Oncogene and Cancer

Eden Dennis

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Edited by **Eden Dennis**

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Preface

This book aims to highlight the current researches and provides a platform to further the scope of innovations in this area. This book is a product of the combined efforts of many researchers and scientists, after going through thorough studies and analysis from different parts of the world. The objective of this book is to provide the readers with the latest information of the field.

The course of cancer development has been presented in this book beginning from normal cells to cancerous form and the genomic instability, the cancer treatment as well as its prevention in the form of the invention of a vaccine. Certain diseases are also elucidated, like leukaemia, glioma, breast cancer, and cervical cancer. Comprehending cancer through its molecular mechanism is required to decrease the cancer incidence. Complications like metastasis and drug resistance and the procedure of treating cancer more efficiently are vividly illuminated in this book along with some research results that could be employed to treat the cancer patients in the not too distant future. The book encompasses topics like HER2 carcinogenesis: treatment, etiology & prevention; DNA repair mechanism & cancer; new approach to cancer mechanism and novel role of oncogenes & tumor suppressor genes.

I would like to express my sincere thanks to the authors for their dedicated efforts in the completion of this book. I acknowledge the efforts of the publisher for providing constant support. Lastly, I would like to thank my family for their support in all academic endeavors.

Editor

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1. Introduction

EGFR and HER2 family with signal pathway and carcinogenesis: The human epidermal growth factor receptors (HER-2) gene is localized to chromosome 17q and encodes a transmembrane tyrosine kinase receptor protein. Numerous studies were done from basic mechanism of HER family for cell proliferation and oncogenesis, HER2 overexpression or amplification in various solid tumors to clinical treatment of breast cancer, gastro-esophageal cancer by trastuzumab in many recent reviews [1-8].

HER2 belongs to a family including epidermal growth factor receptor (EGFR), HER2, HER3 and HER4, which are a group of transmembrane glycoproteins, collectively named receptor tyrosine kinases (RTKs), whose cytoplasmic domains harbor an enzymatic activity, namely tyrosine-specific phosphorylation [9]. The family of epidermal growth factor molecules, which comprises different ligands sharing a 50–60 amino acid receptor-binding domain, bind with subtype RTKs. Each receptor consists of an extracellular ligand-binding domain, a transmembrane domain, and a tyrosine kinase portion [10]. Upon ligand binding, the otherwise inactive monomeric receptors form active homodimers or heterodimers, thereby leading to receptor phosphorylation and signaling via various biochemical pathways (Fig.1), such as the mitogen-activated protein kinase (MAPK), the phosphatidylinositol 3-kinase (PI3K), phospholipase C-γ, and transcription factors like the signal transducers and activators of transcription (STATs) or SMAD proteins [1]. These modules of cellular activation and the respective growth factors (GFs)s are co-opted in several phases of tumor progression.

HER-2 gene amplification in breast cancer has been associated with increased cell proliferation, cell motility, tumor invasiveness, progressive regional and distant metastases, accelerated angiogenesis, and reduced apoptosis [11]. Overexpression of HER2 in human

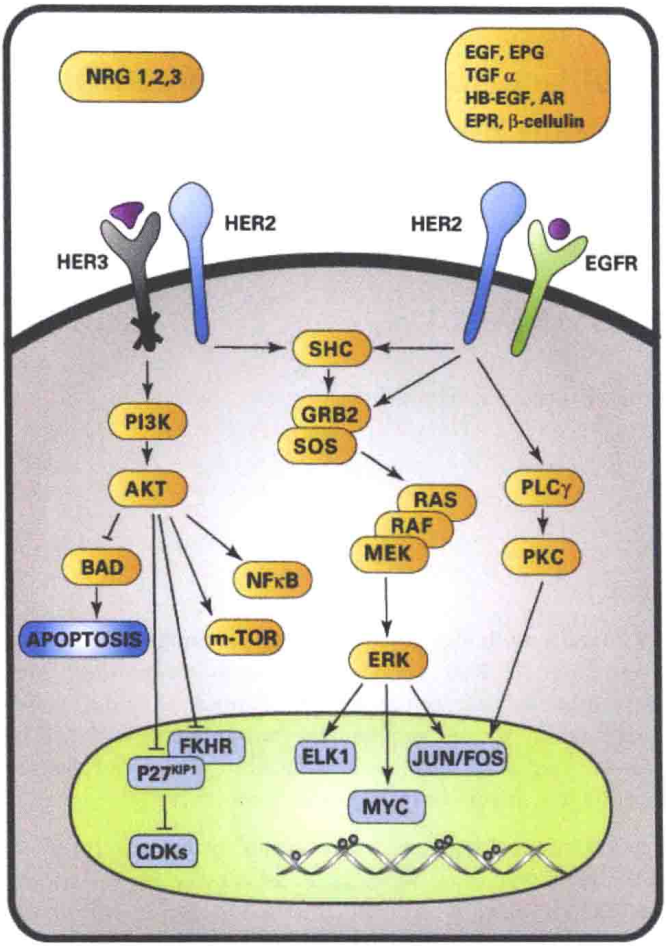

Figure 1. Signal transduction pathways instigated by HER2, co-receptors and EGF-like growth factors. Heterodimers of HER2/ErbB-2 and either EGFR/ErbB-1 or the kinase-defective ErbB-3/HER3 (note the letter X that symbolizes a defective cytoplasm-facing kinase domain) are shown, along with the growth factor ligands they bind. All ligands share an epidermal growth factor (EGF) motif of 50–60 amino acids. They include, in addition to EGF, epiregulin (EPG), transforming growth factor alpha (TGF-alpha), heparin-binding epidermal growth factor-like factor (HB-EGF), amphiregulin (AR), epiregulin (EPR) and betacellulin. Another group includes four classes of neuregulins (NRGs). Note that HER2 is unable to bind a ligand. Nevertheless, HER2 takes part in signaling via its own constitutive phosphorylation, as well as by trans-activation of its heterodimerization partners. Tyrosine phsphorylated receptors are coupled to several biochemical cascades, including the phosphoinositide-3-kinase (PI3K) pathway and the extracellular signal-regulated kinase (ERK), which belongs to the MAPK family. Activation of ERK/MAPK is mediated via the RAS-RAF-MEK pathway and leads to cellular proliferation via the activation of a number of nuclear targets, including the AP1 (FOS and JUN) complex, MYC, which regulates cell cycle progression, and ELK1, a member of the ETS family of transcription factors. SHC and GRB2 are adaptor proteins sharing the ability to bind each other, as well

as tyrosine phosphorylated receptors. The EGFR/HER2 heterodimer also couples to phospholipase C (PLC) and the downstream protein kinase C. On the other hand, ErbB-3/HER3-containing heterodimers strongly activate another kinase, AKT, via a lipid kinase, PI3K, leading to activation of mTOR (mechanistic target of rapamycin). Activation of AKT blocks signaling via BAD, a BH3-only protein, which contributes to tissue homeostasis by regulating initiation of apoptosis. Activation of AKT inhibits FKHR and the cyclin-dependent kinase inhibitor $p27^{KIP}$. The forkhead box O1 (FKHR, FOXO1) transcription factor is a member of the FOXO family of transcription factors, involved in tumor suppression and cell death. (From Emde A, et al. Crit Rev Oncol/Hematol (2010), http://dx.doi.org/10.1016/j.critrevonc.2010.09.002, Permitted by Elsevier Limited).

mammary epithelial cells induces proliferative advantage, transformed characteristics, tumorigenic growth, and induces proliferative and anti-apoptotic changes that mimic early stages of epithelial cell transformation [12]. HER2 amplification is also seen in early in situ ductal carcinomas without any evidence of invasive disease [13, 14]. HER2 status is maintained during progression to invasive disease, nodal metastasis and distant metastasis [14, 15]. HER2 overexpression has been shown to activate multiple signaling complexes, which results in a striking dysregulation of the global transcriptome [1].

Clinical treatment targeting on HER2 receptor: It took a long journey to develop monoantibody to target HER2. Murine origin of mAb to HER2 limits their clinical application since immunoglobulin molecules are immunogenic. When injected into humans, it shortens their half-lives in circulation. Winter and colleagues (1988) generated a mouse–human chimeric antibody [16]. Later transgenic mice whose immunoglobulin loc have been genetically inactive, was used to produce the first fully human antibody, Panitumumab, an antibody to EGFR. Then, trastuzumab which carry all human immunoglobulin genes, a monoclonal antibody to HER2, was approved for clinical use in lymphoma and in breast cancer [17]. So far, only two drugs that target HER2, Trastuzumab and a kinase inhibitor called Lapatinib/Tykerb, are approved for clinical application in breast cancer, but several novel drugs are in development (see figure 2).

Trastuzumab, monoclone antibody on HER2: Trastuzumab, a monoclonal antibody that targets HER2, induces antibody-dependent cellular cytotoxicity, inhibits HER2-mediated signaling and prevents cleavage of the extracellular domain of HER2 [12]. Based on multi-centers and countries clinical trial for HER2 positive breast cancer, [18,19,20] trastuzumab was significantly improve the prognosis of breast cancer. Therefore, it was initially approved for treatment of patients with HER2 overexpressing metastatic breast cancer. Because Trastuzumab also enhances the efficacy of adjuvant chemotherapy in operable or locally advanced HER2-positive tumors [21], the antibody currently represents the standard of care for patients with early or advanced stages of HER2-overexpressing breast cancer.

Since breast cancer showed better prognosis with trastuzumab treatment for HER2 positive breast cancer patients and similar HER2 positive cancers were identified in gastric and gastro-esophageal cancer, clinical trial ToGA was performed in gastric carcinoma. ToGA (Trastuzumab for Gastric Cancer) was an open-label, international, phase 3, randomized controlled trial undertaken in 122 centers in 24 countries [22]. Clinical trial ToGA used trastuzumab combined with standard chemotherapy for HER2 positive gastric cancer and

gastro-esophageal junction cancer which demonstrated a significant improvement of gastric cancer survival. Now, trastuzumab is approved for treatment of gastric cancer in European, United States, Japan and other multiple countries.

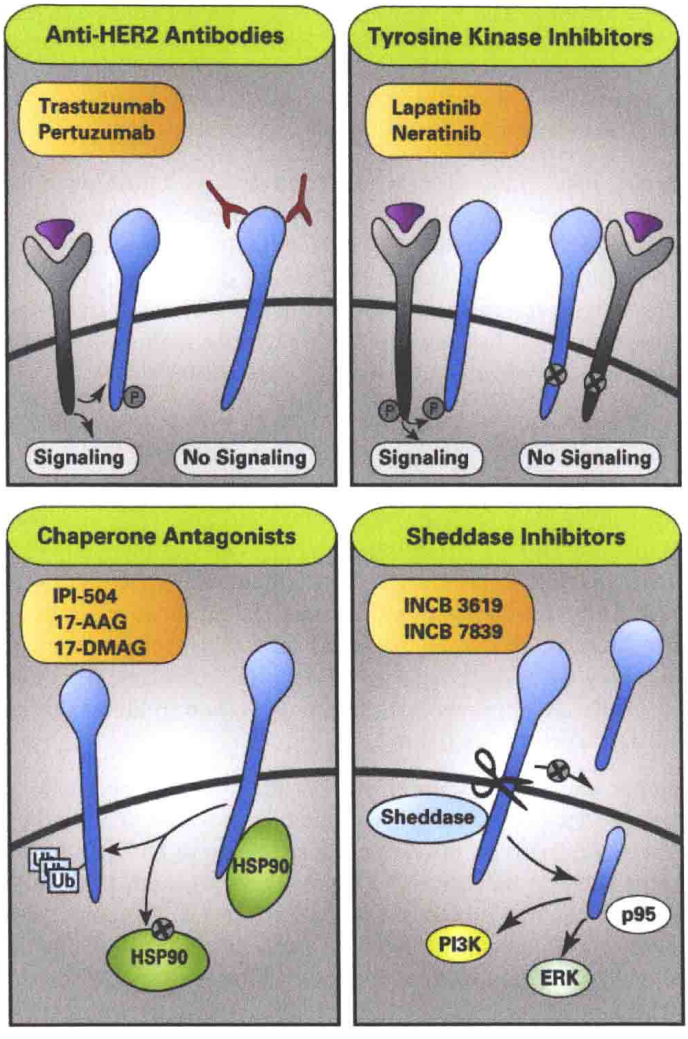

Figure 2. Clinically approved and experimental therapeutic strategies targeting ErbB-2/HER2 in carcinomas. Trastuzumab, a humanized monoclonal antibody directed against the extracellular domain of HER2, is approved for the treatment of HER2-overexpressing breast cancer. The antibody recruits immune effector mechanisms and can induce apoptosis, block angiogenesis and inhibit tumor cell proliferation. Similarly, Pertuzumab is able to prevent heterodimerization of HER2 with other family members. Unlike the ultimate specificity of Trastuzumab and Pertuzumab to HER2, tyrosine kinase inhibitors like the reversible inhibitor Lapatinib (approved for treatment of breast cancer) and the irreversible inhibitor Neratinib variably inhibit a broad range of tyrosine kinases. The drug has

completed phase II clinical trials. HSP90 is a molecular chaperone required for proper folding of protein kinases like HER2. Hence, HSP90 inhibitors, such as 17-AAG, which block the ATP/ADP binding pocket of HSP90 and target HER2 for proteasomal degradation are in clinical trials. A naturally occurring truncated form of HER2, p95-HER2, has been implicated as a mechanism conferring resistance to Trastuzumab. Its formation is mediated by processing of the membrane bound HER2 by matrix metalloproteinases (MMPs) of the ADAM (*a d*isintegrin *a*nd *m*etalloproteinase) family. INCB3619 and INCB7839 are potent inhibitors of ADAM10 and ADAM17. ADAM10 is the principle sheddase for different molecules associated with tumor cell proliferation, whereas ADAM17 is the main sheddase for the EGFR ligands TGF-alpha, AR, NRGs, and HB-EGF. These similar inhibitors may effectively block truncation of HER2 and onset of patient resistance to Trastuzumab, but clinical testing has not been completed. (From Emde A, et al. Crit Rev Oncol/Hematol (2010), http://dx.doi.org/10.1016/j.critrevonc.2010.09.002, Permitted by Elsevier Limited).

The clinical efficacy of Trastuzumab likely entails a combination of immunological and non-immunological mechanisms [1]. The ability of Trastuzumab to elicit antibody-dependent cellular cytotoxicity critically influences the efficacy of Trastuzumab-based therapies. Non-immunological mechanisms of Trastuzumab action include the inhibition of HER2 activation and downstream signaling. Alternatively, Trastuzumab may act by removing HER2 from the cell surface. Because it binds to an epitope near the cleavage site of HER2's extracellular domain, Trastuzumab inhibits HER2 activation by metalloproteinase-mediated shedding of the extracellular domain. The resulting interference with HER2-mediated downstream signaling processes shuts down cell proliferation, angiogenesis, invasive growth, resistance to apoptosis, and DNA repair, thus sensitizing tumor cells to conventional therapeutic modalities such as chemotherapy, endocrine treatment and radiotherapy.

Lapatinib, small molecule kinase inhibitor: Lapatinib, binding either reversibly or irreversibly to the nucleotide-binding cleft of their target kinases, is a highly specific, reversible inhibitor that blocks the catalytic action of both HER2 and EGFR[23]. Experiments in vitro and xenograft models, established the ability of Lapatinib to inhibit both the intact form of HER2 and the truncated intracellular form (p95-HER2), which is not recognized by Trastuzumab.

Similar to Trastuzumab, Lapatinib combined with chemotherapy was found to be better effect than capecitabine alone in HER2-positive women with advanced breast cancer that progressed after treatment with regimens that included Trastuzumab, an anthracycline and a taxane [24]. In addition, Lapatinib demonstrated clinical activity and was well tolerated as first-line monotherapy in HER2-amplified, locally advanced or metastatic breast cancer [25, 26]. Recently, laptinib showed a synergistic effect with trastuzumab in vitro and in vivo to inhibit HER2 amplified human gastric cancer cells and animal model [23]. Clinical phase II trial of lapatinib as first line therapy in patients with advanced or metastatic cancer showed well tolerated, which will be another potential drug to target HER2 receptors.

Lapatinib response correlated with EGFR and HER2 expression levels in patients' tumors, and associated with increased pre-treatment expression of phosphorylated-HER2 (p-

HER2)[27]. Lapatinib is able to induce apoptosis of Trastuzumab-resistant breast cancer cells via alteration of IGF-1 signaling, [28, 29] and also block NRG-induced p95-HER2/HER3 heterodimers formation [30].

2. HER2 in gastric adenocarcinoma

Gastric cancer is the fourth most common cancer worldwide and the second most common cause of cancer-related death in the world [31, 32]. The incidence of gastric cancer varies substantially worldwide, with the highest rates (>20 per 100,000) occurring in Japan, China, Eastern Europe, and South America, but the lowest rates (<10 per 100,000) finding in North America, southern Asia, North and East Africa, Australia, and New Zealand. In addition, it is more common in men than in women (10.9 vas 5.5 per 100,000). Although the survival of gastric cancer is improved in recently years in Western countries the 5 year survival is still around 5-20%. The multimodality treatments including surgery and neoadjuvent chemotherapy have a limited effect on the overall survival. In breast cancer, HER2 overexpression and amplification were reported around 25% and associate with poorer prognosis [2]. Trastuzumab treatment of HER2 positive breast cancer patient improved survival. HER2 overexpression and amplification were reported in gastric and gastro-esophageal junction (GEJ) tumors from 6-43%. In addition, trastuzumab were found to inhibit tumor growth in gastric carcinoma cell lines, animal model and xenograft models [33-35]. Recently international large scale phase III clinical trial called ToGA showed that trastuzumab added to standard chemotherapy significantly improved the response rate, median progression-free survival, and overall survival of gastric adenocarcinoma[22]. Trastuzumab combined with standard chemical therapy (such as capecitabine or 5-fluorouracil and cisplatin) now is approved by European Medicines Agency, United States and Japan etc. for the treatment of patients with HER2 overexpression or amplification. Thus clinical tests for HER2 overexpression and amplification in gastric adenocarcinoma patients become a key to recruit eligible patients for clinical treatment and evaluation of treatment effect.

IHC studies on HER2 overexpression: HER 2 overexpression was reported from 7-34% by many studies [3]. For clinical trial and treatment, it is very important to develop a standard HER2 test to recruit eligible patients for trastuzumab treatment. Before clinical trial ToGA, Hofmann and colleagues (2008)[36] first set up an IHC criteria based on HER2 IHC test on 168 gastric and GEJ resection patients (see Table 2). Based on the standard HER2 test on the breast cancer, they further proposed that strong incompletely membranous stain with basolateral "U" shape in gastric cancer was positive for HER2 overexpression. In addition, the HER2 expression showed higher heterogeneity about 4.8% in gastric samples than about 1.4% in breast cancer. They modified breast criteria in several points including incomplete membranous stain pattern and percentage of cells (≥ 10% cut off), which improved the concordance level between IHC and FISH tests to 93.5%. For ToGA clinical trial, Bang et al [22] reported that HER2 positive rate was a 22.1%. In addition, they found that HER2-