0.74, p = 0.0046).

In a post hoc analysis, patients were divided into two subgroups, with either a high level (immunohistochemistry, IHC, 2+ and FISH-positive or IHC 3+) or low level (IHC 0 and FISH-positive or IHC 1+ and FISH-positive) of HER2 expression in the tumors. Median overall survival periods were 16.0 months in patients assigned to the trastuzumab plus chemotherapy group and 11.8 months in those assigned to the chemotherapy alone group [2]. Consequently, HER2-positive GC is generally defined as a tumor with IHC 2+ and FISH-positive or IHC 3+.

In addition to the effectiveness of trastuzumab as a first-line chemotherapy, a role of trastuzumab after first-line chemotherapy has recently been receiving increasing attention. It has previously been demonstrated that paclitaxel plus trastuzumab as the second-line chemotherapy in HER2-positive GC showed a good response rate (37% at 16 weeks) without additional severe side effects. Furthermore, many clinical trials are ongoing to evaluate the effectiveness of trastuzumab beyond progressive disease. The effectiveness of trastuzumab has already been proven in patients with breast cancer who failed with trastuzumab-combined first-line chemotherapy.

HER2 overexpression is observed in 7–34% of GC cases [2–6] and is correlated with clinicopathological features, including depth of tumor invasion, lymph node metastasis, intestinal-like subtype and tumor stage. However, a prognostic significance of HER2 overexpression in patients with GC is still controversial, unlike in breast cancer. Hence, HER2 expression has become a major concern in GC.

Mechanisms of Resistance to Trastuzumab Therapy

A number of studies on breast cancer have led to the identification of factors associated with inherent or treatment-acquired trastuzumab resistance (fig. 1).

Alterations of HER2 Structure or Surroundings

HER2 is a member of the epidermal growth factor receptor (EGFR) family and consists of an extracellular domain and an intracellular domain. HER2 can activate its downstream signal by dimerization, both as a homodimer and a heterodimer with other EGFR family receptors. Alterations such as increased heterodimerization of HER2 with EGFR or HER3 are thought to induce resistance to trastuzumab therapy. Some proteins, such as the membrane-associated glycoprotein MUC4, are known to mask HER2 and prevent trastuzumab from binding to HER2 [7]. Cleavage of the full-length 185-kDa HER2 protein produces a 110-kDa ECD and a 95-kDa NH2 terminal-truncated membrane-associated fragment (p95HER2) with increased kinase activity. p95HER2 expression has been found in about 30% of breast cancers [8], and patients with p95HER2 showed poor prognosis compared to patients with full-length HER2 [9].

Dysregulation of Downstream Signaling Effectors

The phosphatidylinositol-3-kinase (PI3K) pathway is one of the most important signaling pathways in several malignancies because it activates cell proliferation, cell survival, motility and cell growth [10]. This pathway is activated by many growth factor receptors, including HER2, and transduces the signals (fig. 2). Therefore, PI3K pathway activation is associated with resistance to trastuzumab and trastuzumab exerts its antitumor effects only in the presence of a normal PI3K pathway in HER2 overexpressing breast cancer [11, 12]. A tumor suppressor gene, *phosphatase and tensin homolog (PTEN)* deleted on chromosome 10, negatively regulates the PI3K-Akt pathway. It is well known that dysregulation of the PI3K pathway plays an important role in the development of malignancy and the most common alterations in this pathway are *PIK3CA* mutations and PTEN inactivation [13, 14], both of which can lead to constitutive activation of the PI3K pathway, resulting in resistance to trastuzumab therapy [15].

Interactions of HER2 with Other Membrane Receptors

Interactions and cross-signaling between HER2 and other growth factor receptors may also cause resistance to trastuzumab. For example, insulin-like growth factor receptor 1 (IGF1R) can activate the PI3K-Akt pathway independently of the HER2 signal. Inhibition of IGF1R with an anti-receptor antibody or an IGF1R-specific tyrosine kinase inhibitor sensitizes cells that are resistant to trastuzumab [16]. Moreover, formation of HER2-IGF1R heterodimers results in phosphorylation and activation

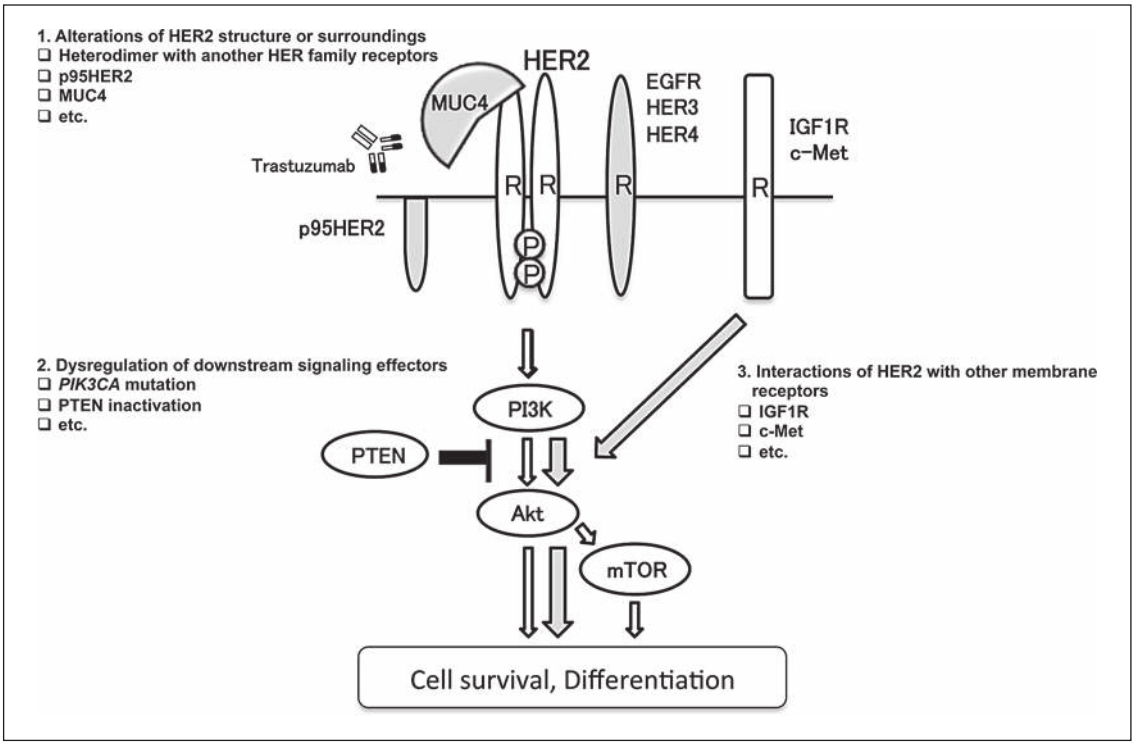

Fig. 1. Mechanisms of resistance to trastuzumab therapy. There are three major mechanisms of resistance to trastuzumab, which binds HER2 and inhibits HER2 signaling. The first mechanism is alteration of HER2 structure or surroundings. This either loses trastuzumab binding site, prevents trastuzumab from binding to HER2 or transduces HER2 signal by heterodimerization which cannot be inhibited by trastuzumab. The second mechanism is dysregulation of downstream signaling effectors such as *PIK3CA* mutation or PTEN inactivation. In this case, the downstream signal can be activated without upstream signals. The third is interactions of HER2 with other membrane receptors.

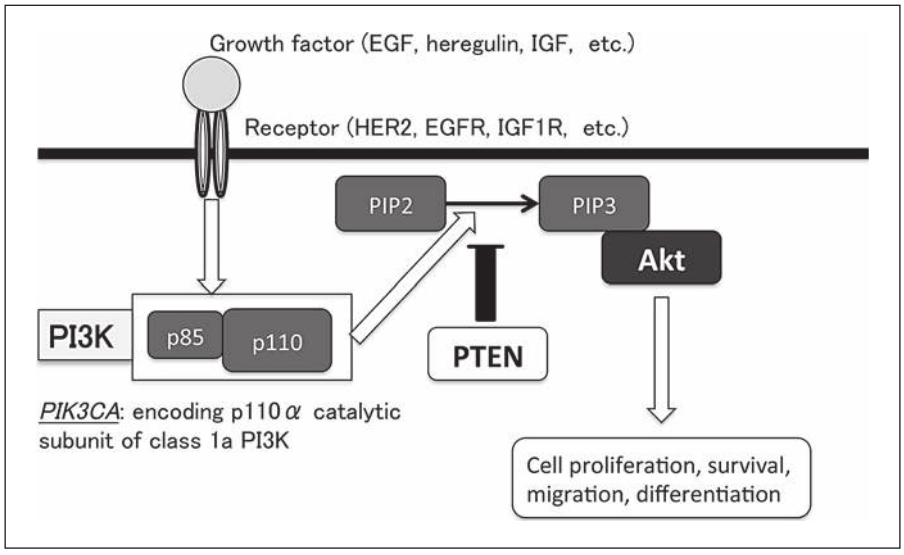

Fig. 2. The PI3K-Akt pathway. PI3K phosphorylates PIP2 [phosphatidylinositol (3,4)-bisphosphate] and produces PIP3 [phosphatidylinositol (3,4,5)-trisphosphate]. Subsequently, PIP3 activates Akt by phosphorylation of Akt and induces cell proliferation, survival, migration and differentiation. PTEN dephosphorylates PIP3 and inhibits the activation of Akt by PIP3.

of HER2 via stimulation of IGF1R by ligands in trastuzumab-resistant breast cancer cells [17]. On the other hand, preclinical studies have shown that lapatinib is able to block the HER2 signal and overcome IGF1R signaling even in the presence of IGF1 [17]. MET, known as a hepatocyte growth factor receptor, also has some interactions with the HER2 signal and therefore might cause trastuzumab resistance [18]. Thus, further understanding of the interactions of HER2 with other membrane receptors is also important for personalized therapy in GC.

Relationship between HER2 Expression and PI3K-Akt Pathway Alterations in GC

PIK3CA Mutations in GC

PIK3CA is mutated in a wide variety of human tumor types, including GC. Activating mutations in this gene upregulate the PI3K-AKT signaling pathway, making it a potentially useful therapeutic target. Furthermore, *PIK3CA* mutations have been receiving increasing attention because Liao et al. [19] showed in a large cohort study that aspirin intake prolonged survival time in patients who had colorectal cancer with *PIK3CA* mutations. Pyrosequencing-based methods facilitate the identification of low-frequency tumor mutations and allow more accurate assessment of the tumor mutation burden [20–22]. We determined *PIK3CA* mutations in GC tissues by using pyrosequencing [23]. The overall prevalence of *PIK3CA* mutations in that study was 8.7%, a value that is within the range (4.3–15.9%) of values in the currently available literature [24]. The mutation frequency was high (21.4%) in T4 cancers and low (6.4%) in T2 cancers. Thus, *PIK3CA* mutations appear to be late events in gastric carcinogenesis, leading to tumor progression.

The most common *PIK3CA* mutation was H1047R as described previously [24]. Importantly, two new types of mutations were found in exon 1. To our knowledge, mutations involving amino acids 88 and 108 (R88Q and R108H) have never been reported before in GC, nor do they appear in the COSMIC database, despite the large number of studies in which that region was investigated. These mutations have been detected in several other types of cancer tissues [25]. Importantly, these mutations have been reported to be gain-of-function mutations [26]. The results have potential clinical implications since the mutational status of *PIK3CA* could stratify patients for genotype-based molecular therapies targeting the PI3K pathway. Thus, exon 1 should be analyzed in GC in those clinical settings.

In our analysis, the frequency of pAkt expression was higher in cancers with exon 20 mutations (100%) than in those with exon 1 (40%) or exon 9 (56%) mutations, although the difference did not reach statistical significance. This finding is consistent with the results of a previous study showing that some *PIK3CA* mutations, mainly exon 9 mutations, caused Akt-independent pathway activation in a breast cancer cell line [27]. These results further support the notion that the functional significance of *PIK3CA* mutations depends on the mutation type and that the H1047R hotspot mutation has high oncogenic activity.

PTEN Alterations in GC

The tumor suppressor gene *PTEN* is located on chromosome 10q23.3 and acts as a plasma membrane lipid phosphatase. Its primary target for dephosphorylation is the second messenger phosphatidylinositol-3,4,5-triphosphate, the product of PI3K. Thereby, PTEN negatively regulates the PI3K-Akt pathway. Loss or downregulation of PTEN function due to mutations, haploinsufficiency from loss of heterozygosity and/or epigenetic down-modulation has been reported in GC. These PTEN alterations were detected in 16–77% of GC and were associated with poor prognosis, deeper invasion, lymph node metastasis and advanced stage [28]. However, the results are conflicting because there are many ways of evaluating PTEN alterations, such as sequencing, FISH, IHC and methylation. Furthermore, we have no definite criteria for PTEN inactivation in IHC analysis. Hence, establishment of a method for evaluation of PTEN alterations and further clarification of the role of PTEN alterations in GC are now of utmost importance.

Recently, Yang et al. [29] reported that miR-21 induced cell survival and cisplatin resistance through downregulation of the expression of PTEN and activation of Akt in GC cells. PTEN may play an important role in resistance to not only HER2-targeting therapy, but also cytotoxic agents such as cisplatin.

HER2 and PI3K-Akt Pathway Alterations in GC

We previously reported associations among HER2 expression, *PIK3CA* mutations and pAkt expression in GC [23]. In our analysis, HER2 overexpression (IHC 3+) was present in 20 samples (8.4%), a value that is within the range (7–34%) of values in the currently available literature [2–6]. HER2 overexpression was significantly correlated with intestinal histological type. We could not find any correlation between HER2 expression and poor prognosis, unlike that in breast cancer. Some studies have suggested that HER2 positivity in GC is associated with poor

prognosis and aggressive disease, but the results are conflicting. It is important to consider that there is heterogeneity in HER2 expression in GC. Although HER-2-positive cancer cells were not always consistent with pAkt-positive cancer cells in each tumor tissue specimen, HER2 overexpression was significantly correlated with pAkt expression in GC tissues (80 vs. 49%, $p < 0.01$). Moreover, pAkt expression was correlated with poor prognosis. Thus, the HER2-Akt axis appears to play an important role in HER2-overexpressing GC.

PIK3CA mutation is one of the mechanisms underlying the resistance to trastuzumab in breast cancer. In our study, *PIK3CA* mutations were present in only 1 case of GC with HER2 expression of IHC 2+. However, data for the analysis consisted mainly of data for patients without indication for chemotherapy. Therefore, we should accumulate more data on patients with advanced cancer with indication for trastuzumab therapy to evaluate whether *PIK3CA* mutation is a major mechanism underlying the resistance to trastuzumab in GC.

To our knowledge, an association between HER2 expression and PTEN alterations in GC has not been clarified. We are investigating PTEN expression in our GC samples. It seems that PTEN inactivation occurs independently of HER2 expression. PTEN inactivation may play a more important role than *PIK3CA* mutations in determining the effectiveness of HER2-targeting therapy because PTEN inactivation is more frequent than *PIK3CA* mutations.

We previously reported that DNA methylation plays an important role in GC [30]. Since DNA methylation is one of the key mechanisms underlying PTEN inactivation, we are also trying to clarify the clinical significance of epigenetic alterations in HER2-overexpressing GC.

Table 1. Drugs targeting HER2 and the PI3K-Akt pathway that are under ongoing clinical trials for gastric cancer

Target	Drug	Phase
HER2	T-DM1	3
	MGAH22	1
EGFR/HER2	Lapatinib	3
	ASLAN001	2
	Afatinib	2
HER2/HER3	LJM716	1
	MM111	2
pan-HER	HM781-36B	1/2
HER dimerization	Pertuzumab	3
PI3K	BYL719	1
PI3K/Akt/mTOR	Everolimus	3
Akt	MK-2206	2

Development of a New Therapeutic Strategy in GC

A number of drugs targeting HER2 or its downstream signals are under development, including an ongoing phase 3 clinical trial in GC (table 1). In some clinical trials, *PIK3CA* mutation or *PTEN* loss has been evaluated as a possible predictive biomarker and has also been used as one of the inclusion criteria. This is why an understanding of the association between HER2 expression and PI3K-Akt pathway alterations is necessary to develop a new therapeutic strategy not only with trastuzumab, but also with other new molecular target drugs.

A prospective study is necessary for revealing a new biomarker for trastuzumab therapy in GC. We have two ongoing analyses. One is an exploratory analysis using serum samples in a phase 2 study to evaluate the efficacy and safety of S-1 plus cisplatin with trastuzumab therapy in HER2-positive GC (WJOG7212G; T-SPACE study). Another is an analysis using serum and cancer tissue samples in a phase 2 study to evaluate the efficacy of continuing trastuzumab beyond progressive disease for patients after failure of first-line chemotherapy with trastuzumab (WJOG7112G; T-ACT study). In these studies, we are going to analyze alterations of HER2-related factors including the PI3K-Akt pathway to identify a new predictive biomarker for trastuzumab therapy.

Conclusion

Trastuzumab has led to an era of personalized therapy in GC. The PI3K-Akt pathway is one of the critical downstream signals from HER2. PI3K-Akt pathway alterations are expected to be biomarkers for predicting the effectiveness of trastuzumab therapy. Clarification of roles of the PI3K-Akt pathway alterations may also contribute to the development of new molecular target drugs.

Disclosure Statement

The authors have no conflicts of interest to declare.

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