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Human Epidermal Growth Factor Receptor Family (HER) in Gastric Cancer

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1. Introduction

The epidermal growth factor receptor family consists of four members with similar structures: HER1/erbB1, HER2/erbB2, HER3/erbB3 and HER4/erbB4. The genes encoded for Erb are proto-oncogenes, or precursor genes, which under normal conditions are present in all cells of an organism. Proto-oncogenes can be activated in several ways, most often it is through structural changes of the cell genome such as point mutation, translocation or amplification (Ghaderi, 2002).

These receptors play an important role in the processes of proliferation and differentiation of normal cells. Hence, any aberrations in their structure or function can be the cause of tumor development and progression. All members of the epidermal growth factor receptor family have a similar structure with an extracellular domain linking the ligand, transmembrane domain and intracytoplasmic domain of the tyrosine kinase. The binding of the ligand to these receptors causes the creation of homodimers and heterodimers as well as the activation of downstream signaling pathways (Ghaderi, 2002). The ligand by inducing extracellular homo and heterodimerization of the ErbB receptors undergoes autophosphorylation using intracellular tyrosine residues by arranging the tyrosine kinase domains next to each other. The phosphorylated tyrosine endings of the cytoplasmic receptor act as sites that bind different intracytoplasmic transduction particles, which participate in the cellular response depending on ErbB stimulation (Tvorogov 2009). For this reason the HER family can contribute to tumor progression. Most research has shown a high level expression of the HER family members in patients suffering from gastric cancers (Ghaderi, 2002).

Signaling through the HER pathway plays a fundamental role in the regulation of correct cell growth, proliferation, migration and takes part in such processes like the healing of wounds, cell repair and skin maintenance. However, it has been shown that signaling through the HER pathway plays a very important role in the growth process, replication, migration and survival of cancer cells. Since the HER signaling pathway cascades, causing the strengthening of the growth signal on progressing levels, small changes in the amount or activity of EGRF can significantly accelerate the development or progression of the tumor by facilitating cell replication and migration, and suppression of the apoptosis process (programmed cell death). What is more, many studies have shown that HER signaling, a fundamental factor in correct cell growth and repair, can be activated as a response to different therapies used to treat cancer, like chemotherapy or radiation therapy, and can

lead to cell and tissue damage. It has been suggested that HER pathway activation can contribute to the development of resistance to cancer therapies (Zhou, 1992; Liang, 2003).

Under normal conditions the activation of the EGFR family is controlled by spatial and periodic expression of its ligands, which belong to the EGF-related peptide growth family, such as EGF, heparin-binding EGF (HB-EGF), transforming growth factor alpha (TNF- α) and neuroregulin. These growth factors are synthesized as transmembrane precursors released from the cell surface by proteolytic cleavage and subsequently activate RTKs of the EGFR family in an autocrine or paracrine fashion. Despite the abundance of ligands identified for EGFR, ErbB3 and ErbB4, no direct ligand for HER2 has been discovered. Instead, HER2 functions as a homo or heterodimer with other members of the EGFR family through interaction with anonic ligands, such as EGF, HB-EGF and TNF- α (Iwamoto, 2006).

Constant activation of receptor kinases leads to excessive activation of the signaling pathway. The causes of kinase over-expression can vary, mutations, autocrine kinase activation or amplification, for example. Elevated signal transfer activity can be connected to an increased risk of tumor development and malignancy (Walles, 1999).

2. HER 1/ EGFR/ HERA/c-erbB1

Epidermal growth factor receptor (EGFR) is one of four receptors in the pathway of epidermal growth factor transfer (HER, human epidermal growth factor receptor). It is a transmembrane glycoprotein consisting of 1186 amino acid residues. The gene encoding ErbB1 is located on chromosome 7 at p12.3-12.1. The emergence of mutation in this region leads to the appearance of mutated forms of EGFR. Three variants of these forms have been identified: I, II, III, with the mutation variant III (Δ EGFR) being most common. It involves the loss of the ligand binding site and leads to permanent spontaneous activation of the tyrosine kinase domain (Wojtukiewicz, 2010).

The EGFR has three domains: extracellular, transmembrane and intracellular. The extracellular domain contains relatively high levels of cysteine residue. It is a site of mitogen activator binding (ligands ErbB1) ex. epidermal growth factor (EGF), tumor necrosis factor α (TNF α), and heparin binding EGF - (HB-EGF). After the ligand attaches to the EGFR there is a change in the conformational isomerism of the receptor particle and dimerization takes place. This interaction allows for the greatest utilization of the characteristics of various combining receptors (Wojtukiewicz, 2010).

3. HER1/EGFR in gastric cancer

Experiments using monoclonal antibodies against c-erbB1 have been carried out during the treatment of different tumors. Among others, tumor fighting properties of the monoclonal human-mouse chimera antibody have been used to neutralize cancer cells in the large intestine both *in vitro* and *in vivo*. The antibody, in the second phase of the experiment, has been adapted for patients with head, neck and lung tumors (Ghaderi, 2002).

Meta-analysis showed the expression of c-erbB1 in gastric cancer in the range from 7.1% to as high as 80.0%. Positive correlation has been shown between the expression of this receptor and the diameter of the tumor, local invasion of the tumor and the spread of cancer cells to surrounding lymph nodes. Additionally, a relationship has been discovered between the stage of the tumor and the expression of c-erbB1. These results suggest c-erbB1

involvement in the progression of gastric cancer in patients from Iran and can be considered to be a prognosticating factor in these tumors. Similarly, high expression of c-erbB1 and its positive correlation with those prognosticating factors can become useful tools for diagnosing and prognosis in gastric patients from Iran. As a result it has been suggested that the expression of this receptor should be monitored as part of routine patient screening (Ghaderi, 2002).

4. c-erbB2, HER2/neu

HER2/neu is a proto-oncogene encoding transmembrane tyrosine kinase with a mass of 185 kDa. c-erbB-2 is encoded by a gene located on chromosome 17 (Ghaderi, 2002). Located on the cell membrane it binds with its extracellular growth factor ligands to HER-2 which leads to dimer formation with another HER-2 molecule or with HER-1, HER-3 or HER-4. Dimerization causes phosphorylation of tyrosine residue in the cytoplasmic domain of the receptor and a further activation of the intracellular transfer pathway, which regulates various biological reactions, including cell proliferation, differentiation, movement and survival. High expression of c-erbB-2 has been described in various types of tumors such as breast cancer, ovarian cancer, lung cancer, salivary gland cancer, cancer of the large intestine, prostate cancer and pancreatic cancer. It has also been suggested that this protein is an indicator of an unfavorable outcome (Satiroglu- Tufan, 2006).

ErbB2 does not have its own ligands and plays the role of a co-activator in relation to the other proteins of the ERBB family. Its basic signaling results from the ability to react with other ERBB receptors. The receptor can undergo stabilization as well as transactivation through the ligands specific to ERBB1 and ERBB3, which allows ERBB2 to take part in signal transfer. Heterodimers created by ERBB2 are considered to be particularly active (Citki, 2003; Lee, 2001).

Attachment of various ligands to the extracellular domain initiates the cascading of signal transduction. The ligand attaching to the EGFR induces homodimerization and heterodimerization with other types of HER proteins. HER2 does not attach to any known ligand but it is a preferred partner of heterodimerization for other members of the HER family. The HER2 gene, located adjacent to the topoisomerase IIa, is related to the oncogene v-erbB of the avian erythroblastosis virus. In tumors HER2 behaves like an oncogene, mainly because high level of gene amplification induces over-expression of the protein on the cell membrane and which then acquires characteristics typical to atypical cells (Gravalos, 2008).

In normal cell signal transduction Her2 plays a role of a growth factor and is connected with the regulation of cell growth, survival and differentiation. Its downstream signaling can be activated by point mutations, gene amplification or gene over-expression. There exists a hypothesis that high ERBB2 expression aids spontaneous dimerization which contributes to ERBB2 activation and downstream signaling (Arrington, 2009).

Amplification of the ERBB2 gene and/or the over-expression of its protein have been discovered in 20-30% of breast cancers. Over-expression of HER2, along with negative estrogen reception and early metastasis of these cancers, is treated as an independent factor predicting survivability and recurrence of the disease (Arrington, 2009).

5. HER2 in gastric cancer

HER2 expression in gastric cancer was described for the first time in 1986 (Gravalos, 2008). In breast tumors ERBB2 functions as an oncogene, with gene amplification and protein over-

expression in the cell membrane. Not only is gene amplification an indicator of unfavorable prognosis it is also a predictive marker for therapies using the monoclonal antibody trastuzumab on patients with breast cancer with metastases. Amplification of ERBB2 has been found not only in breast cancers but in other malignant tumors such ovarian cancer, lung cancer, cancer of the large intestine and gastric cancer. With the use of immunohistochemistry, in gastric cancer the expression of ERBB2 has been shown in 5.2-22.6% of cases, while the percentage of ERBB2 amplification with the use of fluorescent in situ hybridization (FISH) was within the range of 3.8-12.2%. However, clinical significance of ERBB2 amplification/overexpression in gastric cancer patients is still unclear (Barros-Silva, 2009).

An anomaly most commonly found in tumors is gene amplification with an increase of HER2 protein expression. In people with gastric cancer HER2 over-expression/amplification is detected in 15-59% of advanced tumors. In gastric cancer the up-regulation of HER2 expression can control the cell cycle, cell movement and invasion through several intracellular paths. HER2 signaling plays a fundamental role in the development, progression and metastasis of gastric cancer (Lee, 2010).

When the HER2 signal spreads from the cell surface to the intracellular effectors it requires a signal transducer and activates Grb2 (growth factor receptor- bound 2). It is thought that Grb2, which facilitates HER2 signaling, plays a fundamental role in the development of breast cancer, its progression and metastasis. Janes et al. (1994) have shown that in breast cancer cells HER2 over-expression was connected with the Grb2-SOS1 complex, which activated the Raf/MEK/MAPK pathway through Ras. However, the role of Grb2 and its connection to HER2 were seldom described in gastric cancer. Yu et al. (2009) have shown that Grb2 overexpression in the main mass of the tumor as well as in metastasis occurs late in the process of gastric cancer development. Overexpression of Grb2, however, was connected with unfavorable prognosis for these patients. Researchers have also shown a significant correlation between Grb2 and HER2 in stomach tumors (Yu, 2009).

Bao et al. (2010) utilized RNA interference in gastric cancer from SGC-7901 and MNK-45 cultures to halt the activity of the HER2 oncogene. Through this work they have shown that HER2 is not only closely connected to tumor growth but also to its invasiveness. Even as Sarna-HER2 stopped the growth of gastric cancer cells, HER2 reduced the migration and invasiveness of cancer cells. By comparing the HER2- knockdown group with the control group the researchers discovered the presence of several markers of metastasis: COL1A1, ACTA2, E- katherine, MMP-2 and MMP-9. The knockdown of HER2 was accompanied by significant deregulation of MMP-1, despite unchanged levels of MMP-2 and MMP-9. They also demonstrated that HER2 can regulate MMP-1 expression at the transcription level. HER2 does not increase transcription activity through Myc, SRY, CREB or NF- κ B attachment sites. This could be caused by downstream particles that have not been detected in bioinformatic analysis and which have the ability to attach to the MMP-1 promoter region and to regulate its transcription activity. Another interesting phenomenon was the fact that when MMP-1 was reduced the invasiveness of cells was nearly completely blocked. However, transcription of the MMP-1 expressing vector into shRNA-HER2 cells, which displayed a low ability for metastasis, resulted in only a partial restoration of the invasiveness of these cells. This data shows that MMP-1 is a downstream effector of HER2 and that HER2 can have an influence on other particles connected to metastasis, with the exception of MMP-1 (Bao, 2010).

6. HER3

The ERBB3 encoding gene is located on the 12 chromosome at q13. The proteins encoded by it show a low activity of tyrosine kinase. In comparison to ERBB2 and ERBB4, ERBB3 displays a much lower homology of the extracellular and cytoplasmic domains with the ERBB1 receptor, (Kraus, 1989; Lebeau, 2001). In all probability the ERBB3 by itself does not function as an oncogene, but increase of its expression can strengthen the oncogenic effect caused by the over expression of the ERBB2 receptor (Alimandii, 1995).

7. HER3 in gastric cancer

The expression of the HER3 protein is very often observed in advanced gastric tumors. It has been shown that HER3 expression is connected with gastric cancer progression and prognoses, while the HER1 or HER2 expression did not show a similar relationship. In the conducted *in vitro* experiments, HER3 blocking caused the decrease of the downstream signals and the death of tumor cells. It would seem that HER3 could be potentially useful in clinical treatment of cancer patients, especially those with stomach tumors. HER3 is associated with the signals mediated from HER1 or HER2, and it may be also associated with the resistance to anti-HER1 or anti-HER2 therapies. High expression of the HER3 protein could be an indicator of an unfavorable prognosis for gastric cancer patients. Positive staining has been observed more often in advanced tumors with high malignancy when compared to early stage cancers, which can point to the involvement of this protein in the progression process of the disease. Co-expression of HER3 and HER2 has not been connected to gastric cancer prediction. The creation of a heterodimer of HER3/HER1 has been observed in gastric cancer cells. What is more, a relationship between the expression of HER3 and HER1 proteins has been observed. The expression of HER1 has been accepted as a prognosis indicator for patients with gastric cancer. The expression of HER3 protein had a stronger correlation with remote metastases and the survival time of gastric cancer patients than HER1 expression. The role of the HER4 protein expression in gastric cancer has not been determined. A positive immunohistochemical reaction to this protein has been equally often observed in early stage and in advanced gastric cancer. A recent study of gastric cancer cells show that the GER family kinases were targets of amplified fibroblast growth factor receptor 2, and the inhibition of HER3 which resulted in the loss of cell proliferation initiated by the fibroblast growth factor receptor 2. For this reason, therapies involving blocking of HER3 can become part of the new strategy in gastric cancer treatment, along with therapies using anti-HER1 and anti-HER2 treatments (Hayashi, 2008).

Kabayashi et al. (2003) demonstrated that activation of phosphoinositide-3-kinase (PI3K)/Akt triggered by phosphorylation of HER3 was important for dedifferentiated phenotypes of gastric cancer cell cultures. They also showed that HER3 signal pathway contributed to the development of dedifferentiated carcinomas by promoting motility and invasion of adenocarcinoma cells. This evidence supports the possible involvement of HER3 in the dedifferentiation process of gastric cancer.

8. HER4

The gene encoding ERBB4 is located on chromosome 2 at q33.3-34 (Zimonjic, 1995). This gene is activated after combining with a neuroregulator, betacellulin and heparin-binding

EGF-like growth factor. Its activation leads to cell proliferation, chemotaxis or differentiation through the utilization of particular signal transferring proteins like P13K kinase and Shc (Carpentier, 2003). Even though the ERBB4 structure and function is similar to other members of the ERBB family it is still unclear what role, general or specific, ERBB4 plays in human tumor development. Protooncogenes, including EGFR and ERBB2, are most often evaluated in the light of mutation presence in tumors (Lynch, 2004; Peaz, 2004; Pao, 2004; Stephens, 2004; Shigama, 2005). For this reason it can be assumed that ERBB4 as a protooncogene is also subject to mutation in human tumors (Soung, 2006).

Tvorogov et al (2009) has shown that 2 of 10 mutations destroy the catalytic activity of ERBB4 tyrosine kinase. However, despite losing tyrosine kinase activity, two mutated receptors were still able to form a "working" heterodimer with ERBB2 and to activate mitogen-activated protein kinase Erk and phosphoinositide 3-kinase/Akt pathway. The mutant receptors were able to activate Erk and phosphoinositide 3-kinase/Akt signaling pathway to a similar extent as the wild-type ERBB4. ERBB4 kinase activity was required for NRG-induced activation of the signal transducer and activator of transcription 5 (STAT5), resulting in failure of ERBB4 mutants to activate STAT5 (Tvorogov, 2009). Whereas Erk and phosphoinositide 3-kinase/Akt pathway have been implicated in the survival and proliferation of cancer cells, the role of STAT5 signaling in cancer is not yet fully understood, however increased STAT5 signaling has been associated with transformation. (Yu, 2004).

9. HER4 in gastric cancer

The role of ERBB4 in the process of carcinogenesis has not been completely defined. YH Soung et al. (2006) described ERBB4 kinase domain mutation in gastric, breast, lung and large intestine tumors. It is the first report describing mutation of the ERBB4 kinase domain in human tumors. The location of the mutation in the kinase domain, a location very important for functioning, can suggest that the discovery of ERBB4 mutation could be a change in function. (Soung, 2006). Stephens et al. (2005) found ERBB4 mutation in 1 of 25 studied breast tumors and it was found outside the kinase domain. Soung et al. (2006) has shown a convergence in the presence of ERBB4 and K-RAS mutations in gastric cancer, which can occur and could play a role in the process of pathogenesis of gastric cancer. These observations are different from previous observations where the K-RAS mutation in patients with lung cancer was not connected to neither EGFR nor ERBB2 mutations (Kosaka, 2004). The presence of ERBB4 mutation in commonly appearing human tumors, can act as a green light to initiate research into introduction of therapies aimed at eliminating mutated ERBB4.

HER4 gene expression was higher in cancerous tissue in comparison to healthy tissue of a gastric tumor (Kataoka, 2008).

10. HER2 amplification

The amplification of the oncogene HER2 is an important biomarker in identification of patients who could react to HER2 therapy using the humanized monoclonal antibody trastuzumab (herceptin). Fluorescence *in situ* hybridization (FISH) or chromogenic *in situ* hybridization (CISH) can be used to assess whether tissue samples contain gene amplification. The FISH method is currently considered to be the "gold standard" in HER2 amplification detection. This method has a high sensitivity (96.5%) and specificity (100%)

(Pauletti, 1996). An additional advantage of this method is that it can be used on small samples and cuttings preserved in formaldehyde or paraffin. FISH facilitates the direct display of gene amplification in the cell nucleus and enables gene and chromosome count on a cell-by-cell basis (Park, 2006). CISH is an attractive alternative to FISH. Tissue preparation and the process of sample hybridization are the same for both methods. These techniques differ in the method of detection which in CISH involves the initiation of a reaction with peroxidase which can be seen with the help of an optical microscope and that allows for an easy assessment of tissues and amplification products. Additionally, CISH allows the creation of a permanent record and is much cheaper than FISH. Since CISH is a relatively new method, the comparison between CISH and FISH is still being made in the clinical setting (Park, 2006).

Wolf- Yadlin et al. (2006) made an attempt at explaining different effects of HER2 amplification in carcinomas with different growth patterns. These researches suggested that HER2 overexpression causes an increase in cell migration but has a minimal effect on proliferation of cells being stimulated by the epidermal growth factor (EGF) or heregulin. For this reason HER2 amplification can increase cell migration in expanding tumors, while infiltrative carcinomas, which possess high invasive potential, do not gain additional advantages with HER2 amplification.

Many researchers have shown that HER2 overexpression can be used as a prognostic factor for gastric cancer patients. The multi-variate analysis study performed by Brien et al. (1998) showed that the pathological stage and HER2 gene amplification are independent prognostic factors for survivability. Allgayer et al. (2000) confirmed the importance of HER2 status as a prognostic factor in a prospective study of gastric cancer. They have demonstrated a significant association between the level of HER2 expression and shorter recovery and overall survival.

11. Therapies using antibodies against the her family members

11.1 Trastuzumab (herceptin)

Trastuzumab (herceptin) is a recombinant humanized monoclonal antibody anti-HER2mAb (rhUMA HER2) with particle mass of 145531.5 g/mol. It was engineered from a cloned human IgG, with structure and antigen-binding residues of a potent murine mAb 4D5. Exact mechanics of how it behaves are not known, however it has been speculated that it plays a role in blocking the division of the HER2 receptor and dimerization; impedes the intracellular transference path P13K; has an anti-angiogenic effect by modulating the effects of pro and anti-angiogenic factors; or arresting cell proliferation in the G1 phase (Baselga, 2009; Valabrega, 2007; Hayashi, 2008).

Usually trastuzumab is well tolerated. When administered during therapy as the only medication side effects such as bone marrow suppression, nausea and vomiting or baldness are seldom observed (Hudis, 2007). However, trastuzumab therapy is connected with an increased risk of cardiotoxicity. This heart disorder is the most part reversible after discontinuation of the drug (Okines, 2010).

It has been shown that in patients with HER2 positive breast cancer, herceptin treatment does extend survival time. Among breast cancer patients with metastases, high HER2 expression and presence of amplification signified better effectiveness of trastuzumab therapy (Slamon, 2001).

HER2 status is usually determined by immunohistochemistry (IHC) and/or *in situ* hybridization. In IHC the four-tiered scoring system described originally for the Food and

Drug Administration (FDA), the HerceptTest, has been approved. Samples scored as 0 and 1+ are negative, 2+ as equivocal and 3+ as positive. However, the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines require in-house validation of 1+ and 3+ samples with ISH before a certified laboratory can confine ISH retesting to 2+ samples (Batra, 2008). Recently, a modification of the HerceptTest scoring system for gastric carcinomas was proposed (Table 1).

Intensity score	Staining pattern		HER2 expression
	surgical specimen	biopsy specimen	
0	no reactivity or membranous reactivity in <10% of tumor cells	no reactivity or membranous reactivity in any tumor cell	negative
+1	faint/barely perceptible membranous reactivity in $\geq 10\%$ of tumor cells; cells are reactive only in part of their membrane	tumor cell clusters with faint/barely perceptible membranous reactivity, regardless of percentage of tumor cells stained	negative
+2	weak-to-moderate complete, basolateral or lateral membranous reactivity in $\geq 10\%$ of tumor cells	tumor cell clusters with weak-to-moderate complete, basolateral or lateral membranous reactivity, regardless of percentage of tumor cells stained	equivocal
+3	strong complete, basolateral or lateral membranous reactivity in $\geq 10\%$ of tumor cells	tumor cell clusters with strong complete, basolateral or lateral membranous reactivity, regardless of percentage of tumor cells stained	positive

Table 1. Recommended scoring system to evaluate immunohistochemistry staining patterns in patients with advanced gastric cancer. (Yoon, 2011).

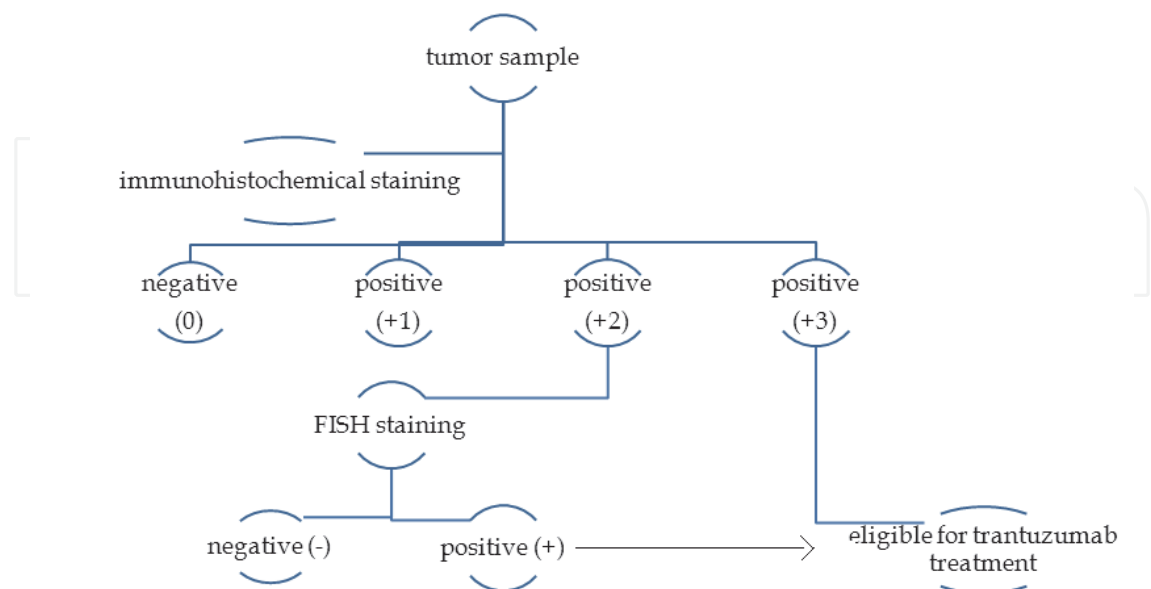


Fig. 1. HER2 testing algorithm in metastatic gastric and esophagogastric junction cancers. FISH: Fluorescence *in situ* hybridization; IHC: Immunohistochemistry (Yoon, 2011).

11.2 Cetuximab (anti-epidermal growth factor receptor monoclonal antibody)

Cetuximab is a class IgG1 monoclonal antibody designed to bind with the epidermal growth factor receptor (GFR) (Martinelli, 2009). Cetuximab binds to the extracellular domain of the EGFR in its non-active configuration and competes to bind with the receptor through sealing the ligand binding site. This interaction of the antibody and the receptor prevents dimerization of the receptor and so blocks the tyrosine kinase activation dependant on the EGFR ligand. Additionally cetuximab induces EGFR internalization, downregulation and degradation. By provoking an anti-cancer response dependant on the immune system, cetuximab represses the proliferation of cancer cells (stops the G1 phase), the production of vascular endothelial growth factor (VEGF), tumor dependant angiogenesis and the invasion of cancer cells (Ciardiello, 2008; Lordick, 2010).

The monoclonal antibody cetuximab has demonstrated antitumor efficacy both as a monotherapy and when combined with chemotherapy. (Lenz, 2006; Van Custen, 2007). Importantly, cetuximab treatment partially indicates that EGFR may improve resistance to irinotecan-based chemotherapy in a group of patients (Cunningham, 2004). Previous studies also reported that the EGFR TKI gefitinib worked well in combination with topo I inhibitors and platinum agents (Nagashima, 2006; Braun, 2005; Stewart, 2004; Van Schaeybroech, 2005). Pinto et al. (2009) published the results of the II phase of a study concerned with the treatment of patients with advanced gastric cancer with the drug combination: cetuximab and cisplatin. The response to this combination of drugs, observed at 41%, was higher than treatment with cisplatin or docetaxel alone. These researches have also shown that the entire progression rate was approximately eight months and was longer than during treatment with irinotecan or %- fluorouracil. Similar results were obtained by Lordick et al. (2010), with an average disease progression rate of 7.6 months. A slightly shorter disease progression time (about 5.5 months) and a response to treatment with cetuximab at 50% were observed by Han et al. (2009) in their research.

11.3 Lapatinib

Lapatinib is a potent ATP - a competitive inhibitor that simultaneously inhibits both EGFR and HER2. In cell-free biochemical kinase assays, lapatinib inhibits the recombinant EGFR and HER2 tyrosine kinase by 50% at concentrations of 10.8 and 9.3 nmol/L, respectively. In cell-based assays, lapatinib inhibits the growth of HER2-overexpressing BT474 breast cancer cells at comparably low concentrations of 100 nmol/L (Konecny, 2006).

Lapatinib showed significant results when combined with trastuzumab in HER2- amplified gastric cancer cells. The combination of lapatinib and trastuzumab induces nearly complete tumor regression in all of the mice that have been treated. Those effects were much more pronounced than either lapatinib or trastuzumab alone (Wainberg, 2010). Although results of Wainberg et al. (2010) were only preliminary, they support the ongoing investigation of lapatinib in gastric cancer as well as its possible combination with trastuzumab in HER2-amplified disease. The addition of anti-HER2 therapy to standard chemotherapy could have direct clinical benefit and makes the investigation of additional anti-HER2 therapies in upper gastrointestinal cancers, very desirable (Wainberg, 2010).

HER2 amplification is an important prognosis factor for the growth inhibitory activity of lapatinib in gastric cancer. Kim et al. (2008) has shown that lapatinib inhibits the phosphorylation of EGFR and HER2, and through this also impedes signal transfer from Akt and Erk in the gastric cancer cells sensitive to lapatinib. Lapatinib halted the G1 phase

of the cell cycle in cell cultures SNU-216, NCI-N87 and SNU-484, which displayed a growth inhibitory effect at higher concentrations. Furthermore, cMyc reduction and p27^{kip1} induction were also observed after lapatinib treatment. Conversely, the induction of apoptosis by lapatinib is linked to the inhibition of the Akt pathway, rather than the Erk pathway (Kim, 2008). Lapatinib blocks Erk phosphorylation through the stimulation of the IGF-1 ligand. However, the inhibitory effects for IGF-1-stimulated phosphorylation of the IGF-1 receptor were not seen in SNU-484. It could be that lapatinib inhibits the downstream signaling of the phosphorylated IGF-1 receptor via EGFR, considering that it is a complex between the IGF-1 receptor and EGFR which activates the Erk pathway (Kim, 2008).

Lapatinib, in combination with 5-FU, is currently used as the prodrug capecitabine in treating patients with breast cancers with HER2 expression in a clinical investigation of solid tumors (Geyer, 2006). It has been shown that lapatinib exhibits a high anticancer effectiveness in cells with high EGFR or HER2 expression (Rusnak, 2007; Konecny, 2006). Overexpression and/or amplification of HER2 in patients with breast cancer have been determined to be important prognostic factors in treating with lapatinib (Konecny, 2006).

11.4 Gefitinib

Gefitinib is an orally active, quinazoline tyrosine kinase inhibitor, selective for EGFR. Its anticancer effectiveness has been shown in lung cancer treatment. Somatic mutations within the ATP-binding pocket of the tyrosine kinase domain of the EGFR, including small in-frame deletions and missense substitutions, are present in lung adenocarcinomas and confer responsiveness to gefitinib in lung cancer patients (Lynch, 2004; Paez, 2004). Yokoyama et al. (2006), have shown for the first time that cell cultures (GLM-1, GLM-2 i GLM-4, NCI-N87) of gastric cancers were more sensitive to gefitinib than trastuzumab. Gefitinib induced apoptosis in cells demonstrating HER2 overexpression, something that has not been observed in commonly used gastric cancer cell cultures without HER2 expression.

It still seems unclear why gefitinib, an EGFR inhibitor, displays anticancer properties with gastric cancer cells that are HER2 positive but not those that are EGFR positive. Anido et al. (2003) have put forward a hypothesis that gefitinib prevents the formation of HER2/HER3 heterodimers by taking part in the sequestration of HER2 and HER3 with inactive (nonphosphorylated) EGFR/HER2 and EGFR/HER3 heterodimers. Yokoyama et al. (2006) has shown that gefitinib can selectively arrest the phosphorylation of Akt only in cells with HER2 overexpression, although cells with low HER2 expression also displayed constitutive activation of P13K/Akt pathway. This suggests that gefitinib can selectively block activated P13K/Akt pathways only because it is simply driven by HER2 overexpression along with relatively high expression of HER3, which permits the formation of the HER2/HER3 heterodimer (Yokoyama, 2006). The other interesting discovery made by these researchers has been the claim that gastric cancer cell cultures with HER2 overexpression become resistant to gefitinib. Gefitinib resistant cells of the GLM-1R culture have displayed an increase of EGFR expression and a more differentiated morphology in comparison to parental cells of the GLM-1 culture. The Shs and Erk1/2, upstream and downstream signaling molecules of the MAPK pathway, were also upregulated in GLM-1R cells. Additionally, the inhibition of the phosphorylation of Akt in GLM-1 parental cells in response to gefitinib treatment was weakened when the path Ras/MAPK was highly stimulated by higher concentrations of EGF. These observations can suggest that the pathway EGFR-Ras-MAPK is really (but in moderation) activated in compensation for the blockage of the HER2-P13K-Akt pathway in GML-1R cells, which results in persistent growth when gefitinib is present and the build up of resistance (Yokoyama, 2006).

12. Immunohistochemical evaluation expression of her2 and her1/egfr

Many investigators subsequently evaluated HER2 status in gastric cancer cells by IHC (immunohistochemistry). The frequency of HER2 overexpression was varied widely from 8 to 31 %. The consensus of almost all reports is that the majority of positive cases are the intestinal type histologically. Methods of IHC which evaluate for HER2 status in gastric cancer have not been standardized and that is a wide range in the frequency of overexpression, furthermore, there have been few reports claiming to have demonstrated HER2 gene amplification in gastric cancer (Sato, 1997; Takehana, 2002).

There are conflicting results in studies of HER2 with regard to its relationship to prognosis in gastric cancer patients. Some studies have reported that HER2 overexpression is a poor prognostic factor for gastric cancer (Uchino, 1993; Chariyalertsah, 1994; Mizutani, 1993). DI Park 2006 demonstrated that HER2 is a prognostic parameter in gastric cancer. Similar finding demonstrated Yonemura et al. (1991, 1991). They showed that immunoreactivity to HER2 can be an independent prognostic value in gastric cancer. Mizutani et al. (1993) reported significantly poorer prognoses for patients suffering from early gastric cancer who were HER2 positive in IHC. However, other studies have failed to find any association with prognosis whatsoever (Hilton, 1992; Kołodziejczyk, 1994; Tateishi, 1992; Sasano, 1993). Orita et al. (1997) elucidated prognostic significance of the expression of c-erbB-2 oncogene in gastric cancer patients. They found out that c-erbB-2 protein expression was associated with considerably shorter postoperative survival time. In patients with positive and negative c-erbB-2 expression, a 5-year survival reached 29% and 47%, respectively. Similar results have been reported by some other authors (Tsugawa, 1998; Nakajima, 1999; Pinto-de-Sousa, 2002). These data suggest that c-erbB-2 expression can be a prognostic factor for gastric cancer patients. However, according to other studies, c-erbB-2 does not exert a significant effect on the overall survival time of gastric cancer patients (Gurel, 1999; Polakowski, 1999).

The first preliminary data concerning the level of EGFR in the gastric wall were described by Yasiu et al. (1988), indicating an increase in the level of EGFR in neoplastic tissue compared to normal mucus. Similar observations have been reported by other authors (Kopp, 2002; Coyle, 1999). Kopp et al. (2002) suggested that in case of chronic inflammation or tissue damage the physiological effect of the ligand for the EGF-receptor pathway, associated with the regulation of regeneration and healing in the gastric mucus, may additionally stimulate the process of neoplastic transformation in the gastric mucus and tumor progression. We observed EGFR expression in 50% of the evaluated cases of gastric cancer. High expression was observed mainly in the intestinal type and poorly differentiated cancers, as well as in those infiltrating the whole gastric wall or at least into the muscular layer. However, we found no statistical significance. As reported by Gamboza-Dominguez et al. (2004), lack or low expression of EGFR protein was significantly correlated with prolonged postoperative survival time, as compared to the moderate and strong expression.

13. Conclusion

Signaling through the HER pathway plays a fundamental role in the regulation of cell growth, proliferation, migration and survival of neoplastic cells. Moreover, HER signaling can be activated as a response to different therapies used to treat cancer, like chemotherapy or radiation therapy, and can lead to cell and tissue damage. Elevated signal transfer activity can be connected to an increased risk of tumor development and malignancy. Positive

correlation has been shown between the expression of these receptors and the local invasion of the tumor, lymph nodes metastases and stage of gastric cancer. Overexpression of these factors may be a prognosticating factor in these tumors. As a result it has been suggested that the expression of HER family receptors should be monitored as part of routine patient screening. It was suggested, that blocking of the action of GER family receptors can be used in the treatment of gastric cancer. These agents, combined with chemotherapy and other targeted can be used in the future as a oncological therapy.

14. References

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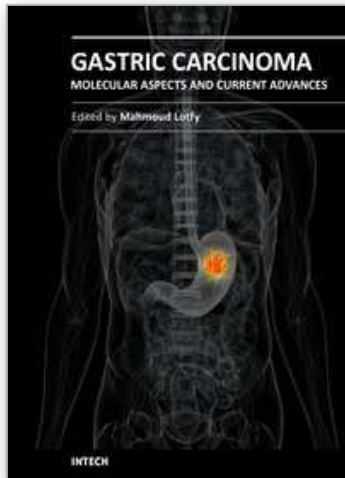
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Gastric Carcinoma - Molecular Aspects and Current Advances

Edited by Prof. Mahmoud Lotfy

ISBN 978-953-307-412-2

Hard cover, 354 pages

Publisher InTech

Published online 15, June, 2011

Published in print edition June, 2011

Gastric cancer is one of the most common tumors worldwide. It has a heterogeneous milieu, where the genetic background, tumor immunology, oxidative stress, and microbial infections are key players in the multiple stages of tumorigenesis. These diverse factors are linked to the prognosis of the gastric cancer and the survival of gastric cancer patients. This book is appropriate for scientists and students in the field of oncology, gastroenterology, molecular biology, immunology, cell biology, biology, biochemistry, and pathology. This authoritative text carefully explains the fundamentals, providing a general overview of the principles followed by more detailed explanations of these recent topics efficiently. The topics presented herein contain the most recent knowledge in gastric cancer concerning the oncogenic signaling, genetic instability, the epigenetic aspect, molecular features and their clinical implications, miRNAs, integrin and E-cadherin, carbohydrate-associated-transferases, free radicals, immune cell responses, mucins, *Helicobacter-pylori*, neoadjuvant and adjuvant therapy, prophylactic strategy for peritoneal recurrence, and hepatic metastasis.

How to reference

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Jolanta Czyzewska (2011). Human Epidermal Growth Factor (Her) in Gastric Cancer, *Gastric Carcinoma - Molecular Aspects and Current Advances*, Prof. Mahmoud Lotfy (Ed.), ISBN: 978-953-307-412-2, InTech, Available from: <http://www.intechopen.com/books/gastric-carcinoma-molecular-aspects-and-current-advances/human-epidermal-growth-factor-her-in-gastric-cancer>

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