The human epidermal receptors in gastric cancer: molecular alterations and its role as therapeutic targets

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Abstract

Gastric cancer (GC) is the third leading cause of cancer death worldwide; both environmental and genetic factors are involved in the etiology of this neoplasia. The human epidermal receptor (HER) pathway is essential for proliferation and differentiation of normal cells; but it is also implicated in the growth of cancer cells. In this work we investigate the molecular alterations in genes that encodes for HER receptors reported in GC, as well the role as therapeutic targets. We reviewed the literature reported to date regarding overexpression of HER-receptors, amplification and somatic mutations in ERBB genes occurred in gastric tumors, as well as the anti-HER therapies tested for treatment of GC. In GC, the overexpression of HER family is reported in a range of 12–87% of cases; up to 67% of cases with amplification, and 90 somatic mutations in ERBB genes. The only drug anti-HER approved for using combined with chemotherapy, in treatment of patients with advanced GC is trastuzumab; however, other targeted therapies are being investigated. The role of the HER family as a therapeutic target has not shown significant improvements in recent years; hence, further studies are required to find better options for treatment of GC.


Introduction

Globally, gastric cancer (GC) is the fifth most common type of cancer and the third cause of cancer-related death¹. Several cancer-related signaling pathways are activated in GC. The human epidermal receptor (HER) pathway is one of the most important signal-transduction pathways implicated in tumor growth and differentiation in different types of cancer, including GC². The HER family is a group of four tyrosine kinase transmembrane proteins: HER1 (EGFR or ERBB1), HER2 (NEU or p185HER2), HER3 and HER4. The HER family plays an important role in cell proliferation, differentiation and migration in normal cells, as well as in invasion, angiogenesis, metastasis and apoptosis in tumor cells³ (Fig. 1).

Three pathways are recognized in HER signaling: phosphatidylinositol 3-kinase (PI3K)/AKT (PKB), RAS/RAF/MEK/ERK1/2 and phospholipase C (PLCg)³. The PI3K/AKT pathway plays an important role in cell survival mediation, whereas RAS/ERK1/2 and the PLCg pathways participate in cell proliferation.

Molecular alterations in the HER family

Overexpression

Immunoreactivity for HER overexpression is categorized as 0 (< 10% of cells with weak membrane
reactivity), 1+ (> 10% of cells with partial and weak membrane activity), 2+ (> 10% of tumor cells with mild to moderate activity at the basolateral or complete membrane). Gastric tumors with an IHC 3+ classification are considered to be HER-positive (overexpression); in contrast, samples with IHC 2+ must be evaluated with in situ hybridization in order to establish the HER expression status.

HER1 overexpression in gastric tumors broadly varies (2-63% of cases). HER1 overexpression is mainly localized in the cytoplasm (45% of cases), while only in 9% it exhibits membrane expression and is not found in the nucleus. Overexpression has been associated with old age, a more aggressive course of the disease (poor differentiation, diffuse type and infiltrating capacity), proximal localization and advanced stage of disease; however the prognostic role of HER1 overexpression in GC is not clear since, in some studies, HER 1 positivity was significantly associated with poor prognosis, whereas other authors failed to demonstrate a significant correlation between these factors.

Figure 1. General diagram of the dimerization process and the main signaling pathways of the HER receptor family. Binding to the ligand affects the I and III domains (except for HER2).
HER2 overexpression also broadly varies in GC (from 4.4 to 53.4% of cases)\(^4\). Overexpression is more common in the cytoplasm (62%) than in the membrane (17%), and is also more common in the intestinal (32%) than in the diffuse subtype (21%)\(^6,14\), as well as in older patients\(^7\).

HER3 is overexpressed in 87% of gastric tumors\(^6\), and is more common in the cytoplasm (64%) than in the nucleus (34%) or the membrane (2%)\(^6,7\), although Choi et al.\(^15\) observed that HER3 is mainly found in the nucleus. For some authors, HER 3 overexpression is associated with intestinal subtype GC\(^6,7,16\), while for others, it is related to the diffuse subtype\(^7\). On the other hand, a lack of association with any GC subtype has also been described\(^8,19\). In addition, overexpression is associated with well- and moderately-differentiated tumors, older age, greater tumor invasion, lymph node involvement, tumor metastasis and poor survival rate\(^6,7,18\). HER3 nuclear expression in GC is associated with vascular and lymphatic invasion, as well as with poor survival (HER3+ 24-38 months vs. HER3- 45-47 months)\(^6,16\).

HER4 expression appears to be higher in gastric tumor tissues than in adjacent gastric mucosa\(^9\). Overexpression is cytoplasmic in 23-24% of cases, membranous in 15-18% and nuclear in 2%-6,7. HER4 overexpression is associated with tumor characteristics of good prognosis, such as intestinal subtype, good or moderate differentiation and no vascular, lymphatic or perineural invasion\(^6\). This is consistent with the role of HER4 in differentiation and antiproliferative response\(^9\). In spite of its alleged implication in a better prognosis in patients with GC, some reports have demonstrated that HER4 overexpression is associated with advanced stages of the disease\(^6\) and with the presence of signet-ring cells\(^21\).

**Amplification**

**ERBB** genes amplification is defined as positive when the HER: CEP signals ratio is ≥ 2. Chromosome polysomy is defined as ≥ 3 CEP signals on average per cell. In the fluorescent or chromogenic in situ hybridization-based analysis, a dual coloration system is used, with the probe for any of the **EGFR**, **ERBB2**, **ERBB3** or **ERBB4** and with the respective chromosome-specific centromeric probe (CEP). **EGFR** gene amplification has been identified in 2-29%\(^22-29\), of GC cases, and chromosome 7 polysomy, in 3-10% of cases. **ERBB2** amplification is reported in 8 to 22.1% of gastric tumors\(^5,6,22,26-30\), and is associated with the intestine al subtype, with well- or moderately-differentiated gastric tumors, and with reduced survival (17 months for HER2+ vs 40 months for HER2-)\(^6\). **ERBB3** amplification has not yet been observed in GC\(^3\). **ERBB4** in GC was reported by Nielsen et al.\(^20\) in 67% of cases, but Begnami et al.\(^6\) did not observe **ERBB4** gene amplification, which denotes the heterogeneity between gastric tumors.

**Mutations in genes that encode the HER family**

The analysis of mutations in the HER family genes has been carried out more frequently in the tyrosine kinase domain than in other domains\(^23,31-37\). Mutations have not been detected in all studies, in part due to the analyzed tumor (diffuse or intestinal), tumor status, and even due to ethnic differences\(^33,34,38-42\).

In GC, at least 90 somatic non-synonym mutations have been reported in **ERBB** genes, out of which 86 are missense, three are nonsense mutations and one is the deletion of an entire codon (Table 1).

The distribution of these mutations in each **ERBB** gene is: 19 in **EGFR**, 34 in **ERBB2**, 20 in **ERBB3** and 17 in **ERBB4**. These mutations affect all domains of the receptor, although more frequently the tyrosine kinase domain (27/90, 30.0%) (Fig. 1). Some recurrent somatic mutations were observed in two or more cases of GC: V308A, V505G and Y1016S. Holbrook et al.\(^43\) identified 50% (44/88) of these mutations and determined their possible functional impact; furthermore, they predicted that 28 of them can have an important role in the development or progression of cancer (Table 1).

**Mutations in the EGFR gene**

Mutations in the **EGFR** gene in GC are rare or absent, according to most reports. Their incidence varies in different studies from 0%-33,38-41, to 5.1%-31,32 and up to 30%\(^43\). Nineteen different somatic mutations have been observed (17 missense and two nonsense), mainly occurring in the tyrosine kinase domain (7/90, 30.0%) (Fig. 2). Some recurrent somatic mutations were observed in two or more cases of GC: V308A, V505G and Y1016S. Moutinho et al.\(^23\) carried out an analysis of the correlation between alterations in the **EGFR** gene and clinical characteristics, and suggested that **EGFR** is implicated in tumor size and progression regulation. Activating mutations in **EGFR** are not frequent in GC, but other alterations, such as mutations or copy number variations, are implicated in an
increase of diffuse tumors size; in addition, alterations in this gene have been suggested to confer an invasive behavior in neoplastic cells.

**ERBB2 gene mutations**

Only few studies have been conducted to identify ERBB2 somatic mutations in GC in comparison with lung and breast cancers. ERBB2 mutation rate in GC ranges from 2%33-35 to 60%43; however, of the 30 mutations detected by Holbrook et al.43, 14 seem to be of little importance for the development or progression of cancer, thus decreasing the frequency of ERBB2 mutations with tumoral impact to 32%. So far, 34 ERBB2 different missense variants have been described, out of which 13 were detected in the tyrosine kinase domain33-35,42,43 (Fig. 2) and in advanced GC44. Similarly as observed for EGFR, most mutations in ERBB2 are heterogeneous in different types of tumors. Very few mutations are recurrent, such as D204A, L755S, R678Q and V777L, among others44,42,43. Some mutations are observed in several patients with the same type of cancer and other in patients with different types of cancer. On the other hand, the same codon is changed by different amino acids, suggesting the presence of hot spots; for example, L755S/W/P, D769H/Y, G776S/L/V and V777L/M33-35,45-47. The L755S mutation (called L725S by Holbrook et al.43) is one of the most frequently observed mutations in several types of cancer. The somatic mutations D769H, D769Y, V777L and V842I are activating mutations that can promote cell proliferation by themselves45.

**ERBB3 gene mutations**

The frequency of mutations in the ERBB3 gene in GC ranges from 0.6%46 to 13%.44 Currently, at least 20

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**Table 1. Somatic mutations in ERBB family genes reported in gastric cancer**

<table>
<thead>
<tr>
<th>EGFR (n = 19)</th>
<th>HER2 (n = 34)</th>
<th>HER3 (n = 20)</th>
<th>HER4 (n = 17)</th>
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<td>^d769H^44</td>
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<td>^g776S^36</td>
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<td>^D234A^43</td>
<td>^V777L^34</td>
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<td>^D277Y^43</td>
<td>^V842I^35</td>
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<td>^V296L^43</td>
<td>^T862A^42</td>
<td>^P262H^44</td>
</tr>
<tr>
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<td>^x308G^43</td>
<td>^L869Q^34</td>
<td>^G284R^42</td>
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<td>^L994W^43</td>
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<td>^G995A^43</td>
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<td>^L930W^43</td>
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<td>^aL755S^43</td>
<td>^d1218delE^48</td>
<td>^i1218delE^48</td>
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</table>

Number of sequences used to name each mutation: *a*M_201282 (628 aa); *b*M_201284 (705 aa); *c*M_0055228 (1210 aa); *d*M_004448 (1255 aa); *e*mutations described by Holbrook et al.43 considering the 1225 aa (NM_001005862) isoform were named by us according to isoform 1255 aa (NM_004448); *f*mutations described by Holbrook et al.43 considering the 1225 aa (NM_004448) isoform were named by us according to isoform 1255 aa (NM_004448); *g*N_001982 (1342 aa); *h*N_005235 (1308 aa); *i*mutations with a SIFT score > 0.05: the amino acid change possibly does not significantly affect the protein function; evidence of wild-type HER2 oncogenic activity.
somatic mutations in ERBB3 have already been identified (19 missense and one complete codon deletion). Unlike observations for EGFR and ERBB2, most mutations occur within domain III, which participates in the ligand binding\(^{36,42,43}\) (Fig. 2). Jaiswal et al.\(^{44}\) analyzed the functional impact of four ERBB3 gene mutations (V104M, A232V, P262V, P262H and Q809R) and found evidence of oncogenic potential in all of them. On the other hand, Holbrook et al.\(^{43}\) analyzed five mutations of the ERBB3 gene (A172P, D297Y, V654G, K926R and L930W) and found a possible clinical relevance for GC. Most these mutations have functional importance, as they affect interactions that are necessary for dimerization or ligand binding\(^{44}\).
Mutations in the ERBB4 gene

The frequency of ERBB4 mutations in GC ranges from 0.6% to 28%. There are at least 17 different somatic mutations reported in GC (16 are missense and one nonsense). Mutations are distributed across the entire gene; however, a slight accumulation is observed at the C-terminal domain (Fig. 2 and Table 1). Although no functional characterization of ERBB4 gene mutations has been made in GC, Holbrook et al. calculated the potential of 10 variants and found that at least 4 mutations (K324N, W513G, F974V and E1201X) can be clinically important for the development of cancer.

Targeted therapies against the HER receptor family

There are two classes of anti-HER therapy: monoclonal antibodies and small molecule tyrosine kinase inhibitors. Anti-HER monotherapy for GC is less toxic, but also less efficient, and combination of agents targeted against HER with traditional chemotherapeutic agents is therefore most commonly used.

Monoclonal antibodies

Anti-HER1 therapies

Cetuximab is a chimeric monoclonal antibody-type G1 immunoglobulin (IgG1) that binds to HER1 extracellular domain and competitively inhibits the binding to EGF ligand and other ligands, as well as ligand-induced tyrosine kinase phosphorylation. Cetuximab also induces EGFR internalization, downregulation and degradation. It was the first anti-EGFR antibody approved by the US Food and Drug Administration (FDA) for the treatment of squamous cell carcinoma and advanced wild-type KRAS colorectal cancer. It is the most widely investigated anti-HER1 therapy in GC. It hadn’t had a significant impact on survival (3.1-16.6 months) or on progression-free survival (1.6-11 months) in patients with GC and gastroesophageal cancer (GEC) (Table 2); nevertheless, there is the registry of one patient with metastatic GC treated with cetuximab with the longest progression-free survival reported (7 years and 11 months).

Panitumumab is the first completely human IgG2 monoclonal antibody approved for the treatment of EGFR-expressing metastatic colorectal cancer, based on results that showed clinical benefits. One phase III trial (REAL-3) assessed panitumumab in treatment-naive patients with advanced esophageal cancer and GC, but the results showed no survival increase (Table 2). Other four clinical trials were discontinued owing to a lack of efficacy of panitumumab added to chemotherapy. The failure of randomized phase III trials using cetuximab or panitumumab in combination with chemotherapy was due to the lack of selection of a specific patient population according to EGFR expression and to the negative interaction of the anti-EGFR monoclonal antibody and the therapeutic agent. More recent studies are assessing panitumumab efficacy in combination with other components.

Matuzumab is a humanized IgG1 monoclonal antibody against HER1. In a randomized phase II trial conducted in patients with advanced GC with HER1 overexpression, matuzumab + epirubicin + cisplatin + capecitabine were evaluated as first-line therapy, and the results showed that the combination of matuzumab with chemotherapy does not improve survival rates (Table 2); therefore, matuzumab was not tested in phase III trials.

Nimotuzumab is a humanized IgG1 that has demonstrated efficacy without serious skin toxicity as the one caused by other HER1-binding therapies; however, survival is similar to that observed with other drugs (Table 2).

Anti-HER2 therapies

Trastuzumab is a humanized monoclonal antibody that binds to HER2 extracellular domain IV and prevents intracellular tyrosine kinase activation. It was approved for use in combination with chemotherapy as an adjuvant for patients with HER2+ breast cancer and for advanced GC therapy in HER2+ treatment-naive patients in combination with chemotherapy. However, trastuzumab confers higher risk of cardiotoxicity, which is partially reversible after the antibody is eliminated. The only study that has demonstrated strong evidence for survival improvement was the phase III ToGA trial, which included patients with HER2+ GC (Table 2); patients with IHC 2+ tumors and positive fluorescent in situ hybridization or IHC 3+ tumors had a marked survival improvement (16.0 months).

Pertuzumab is a humanized monoclonal antibody that binds to the HER2 dimerization domain II, unlike trastuzumab, which binds to domain IV. It inhibits
Table 2. HER-targeted therapies for patients with gastric cancer (studies with published results)

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<tr>
<th>Drug</th>
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<th>Combined with chemotherapy</th>
<th>PFS (months)</th>
<th>MS (months)</th>
<th>Reference</th>
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<td>Irinotecan, leucovorin, 5FU†</td>
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<td>16–16.6</td>
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MS: mean survival; PFS: progression-free survival; †: first line treatment; ‡: second line treatment.
HER2 dimerization with other HER family members and exhibits antibody-dependent cell cytotoxicity (ADCC)-related anti-tumor activity.88,89 The effect of adding pertuzumab to chemotherapy is currently being investigated.84

One meta-analysis suggested that anti-HER1 monoclonal antibodies-based therapies result in lower survival rates than anti-HER2 therapies. However, chemotherapy together with anti-HER2 targeted therapy significantly increases the risk of diarrhea, hypocalcemia, mucositis and rash in comparison with chemotherapy alone.85

Trastuzumab emtansine (T-DM1) is an antibody that combines trastuzumab and a maitansine-derived microtubule inhibitor (DM1). This drug combines two strategies: trastuzumab anti-HER2 activity and targeted intracellular DM1 delivery, which interferes with mitosis and promotes apoptosis. Its use in HER2+ breast cancer has already been approved.86 Clinical trials are recruiting patients in order to assess T-DM1 together with chemotherapy in patients with GC84,88,91.

Therapies against HER2-HER3 heterodimers

MM-111 is a bispecific fusion antibody that comprises anti-HER2 and anti-HER3 antibodies bound by human serum albumin. MM-111 binds to HER2 and HER3-expressing cells and blocks ligand-induced signaling.92

Tyrosine kinase inhibitors

HER1 inhibitors

Erlotinib has been approved in the treatment of lung and pancreatic cancer. In a phase II trial, erlotinib was found to be active in patients with gastroesophageal cancer, but good response was not obtained in patients with GC (Table 2). In a phase II trial, a combination of erlotinib, oxaliplatin, leucovorin and 5-fluorouracil (5FU) was administered to treatment-naive patients with advanced or metastatic esophageal cancer and gastroesophageal cancer; the results were similar to those previously reported (Table 2).

Gefitinib was approved by the FDA for the treatment of advanced non-small cell lung cancer. As monotherapy, it is associated to low survival, but in combination with cisplatin, 5FU and radiotherapy, it has shown the highest survival rate (24.2 months) in esophageal and gastroesophageal cancer (Table 2).

Neratinib acts by covalently binding to a cysteine lateral chain in the HER receptor. It is directed to patients with activating mutations in the EGFR, ERBB2 or ERBB3 genes and to patients with EGFR amplification.

HER1/HER2 inhibitors

Lapatinib is an orally-active molecule for HER1 and HER2 double-inhibition that has been approved to be used in HER2+ breast cancer. It is an inhibitor more potent for HER1 and HER2 than for HER4 (> 10x). It obtained the best results in patients with advanced GC with paclitaxel and in combination with capecitabine and oxaliplatin, in comparison with single-agent administration or in combination only with capecitabine (Table 2).

Afatinib is an irreversible HER1 and HER2 inhibitor that has demonstrated anti-tumor activity in vivo in patients with HER2+ GC. Clinical trials are assessing its efficacy in combination with trastuzumab and with cisplatin plus 5FU.

Pan-inhibitors (HER1/HER2/HER4)

AST1306 is an orally active, highly selective and irreversible HER inhibitor with promising anticancer activity in patients with previously-treated, advanced solid tumors. Partial response was confirmed in 12.7% of patients (among them, one with GC), and stable disease for ≥ 6 months was observed in 12.7% of patients. AST1306 can potently inhibit the EGFR T790M mutation, which is commonly associated with acquired resistance to first-generation HER1 inhibitors in non-small cell lung cancer.94

Dacomitinib induces apoptosis and arrests the cell cycle in G1, and also inhibits signaling pathways phosphorylation and transduction in HER2+ GC cells. In addition, it blocks the formation of HER1/HER2, HER2/HER3 and HER3/HER4 heterodimers. Synergy has been observed with many commonly employed cytotoxic agents (5FU, cisplatin, docetaxel and paclitaxel) and with targeted agents, such as trastuzumab. Dacomitinib was used in patients with HER2+ advanced GC as single agent after failure of at least one previous chemotherapy regimen, but no substantial survival improvement was observed.
Poziotinib inhibits the phosphorylation of the HER family members and molecules of the signaling cascade. It also induces apoptosis and cell cycle arrest at phase G1. Although this agent was inactive as monotherapy in HER2- cell lines, synergy was reported in both HER2+ and HER2- models. AZD8931 provides EGFR, HER2 and HER3-signaling inhibition. The efficacy of this drug in combination with paclitaxel was assessed in patients with advanced GC; however, the trial was prematurely stopped due to the low response observed.

Conclusions

The conducted review allows observing that there is broad heterogeneity in molecular alterations such as overexpression and amplification in GC; somatic mutations are not common since, worldwide, only 88 different mutations have been reported in the four genes that encode the HER proteins.

Meanwhile, the treatments focused on improving the quality of life and prolonging survival in patients with advanced GC have not shown significant improvements in the past few years; therefore, further studies are required in order to identify the best options for the treatment of these patients. The fact that ethnic differences have been observed in the survival results in patients with other malignancies in response to the treatment with tyrosine kinase inhibitors and chemotherapy (which also were observed in cases of GC) is of great importance, and it should therefore be taken into account. Fortunately, a larger number of studies are currently considering the patients’ molecular profile in the search for treatments, which may generate a better response to the drugs.

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References