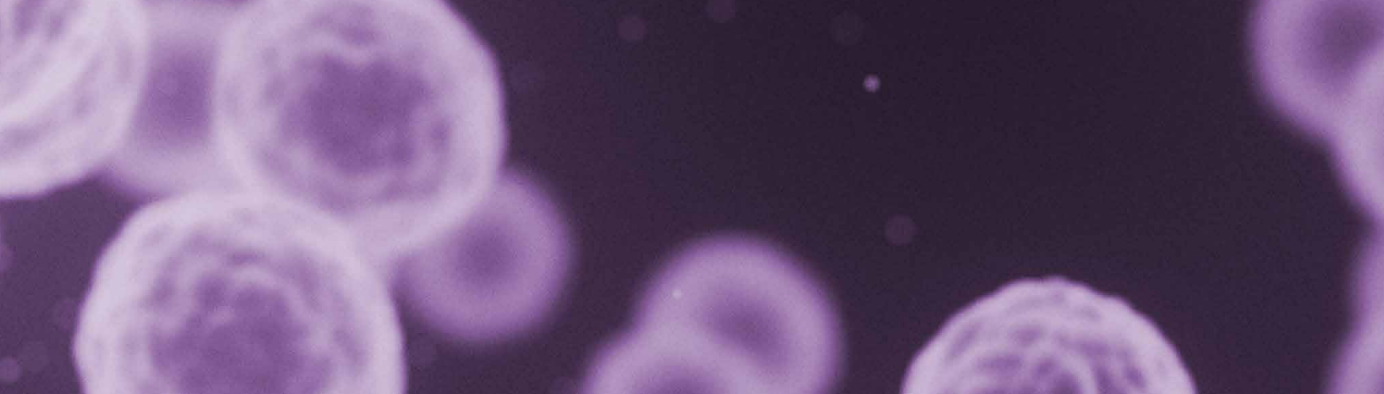




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Role of HER2

From Molecular Mechanisms
to Targeted Therapies

Edited by Ammara Riaz



Role of HER2 - From Molecular Mechanisms to Targeted Therapies

Edited by Ammara Riaz

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Role of HER2 – From Molecular Mechanisms to Targeted Therapies

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Volume 10

Aims and Scope of the Series

The field of oncology has undergone extraordinary change and progress over the past several decades. Today, information is evolving at a rapid rate, with standards of management far different than standards of care applied during the training of most practicing oncologists. Oncology practitioners in all disciplines must remain current to optimize patient care. Basic and translational science remain critical in developing process improvements for patient care. The closer we understand the mechanism, the more we can improve targeted therapies and apply them to patient care. The pace of information is moving faster than at any previous time in history, and all oncology disciplines must remain current to provide excellent service to patients. The modern oncologist must be fluent in using big data and the volume of information generated in clinical trials. As we move closer to personalized patient care based on genomics and molecular biomarkers, the modern oncologist has to be nimble in assessing all available information and how this would be applied to each patient, balanced by the clinical status and medical co-morbidities of each patient. Targeted therapies can bring new and different sequelae, and oncology teams need to remain fluent in managing the consequences of therapy and primary management. In this book series, we will present how modern care has progressed in multiple disease areas and how modern oncology teams need to adapt in order to manage the cancer patients of today successfully. Surgery, radiation therapy, and medical oncology are practiced today with the support of exceptional modern technology, and in this series, we will review how these improvements are applied to each disease site to maintain excellence in patient care.

Meet the Series Editor



Dr. FitzGerald is the professor and chair of the Department of Radiation Oncology at UMass Chan Medical School in the USA. He serves as one of the principal investigators of the Imaging and Radiation Oncology Core (IROC) service for the National Cancer Institute clinical trials program and is directly involved in the quality assurance of clinical trials in the National Clinical Trials Network (NCTN). Dr. Fitzgerald manages NCTN clinical trials with a real-time pre-therapy review of imaging and radiation therapy treatment objects to ensure the care plan complies with study objectives and the patient stage has been assigned to the correct study. His basic science interest is in hematopoietic stem cell biology and cellular adhesion molecules as they pertain to therapeutic resistance and mitigation of injury from therapy.

Meet the Volume Editor



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Preface

The book, entitled *Role of HER2: From Molecular Mechanisms to Targeted Therapies*, is structured according to the research interests of both molecular biologists and medical oncologists.

HER2, also known as Human Epidermal Growth Factor 2, is involved in cell growth, division, and repair; however, its elevated levels lead to the development of aggressive cancers. The HER2 gene provides the instructions for making the HER2 protein, which is found on the surface of many cells. The status of HER2 plays a crucial role in diagnosis and predicting the response to specific targeted treatments.

This book explores the role of HER2 in diagnosis, treatment options, and testing for HER status in cells. This book is helpful from both clinical and academic perspectives, as it serves as a reliable source for researchers. The valuable opinions, criticisms, suggestions, and queries are welcome for bringing out the improvements in the book.

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Section 1

What is HER2?

Introductory Chapter: HER2 – A Key Player in Cancer Biology

Ammara Riaz

1. Introduction to HER2

Cell division and differentiation are regulated by peptide growth factors. They play an essential part in the maintenance of neoplastic alterations. Many activated proto-oncogenes produce growth factors and their receptors. Type I receptor tyrosine kinase (RTKs) is the most widely researched of these. The four homologous receptors in this family—HER-1, HER-2, HER-3, and HER-4—are the offsprings of the proto-oncogenes c-erbB1, c-erbB2, c-erbB3, and c-erbB4, respectively. Because HER-2 has unique characteristics, it is the most well-known and significant receptor [1]. On the long arm of chromosome 17 (17q21), HER-2, alternatively referred to as c-erbB2, is a naturally occurring human proto-oncogene. It can be amplified by unidentified mechanisms and transformed into the HER-2 oncogene. HER-2 is a trans-membrane epidermal growth factor receptor with an extracellular and an intracellular component and is the member of the family of epidermal growth factor receptors. The central nervous system, kidneys, digestive system, lung, ovary, and breast tissues contain this protein. About one-third of invasive breast tumors have amplified HER-2 genes, which means that each cell produces 50–100 copies of the gene instead of two copies (one in each chromosome). As a result, the HER-2 protein is overexpressed, and neoplastic cells may have up to 2,000,000 HER-2 molecules rather than the 20,000–50,000 copies found in normal tissues [2].

1.1 HER2 protein

One receptor tyrosine kinase that helps regulate cell division and proliferation is the transmembrane protein of cells known as HER2. HER2 can form homodimers or heterodimers with other EGFR family members in both ligand-dependent and ligand-independent ways. When the EGFR and HER2 families bind to certain growth factors in heterodimers, signaling pathways that promote cell migration, survival, and proliferation are activated. When HER2 is overexpressed because there are too many copies of the HER2 gene, there may be too much HER2 protein on the transmembrane of cancer cells. This overabundance can lead to unregulated cell proliferation and is associated with more aggressive forms of cancer [3].

About 20–30% of breast tumors overexpress HER2. Compared to HER2-negative breast cancers, this tumor is more likely to be aggressive and to recur. Metastatic breast cancer can result from some HER2-activating mutations that were shown to be

negative in the HER2 IHC clinical group with hyper-activated signaling. Following the identification of HER2 mutations, tailored treatments intended to block HER2 signaling were created. The spread of HER2-positive breast cancer cells can be slowed or stopped by these medications' efficient blocking of HER2 signaling [3]. One crucial prognostic and predictive indicator for breast cancer is HER2 status. Compared to HER2-negative breast cancer, HER2-positive breast cancer typically has a worse prognosis. However, patients with HER2-positive breast cancer now have far better results thanks to targeted therapy. Breast cancer, particularly HER2-mutated metastatic cancer, has presented issues due to adaptive and acquired treatment resistance. In addition to breast cancer, various cancer types have been found to contain HER2 changes, including activating mutations and overexpression, including gastric and gastro-esophageal cancers (4.4–53.4%), endometrial cancer (20–40%), non-small-cell lung cancer (4%) and ovarian cancers. This tumor is the subject of ongoing research on HER2 and novel treatments that target HER2 signaling [4].

1.2 HER2 function

There is no known natural ligand that the HER2 extracellular domain can bind. The shape that HER2 naturally adopts promotes oligomerisation and HER2 kinase activation, whereas other members of the ErbB family necessitate ligand activation. The dimerisation arm of HER2 is permanently accessible for homo- or hetero-dimerization with receptors of ERBB-family due to its shape. When soluble growth factors activate these receptors, homo-dimeric or hetero-dimeric interactions between members of the monomeric family occur, along with conformational changes, which trigger signal transduction and intracellular kinase domain auto-phosphorylation. Overexpression of HER2 decreases the pace at which ligands dissociate from active dimers and increases the affinity of EGF and neuregulins for their receptors. The degradation rate of HER2 has also been demonstrated to be impacted by HER2 overexpression. EGFR-HER2 heterodimers undergo endocytic recycling instead of destruction, which prolongs EGFR signaling. In HER2-amplified tumors, the HER2-HER3 heterodimer seems to be effective signaling complex among the heterodimers created during ligand activation. HER3-dependent phosphorylation and subsequent PI3K/Akt signaling pathway activation facilitate signaling via the HER2-HER3 complex. Reduced heregulin (HRG)-induced HER3 degradation due to HER2 overexpression prolongs signaling pathway stimulation. According to in vitro research, HER2 overexpression causes drug resistance, increased invasiveness, malignant transformation, and the emergence of anti-apoptotic characteristics. One of the main processes causing the cell proliferation seen in HER2 overexpressing cells is probably receptor activation via HER2-hetero-oligomerization [5].

1.3 Role of HER2 in cell signaling and growth regulation

In particular, HER2 signaling pathways are essential regulatory mechanisms for cell growth, survival, and differentiation. There is currently no familiar ligand that binds with HER2 receptor directly. Instead, HER2 is the most common partner for making heterodimers (pairing) with other EGFR receptors. A key component of its signaling system, HER2 dimerization is important for the biology of many types of cancer. A crucial stage in this pathway is the production of dimers, either homo- or hetero-dimers. The characteristics and outcomes of HER2 dimerization might change greatly depending on the type of malignancy. With different patterns of expression

both within and between tumors, the variability of HER2 expression is higher in gastric cancer than breast cancer [5].

In addition to dimerising with HER3, HER2 in gastric cancer may also dimerise with EGFR family members, which could lead more aggressive tumor. In colorectal cancer, HER2 can dimerise with EGFR, affecting the tumor's receptiveness to treatments that target EGFR, including cetuximab. A subset of ovarian tumors has overexpressed HER2, which frequently forms dimers with EGFR family members. With EGFR family members, HER2 can ligand-independently make homo- and heterodimers. HER2 homodimers signal less strongly than heterodimers. HER2/HER3 heterodimers, on the other hand, are especially strong and activate strong downstream signaling pathways. When dimerised with HER2, HER3's six binding sites for the p85 subunit of PI3K are essential for the activation of the PI3K/AKT pathway [2]. HER2 uses downstream targets to interact with other signaling pathways. In addition to encouraging cell growth and survival, Akt activation interacts with additional pathways. Ras is a small GTPase protein that can also be activated by HER2. Raf, which is activated by Ras, starts a chain reaction that stimulates ERK (extracellular signal-regulated kinase). By either directly phosphorylating or inhibiting TSC2 or phosphorylating and activating mTORC1, ERK activation can interact with the mTOR/ PI3K/Akt pathway [6].

Additionally, ERK can interact with the JNK (c-Jun N-terminal kinase) pathway to affect cellular reactions including proliferation and death. The Wnt/ β -catenin pathway, which is essential for controlling the growth of tumors, can interact with HER2 signaling. B-catenin can be stabilized and nuclear translocated as a result of HER2 signaling activation, which also promotes the transcription of Wnt target genes essential for cell survival and proliferation. The NF- κ B pathway, which controls genes related to inflammation, cell survival, and immunity, can be activated by HER2 signaling. When HER2 signaling is activated, I κ B α (an inhibitor of NF- κ B) may be phosphorylated and degraded, which causes NF- κ B to move nuclearly and its target genes to become transcriptionally active. HER2 signaling can interact with estrogen receptor (ER) signaling in hormone receptor-positive breast cancer and affect how well endocrine therapy works. ER can become phosphorylated and activated as a result of HER2 activation, which increases its transcriptional activity and encourages cell division. Clarifying the intricate processes behind cancer growth and treatment resistance requires an understanding of the interactions between HER2 signaling and other pathways. It could be essential to target several signaling pathways at once in order to effectively stop tumor growth and enhance patient outcomes [5].

2. Role of HER2 in cancer development and progression

2.1 HER2 overexpression and amplification in cancer

Overexpression of HER2 has been proposed to be related to the aggressiveness of the tumors, prognosis, and sensitivity to hormone and cytotoxic agents among the patients of breast cancer. No known ligand has direct interaction with HER2 receptor. Rather, HER2 is the partner of choice in the formation of heterodimers with EGFR family members. HER2 dimerization is an important attribute of its signaling pathway and is prominent in the biology of many cancers, including cell proliferation [5]. In other scenarios, HER2 is over-expressed, and the HER2 gene had excessive copies; hence, excessively, the HER2 protein is expressed on the transmembrane of the cancer

cells. Uncontrolled cell growth may result because of this overexpression and it is linked to more aggressive types of cancer [5].

In vitro research and animal research have put it clear that HER2 protein overexpression is a key factor in the oncogenic transformation and tumorigenesis. Research into the use of NIH 3 T3 cells incriminates the overexpression of HER2 in malignant change and tumorigenesis. The HER2 gene transfection into human breast and ovarian tumor cell lines resulted in the development of more aggressive growth properties. Slamon initially noted that HER2-gene amplification was an independent predictor of overall (OS) and diseasefree survival (DFS), and numerous investigations have supported the fact that the HER2 overexpression is a determinant of poor prognosis in women suffering from breast cancer [7].

HER2 gene encodes HER2 protein and the amplification of the latter seems to be the most widespread mechanism of the HER2 protein overexpression. Nevertheless, amplification does not always result in overexpression. According to some tumors, it has thus been proposed that HER2 overexpression can be due to transcriptional or post-transcriptional dysregulation. The architecture of the protein that is overexpressed to the HER2 is identical to the structure of any standard healthy cell, as no mutational modifications have been displayed in the HER2 gene product have been found to occur in human cancers [8]. The common progression of oncogenic transformation is supposedly caused by early HER2 gene amplification which produces more than the two copies of normal genes in the epithelial cell; the excess of more than 10 copies of the gene is more which is preferentially observed in the amplified form [9]. The exact causes which cause amplification of HER2 gene have not been fully understood. HER2 gene amplification causes an augmentation in the transcription of the HER2 gene, which leads to elevated levels of HER2 mRNA and concomitant augmented the production of HER2 protein. HER2 protein is then in its turn overexpressed on the cell surface. The levels of HER2 protein range between 10 and 100 times.

As more on cell surface of her 2-positive breast comparative cancer cells with surrounding normal breast epithelial cells. Cell surface HER2 protein overexpression is likely to result in constitutive activation of HER2 homodimer receptors with no ligands are required to bind. This leads to uncontrolled cell proliferation and oncogenic change, which in certain cases leads to the viable cancer [8]. Due to the spontaneous occurrence of receptor. HER2 is highly basally active in tumors in dimers. This is overexpressed, which can influence the activity and/or other HER family members that are the ones expressed. The observation that HER3 possesses a higher level of phosphotyrosine in tumors that are HER2 positive means that HER2 facilitates malignant growth through HER3. Overexpressed HER2 receptor preferentially associates with the HER3 receptor, and hyperactivation of cell-signaling networks is maintained which result in high cell cycle regulator levels. This causes uncontrolled cell growth, tumorigenesis, and proliferation [9].

2.2 HER2 impact on tumor growth, metastasis, and prognosis

The persistent activation of HER2 signaling results in accelerated cellular proliferation and resistance to apoptosis. HER2-positive tumors often exhibit high histological grade, increased mitotic index, and enhanced angiogenesis, all of which contribute to rapid tumor expansion [10].

The chemokine receptor CXCR4 and its ligand SDF-1alpha facilitate the migration of metastatic breast cancer cells to organs such as the lung and bone. High levels of

SDF-1 α attract CXCR4-expressing cells, leading to their proliferation and angiogenesis in these areas. HER2 expression up-regulates CXCR4, promoting metastasis and inhibiting CXCR4 degradation. A kind of synergy between HER2 and CXCR4 in breast tumors indicates that CXCR4 is linked to poor survival rates. Additional studies have identified other molecular species involved in breast cancer metastasis. Additionally, cytokeratin-positive cells, found in the bone marrow of many breast cancer patients, serve as significant prognostic indicators for metastasis and survival outcomes [11]. The fact that HER2 expression on micrometastatic cells in the bone marrow is high implies that this group of cells was perhaps positively selected at early phases of metastasis. On the same note, genomic studies of single CK-positive bone marrow cells can detect early mutation in breast cancer, like extremely early amplification of the HER2 [12].

The role of HER2-initiated signaling in the process of cancer development is central as it increases the number of pathways that help to maintain cellular homeostasis and resist apoptosis. When HER2 is dimerized, it activates PI3K/AKT/mTOR pathway [13]. Moreover, the pathway facilitates adaptation of metabolism that allows tumor cells to survive in hypoxic or nutrient deprived environments. At the same time, the MAPK pathway activation promotes tumor invasion and metastasis. Such cascade regulates cytoskeleton dynamics, cell adhesion, and extracellular matrix remodeling, which play a key role in metastatic dissemination [14]. Disturbances in the normal mechanisms of HER2 recycling and degradation result in increased receptor signaling, which creates downstream signaling and causes therapy resistance [5, 15].

In the past, HER2 overexpression was considered to be a sign of adverse clinical prognosis, decrease in the overall survival, and recurrence rates. Breast cancers which were positive as compared to those which were negative in HER2 were aggressive. These agents not only improved the patients survival but also the definition of HER2 positivity as poor outcome predictive marker has been changed to predictive success biomarker of targeted treatment [16].

3. HER2 positive cancers

3.1 HER2 in breast cancer

The overexpression of HER2 is observed in 1530 percent of invasive breast cancer, which has prognostic and predictive implications. The number of copies of the HER2 in breast cancers can be up to 25–50 copies and an increase of 40–100 fold of HER2 protein leading to expression of 2 million receptors at the tumor cell surface [2]. Even the estrogen, acting by a nongenomic mechanism of estrogen receptor (ER) in the extracellular domain has been reported to stimulate HER2 signaling. p95 is a constitutively active aberrant form of HER2 (with the extracellular domain deleted) and has been found to mediate resistance to trastuzumab binding to the extracellular domain. The inability of antibodies against the extracellular domain to react with p95 is also, because of the same reason [17]. Breast cancer has been linked to shorter disease-free and overall survival with respect to HER2 gene amplification. It was discovered that amplification of HER2 gene was an important prognostic variable, both in overall survival ($P < 0.001$) and time to relapse ($P < 0.0001$) [2]. In one study, the HER2 expression in 704 node-negative breast cancer was studied and the study has revealed that cancerous breast in women with high HER2 was 9.5 times more likely to recur than a cancerous breast that had normal HER2 expression ($P = 0.0001$) [18].

The study of different subgroups revealed that the elevated risk of recurrence was spread through multiple subgroups of the patients with node-negative breast cancer. The researchers of 1056 patients with Stage I-III breast cancer discovered that 3-fold (or more) HER2 amplification was correlated with a substantially reduced disease-free survival ($P = 0.0027$) [2]. HER2 amplification was reported as well to have a strong correlation with pathologic stage of disease, the number of axillary tumor nodes, histologic type, and absence of estrogen receptor (ER) and progesterone receptor (PgR). It has been suggested that one of the initial alterations that happens during tumorigenesis of the human breast is the HER2 amplification. Almost half of in situ ductal carcinoma with no indication of the presence of invasive disease also show HER2 amplification, and the status is preserved in the course of invasive disease development, nodal metastasis and distant [19]. In the absence of proper treatment, HER2-positivity correlates with aggressive disease, high rates of recurrence, and poor prognosis [20]. The emergence of HER2-targeted therapies has largely transformed the disease course of patients with HER2 + breast cancer by reducing relapse rates and increasing survival [20, 21]. In addition to trastuzumab, a variety of HER2-targeted agents are now clinically effective (including pertuzumab, margetuximab, and trastuzumab emtansine (even though novel systemic treatment options have enhanced control over extracranial HER2+ breast cancer, there is an increasing need to develop effective therapies to treat intracranial disease in patients with brain metastases (BM)) [22].

3.2 HER2 in gastric cancer

Gastric cancer patients have reported HER2 overexpression (between 10 and 30 percent) and this has been associated with poor prognosis and disease aggression. Immunohistochemistry (IHC) Overexpression HER2 protein in gastric cancer was first reported in 1986. The HER2 overexpressions of gastric and gastroesophageal cancer lies between 4.4 and 53.4%, with the average being [23]. This was found in one study where the HER2 overexpression by IHC was identified in 23 percent and the amplification of the gene by FISH was detected in 27 percent of 200 resected tumors. The higher percentage of HER2 positivity in GEJ tumors as well as in intestinal subtype was also supported by other researchers. The direct relationship between the overexpression of HER2 and the poor outcome in gastric cancer has been proved. Results of 260 gastric tumors revealed that the HER2 overexpression was negative prognostic and the intensity of the HER2 staining was associated with the tumor size, serosal invasion, and metastases of the tumor in the lymph node. The outcome of the other studies indicated the adverse role of the HER2 overexpression in gastric cancer [24].

The disease biology of gastric cancer that is HER2 expressing has been found to have established expression of HER2, and targeted therapy of the HER2 has radically changed the prognosis of gastric cancer at the early and late stages that express HER2. The only drug that protracts OS and PFS is trastuzumab, which is a first line standard of care [25]. Furthermore, the intratumoral, inpatient and outpatient heterogeneity of the gastric cancer is another critical issue to the development of targeted therapy drugs. At the same time, off label immune checkpoint inhibitor monotherapy is not active with a majority of gastric cancer, and a combination of immunotherapy and anti-HER2 monoclonal antibodies may be required. To deal with these issues, novel HER2-targeted medications are planned, such as ADCs, TKI, and bispecific antibodies [26].

3.3 HER2 in esophageal cancer

HER2 has been reported as over expressed in 0–83% of esophageal cancer, with an overexpression expressed higher in adenocarcinoma than in squamous cell carcinoma (10–83 and 0–56, respectively) [19]. In the esophagus of EACs that have Barrett esophagus (BE), HER2 positivity was significantly predictive of both DSS [HR = 0.54 (95% CI: 0.35 0.84), $P = 0.0065$] and overall survival ($P = 0.0022$), regardless of its pathologic features. However, this is not how it turned out to be in another study by the same authors who found that the heterogeneity of HER2 among the EACs which were amplified with HER2 was an independent predictor of a poor cancer specific survival. HER2 overexpression was also found to be a negative prognostic factor of the esophageal squamous cell carcinoma besides EAC [27]. Neoadjuvant chemoradiotherapy followed by resection or definitive chemo-radiotherapy is considered the treatment choices in case of localized or locally advanced esophageal squamous cell carcinoma (ESCC). A majority of the patients are however ineligible to curative treatment and they receive palliative chemotherapy which has had little effect in overall survival. There is no agreement on the best regimen, yet first- and second-line agents are fluoropyridines, platinum, taxanes and irinotecan. On the other hand, EMA has approved Nivolumab that increased overall survival among pre-treated patients with advanced ESCC [28].

3.4 HER2 in ovarian cancer

In 20–30 percent of patients with the ovarian cancer, HER2 is over expressed. It is the first time that Berchuck realizes that HER2 overexpression is associated with poor survival in advanced epithelial ovarian cancer. In a cohort of 73 patients who were ovarian cancer patients, those who had been overexpressed in HER2 succumbed a lot sooner than those whose HER2 was normally expressed [29]. Moreover, they discovered that patients with tumors that had a high level of EGF receptor mRNA was much less likely to experience complete response following the initial treatment, or experience a negative result in the second-look laparotomy, in contrast to the patients whose tumors had negative expression. Despite being discovered that poorer survival is correlated by HER2 overexpression, the application of HER2 directed therapies is less useful because strong expression occurs infrequently [29]. HER2-targeted therapy has proven to be utilized in breast cancer, and research has been conducted to determine its use in other types of cancers. Anti-HER2 anti-cancer agents (trastuzumab and lapatinib) were also tested during phase II trials but had limited efficacy in ovarian cancer (OC). Nonetheless, a recent trial, the National Cancer Institute trial with trastuzumab emtansine, reported a stable disease response in a few OC patients, and the DESTINY-PanTumor02 trial reported trastuzumab deruxtecan (T-DXd) with high response rates, particularly with HER2 3+ tumors, which demonstrates its ability to act as a tumor-agnostic therapy [30].

3.5 HER2 in endometrial cancer

The prevalence of the HER2 overexpression has been reported to range between 14 and 80 percent with HER2 amplification (by fluorescence in situ hybridization [FISH]) between 21 and 47 percent in endometrial serous carcinoma. It has also been reported that endometrioid carcinomas overexpress the HER2/neu and amplify it 1 to 47 percent and 0 to 38 percent respectively [31]. Bad prognosis in endometrial

carcinoma has been linked with the over expression of HER2 in addition to amplification. It is reported to lead to a drastic decrease in overall survival of patients having HER2-amplified endometrial serous carcinoma compared to none. In addition to that, patients having HER2 copy numbers exceeding the ratio (>2.5) had a worse performance by a significant margin compared to patients with lower HER2 copy numbers (ratio 2.0–2.5) [32].

3.6 HER2 in other cancers

Overexpression of HER2 was reported in approximately 20% in lung cancers. The other mutation of HER2 was expressed in lung adenocarcinomas besides overexpression. The targeted mutations were those related to never smokers and light smokers, ethnicity of Orientalics, and gender (female). Overexpression and amplification, respectively, are amplified and/or overexpressed in between 23 and 80 percent and 0 and 32 percent in 33 cases of invasive urothelial bladder carcinomas [19]. For blocking the HER2 signaling pathway, Anti-HER2 antibodies are capable. A randomized phase II study established that trastuzumab in combination with carboplatin and paclitaxel is more effective than carboplatin and paclitaxel used as the sole agents in improving the survival rates of patients with advanced uterine serous carcinoma that is HER2 positive [33]. Antibody-drug conjugates such as trastuzumab-deruxtecan have been given approvals in patients with unresectable or metastatic solid tumors that express HER2. It was approved because its phase II trial demonstrates good response rates, especially in cases of endometrial carcinoma, which correlate with the intensity of HER2 expression. Best practices in the HER2 testing of endometrial carcinoma are expected. In the trastuzumab trial, the HER2 positivity was decided on the basis of 3 + or amplification assessed by FISH and 21 which followed the ASCO/CAP guidelines [33].

4. Current and emerging therapeutic strategies

4.1 Monoclonal antibodies (mAb)

mAb, single B-cell homogenates targeting specific antigen epitope, consists of Fab (antigen-binding fragment) as well as Fc (crystalline fragment). Fab regulates the downstream pathways after recognizing the tumor associated antigens while Fc binds to immune cells expressing Fc receptors and serum bind to initiate antibody dependent phagocytosis and as well as cytotoxicity. Moreover, it also leads to complement-dependent cytotoxicity. The examples of mAb include pertuzumab, margetuximab, and trastuzumab evaluated in clinical trials for HER2+ cancers [34, 35].

The first anti HER2+ antibody was trastuzumab which was developed in 1990. In 2001, at the initial stages of its clinical trials, when this mAb was added to chemotherapy, it enhanced the overall survival rate in the female HER2+ metastatic breast cancer. These results were also supported by the evidences in 2005 when trastuzumab was used as an adjuvant treatment with early stage malignancy [35].

4.2 Tyrosine kinase inhibitors

Tyrosine kinase inhibitors refer to the compounds which inhibit the tyrosine kinase activity. These compounds may lead to the residual protein phosphorylations,

inhibiting the downstream signaling cascades and inhibiting the metastatic development. Targeted therapies for HER+ cancers with broader therapeutic potential lead to the efficient levels of cure in HER2+ cancers also. For example, after mAb-based therapy (8.4 mon versus 4.4 mon), lapatinib an inhibitor of HER1 as well as HER2 has profound potential to enhance the survival of the patients as compared to capecitabine alone [35].

4.3 Antibody drug conjugates

Antibody-drug conjugates (ADC) refer to as the chemically bonded mAb and cytotoxic drugs complexes. In this type of conjugates, mAb serve to carry the cytotoxic drugs to targeted cells leading to the death of tumor cells. Hence, ADC possess string cytotoxic potential in addition to their specific nature and stability. Some of the examples of ADC include RC48-ADC, T-DM1, and DS-8201a which have been currently utilized for the treatment of gastric cancers [34, 35]. HER2-targeted therapies include trastuzumab emtansine (T-DM1), an antibody–drug conjugate consisting of trastuzumab linked to the tubulin-binding agent DM1 via a stable thioether linker17. T-DM1 has shown efficacy in women with HER2-positive advanced-stage breast cancer previously treated with trastuzumab and a taxane 18 and in those with HER2-positive early-stage breast cancer [34].

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HER2: Biology, Definition, Diagnosis, and its Role in Cancers

Mina Naderi, Fereshteh Ameli and Sahand Golestanian

Abstract

Amplification or overexpression of the transmembrane epidermal growth factor receptor 2 (HER2) oncogene (also known as c-erbB-2) is a well-established driver of carcinogenesis and a negative prognostic factor across multiple cancer types. Its intracytoplasmic tyrosine kinase domain activates intracellular signaling pathways that promote tumor proliferation, disrupt cell-cell adhesion, and enhance invasiveness. HER2-amplified cancers demonstrate aggressive clinical behavior due to their inherent metastatic potential, correlating with reduced overall survival rates. Immunohistochemistry (IHC) remains the primary method for detecting HER2 protein overexpression in tumor tissues, with results categorized as positive, equivocal, or negative based on standardized scoring criteria. Complementary techniques such as fluorescence in situ hybridization (FISH) and chromogenic in situ hybridization (CISH) are critical for confirming HER2 gene amplification. These methods form the cornerstone of diagnostic protocols not only in breast cancer but also in HER2-positive advanced gastric, colorectal, and endometrial malignancies. Accurate HER2 status determination through guideline-adherent testing is essential for therapeutic decision-making. HER2-targeted therapies, including monoclonal antibodies and tyrosine kinase inhibitors, have demonstrated efficacy as neoadjuvant/adjuvant treatments and as systemic therapies for unresectable or metastatic disease. Standardized biomarker testing and targeted intervention strategies hold significant potential to improve survival outcomes in HER2-driven cancers.

Keywords: HER2, erb-B2, breast cancer, anti-HER2 therapy, gastric cancer

1. Introduction

Twenty-five years ago, researchers identified the human epidermal growth factor receptor-2 (HER2/neu, c-erbB2) as part of a family of four membrane tyrosine kinases. Two years later, they demonstrated that HER2 amplification plays a critical role in the pathogenesis and progression of human breast cancer [1, 2]. Subsequently, HER2 amplification and the resulting overexpression of HER2 protein have been recognized as important biomarkers involved in tumor cell proliferation, invasiveness, and survival pathways. HER2 amplification has also been observed in other cancers, where it influences survival outcomes. In response, several targeted therapies have been developed to inhibit the HER2 pathway, and HER2 status has become a routine prognostic and predictive marker in certain malignancies.

The aim of this review was to highlight the critical role of HER2 in various tumors, explore its biological function, discuss the clinical significance of its assessment, and identify valuable treatment targets.

2. Biology of HER2

A transforming gene identified through transfection studies using DNA from chemically induced rat neuroglioblastomas was demonstrated to be associated with, yet distinct from, the c-erbB proto-oncogene [3, 4]. The human epidermal growth factor receptor-2 (HER-2/neu) gene encodes a unique member of the tyrosine kinase family, closely related to, but separate from the epidermal growth factor receptor (EGFR) gene. Notably, HER-2/neu is located on band q21 of chromosome 17, distinguishing it from the EGFR gene, which is situated on the p13 region of the long arm of chromosome 7 (7q21) [5–7].

The extracellular domain (ECD) of HER2 contains approximately 600 residues, with a molecular weight of (90–110 kDa). It can be divided into four subdomains (I–IV). Subdomains I and III have the potential to serve as a binding site for the receptor’s prospective ligands [8].

There are two conformations of the ECD, the closed configuration (inactive state) and the open configuration (active state).

The crystallographic data indicates that the majority of HER2 receptors are predominantly in an open conformation [9]. This suggests that the dimerization arm of HER2 is consistently poised for dimerization with other receptors. This may elucidate a mechanistic basis for the HER2 role as a preferred dimerization partner among the members of the HER family.

The input layer comprises four membrane receptors/tyrosine kinases (TKs): HER1, HER2, HER3, and HER4, along with their numerous ligands (at least 11, as detailed in **Table 1**) [10]. When ligands bind to the extracellular domains of these HER proteins, they promote receptor dimerization that then triggers transphosphorylation of their intracellular tyrosine residues. Unlike other HER family members, HER2 does not have a known ligand and instead requires heterodimerization with another HER receptor or homodimerization—particularly when HER2 is overexpressed—to become activated. The phosphorylated tyrosine residues serve as docking sites for various intracellular signaling molecules, initiating the activation of multiple downstream second messenger pathways and facilitating crosstalk with other membrane signaling networks [11–15]. This signaling cascade ultimately influences gene expression through transcription factors modulated by

Receptors for HER family membrane		
Receptor	Tyrosine kinase activity	Major ligands
HER1 (=EGFR)	+	EGF, amphiregulin, TGF α
HER 2	+	None
HER 3	+	Heregulin
HER 4	+	Heregulin

Table 1.
Four membrane receptors/tyrosine kinases (TKs) (HER1–4) and their ligands. Ref [10].

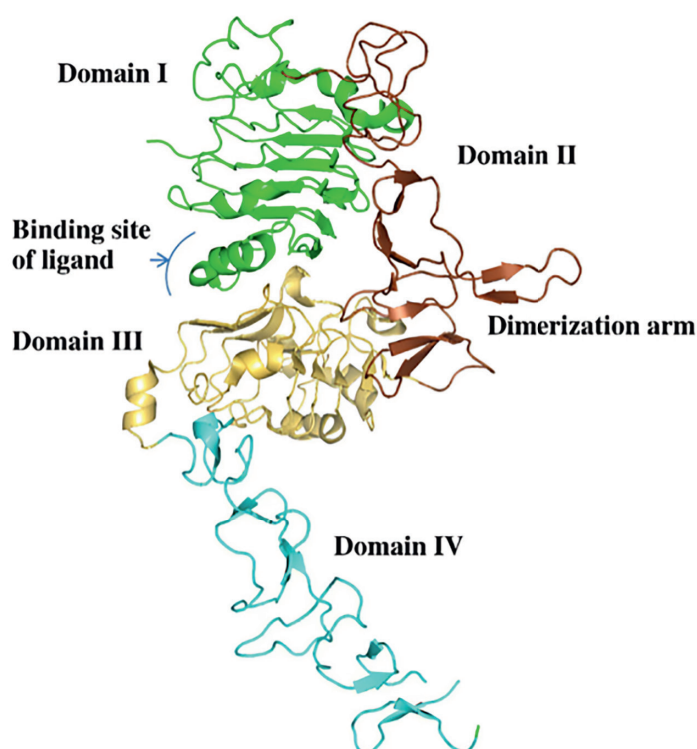


Figure 1.
 Diagram of HER2 ECD. The highlighted domains are as follows: Domain I (green), domain II (brown), domain III (light yellow), and domain IV (cyan). Additionally, the dimerization arm in domain II is indicated.

these pathways, notably the PI3K/AKT and Ras/Raf/MEK/MAPK pathways, which regulates processes such as cell proliferation, survival, differentiation, angiogenesis, and invasion/metastasis. HER2 adopts an open conformation that exposes its dimerization domains, making it a preferred dimerization partner among the HER family members (**Figure 1**) [16].

Figure 1 was generated using the open-source software Pymol [17].

3.HER2 assessment

3.1 Immunohistochemistry

Immunohistochemistry (IHC) is a technique used to detect overexpression of the HER2 protein. This method employs monoclonal or polyclonal antibodies that specifically bind to the HER2 antigen in tissue samples. The results of HER2 testing *via* IHC are categorized into three groups: positive, equivocal, and negative (see **Table 2** and **Figure 2**). These classifications influence different patient management strategies [18].

Furthermore, several additional criteria have been proposed to improve the interpretation of HER2 IHC results. These include assessing the quality of controls, evaluating the staining pattern of the sample, considering only the invasive

	Surgical specimen–staining pattern	Biopsy specimen–staining pattern	Score	HER2 expression assessment
Gastric carcinoma	Weak to moderate, complete, basolateral or lateral membranous reactivity in 10% of tumor cells	Weak to moderate membrane reactivity: Tumor cell clusters® exhibiting weak to moderate, complete basolateral, or lateral membranous reactivity, regardless of the percentage of tumor cells stained.	2+	Equivocal*
	Strong, complete, basolateral, or lateral membranous reactivity in 10% of tumor cells	Strong membrane reactivity: tumor cell clusters showing strong, complete basolateral, or lateral membranous reactivity, irrespective of the percentage of tumor cells stained.	3+	Positive
Breast carcinoma	Circumferential membrane staining; that is complete, intense, and observed in more than 10% of tumor cells.*		3+	Positive
	Weak-to-moderate complete membrane staining present in more than 10% of tumor cells.		2+	Equivocal*
Colorectal carcinomas	Intense circumferential staining: circumferential, basolateral, or lateral intense staining observed in more than 50% of tumor cells		3+	Positive
	Circumferential, basolateral or lateral intense staining in >10% <50% of cells		Retest IHC—if result confirmed reflex to FISH/SIH	Positive
Endometrial serous carcinoma	Intense, complete, or basolateral/ lateral membrane staining in over 30% of tumor cells.		3+	Positive
	Intense, complete, or basolateral/ lateral membrane staining in 30% of tumor cells or fewer, or weak to moderate staining in 10% or more of tumor cells.		2+	Equivocal *
®Tumor cell cluster (five neoplastic cells).				
*According to the guideline, must order reflex test (same specimen using ISH) or order a new test (new specimen if available, using IHC or ISH).				
This table is based on an ASCO and CAP guideline 2023.				

Table 2.
Scoring guidelines for interpretation of HER2 positive IHC in carcinoma.

carcinoma when scoring, and reviewing the adjacent normal tissue, which should not exhibit staining. The intensity of staining is scored on a scale (+1, +2, or +3), and this score is critical in guiding decisions regarding targeted therapies.

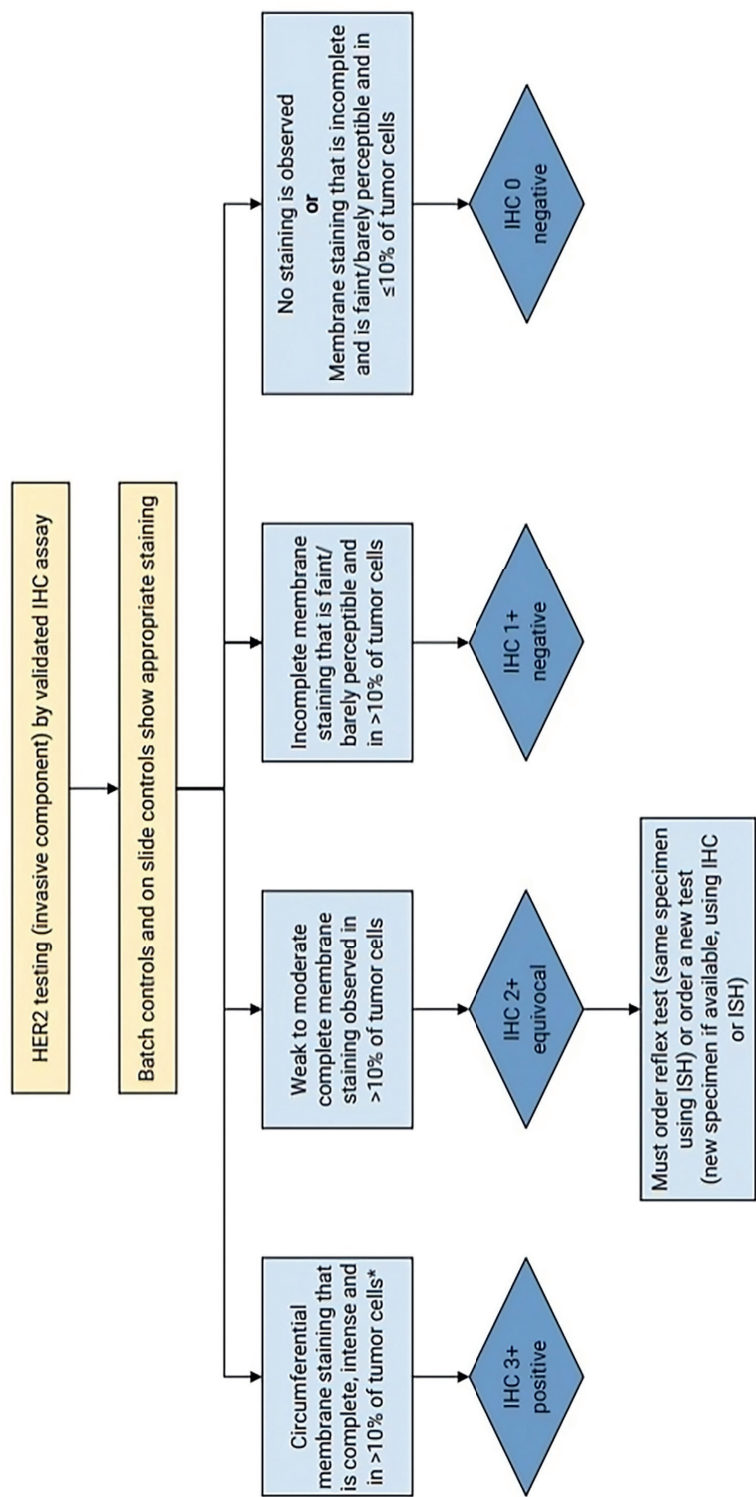


Figure 2.

The following algorithm outlines the process for evaluating the expression of the human epidermal growth factor receptor 2 (HER2) protein in an invasive breast cancer specimen through immunohistochemistry (IHC) assay. Note. The final reported results are contingent upon the absence of any discernible histopathologic discordance as determined by the pathologist. Occasionally, atypical HER2 staining patterns by immunohistochemistry (IHC) may occur that fall outside the standard criteria. When such unusual patterns are observed, they should be classified as IHC 2+, indicating an equivocal result. For example, certain breast cancer subtypes may exhibit moderate-to-intense staining that is incomplete—appearing basolateral or lateral—and may still demonstrate HER2 gene amplification. Another instance includes circumferential membrane staining that is intense but present in less than 10% of tumor cells, reflecting a heterogeneous but limited extent of HER2 expression. In these cases, a 2+ equivocal rating may be appropriate; however, analyzing additional samples could lead to different assessments regarding the percentage of HER2-positive cells. The algorithm is obtained from the recommendations set forth in the article "Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer." An update to the ASCO-CAP guideline is forthcoming. Wolff AC, Somerfield MR, Dousett M, et al. "Human epidermal growth factor receptor 2 testing in breast cancer." The most recent published update of ASCO-CAP guideline was online on June 7, 2023. Arch Pathol Lab Med. 2023. DOI: 10.5858/arpa.2023-0950-SA.

3.2 *In situ* hybridization

An alternative method for identifying HER2 status is fluorescent *in situ* hybridization (FISH) and chromogenic *in situ* hybridization (CISH), which are the primary techniques used to detect HER2 gene amplification. These *in situ* hybridization (ISH) methods have become essential components of the diagnostic workflow for breast cancer. ISH involves the use of DNA probes that are complementary to specific genomic sequences, which are labeled and then hybridized to the target tissue. The hybridization process entails applying these probes to various tissue samples, including cell lines, frozen tissue, formalin-fixed paraffin-embedded tissue, and micro-tissue arrays. FISH uses fluorescence microscopy to visualize the hybridized probes, while CISH employs light microscopy for detection.

In HER2 FISH assays, a HER2 gene copy number exceeding six per nucleus indicates gene amplification, especially in testing systems that lack an internal control probe. Additionally, a HER2/CEP17 ratio greater than 2.2 is considered indicative of HER2 amplification. Since CEP17 serves as a centromeric probe for chromosome 17, it provides a reference point for assessing HER2 gene amplification (**Figure 2**).

For FISH assays, HER2 amplification is typically defined by a HER2/CEP17 ratio between 1.8 and 2.2 or an average HER2 gene copy number between 4.0 and 6.0 in systems that do not include an internal control probe. Conversely, a negative HER2 FISH result is characterized by a HER2/CEP17 ratio of less than 1.8 or an average of fewer than four HER2 gene copies per nucleus in such systems [19].

In other cancers, such as gastric, colorectal, endometrial serous, or clear cell carcinomas, the interpretation criteria for IHC and FISH differ from those used in breast cancer. Notably, in endometrial serous and clear cell carcinomas, there is no universally established or precise definition of HER2 positivity *via* IHC.

HER2 detection techniques such as CISH and SISH are delicate methods that require fewer reagents compared to FISH. SISH, similar to CISH, produces staining that is permanent and does not fade over time, allowing for specimen archiving. Unlike CISH, SISH enables the quantitative assessment of gene copy number. In a comparative study of ISH techniques on excisional biopsy specimens, HER2 FISH and HER2 SISH results were identical in 50 out of 53 cases (**Figures 3 and 4**) [20].

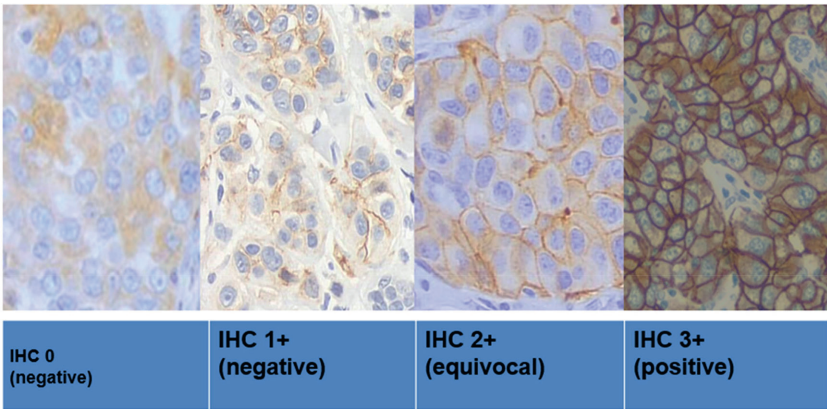


Figure 3. HER2 immunohistochemistry scoring in breast cancer. Performed by the ASCO/CAP guidelines. 20x magnification. (Using rabbit anti humanc-erbB2 monoclonal antibody, clone SP3, Master diagnostic: spain). Cancer institute at Imam Khomeini Hospital, Tehran Iran.

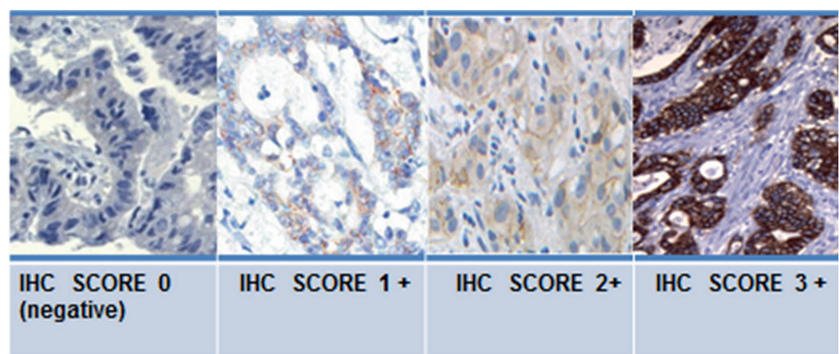


Figure 4.
HER2 immunohistochemistry scoring in gastric cancer. Performed by the ASCO/CAP guidelines. 20x magnification. (Using rabbit anti humanc-erbB2 monoclonal antibody, clone SP3, Master diagnostic: spain). Cancer institute at Imam Khomeini Hospital, Tehran Iran.

4. HER2-positive cancers

Normal tissues exhibit low levels of HER2 membrane protein, which play essential roles throughout various stages of cell development. However, mutations or overexpression of HER2 can amplify and prolong signaling pathways that promote cellular transformation and proliferation, thereby contributing to tumorigenesis and metastasis.

In human cancers, HER2 overexpression is frequently observed: It occurs in approximately 15–20% of breast cancers [21, 22], 23–38% of gastroesophageal cancers [23, 24], 3–5% of colorectal cancers (CRC) [25], 1–3% of lung cancers [26, 27], and in other cancer types.

HER2 overexpression is associated with more aggressive tumor behavior and poorer clinical outcomes.

4.1 Breast cancer and HER2 as a target for cancer therapy

HER2 overexpression is observed in approximately 25% of breast cancer patients and is associated with malignant transformation, increased proliferation, more aggressive tumor behavior, resistance to endocrine therapy, higher likelihood of lymph node positivity, and poorer survival outcomes. Patients with HER2-positive breast cancer tend to have a shorter survival rate compared to those with HER2 overexpression alone [25]. HER2 is a vital prognostic and therapeutic target in breast cancer management [26]. In 1998, the Food And Drug Administration approved the monoclonal humanized antibody trastuzumab for treating HER2-positive breast cancers. Trastuzumab inhibits tumor growth and induces apoptosis, leading to improved survival [27, 28].

Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate that combines trastuzumab with the cytotoxic agent emtansine (DM1), a derivative of maytansine, which functions as a microtubule inhibitor. T-DM1 has been approved for use in patients with HER2-positive metastatic breast cancer who have previously been treated with trastuzumab and taxanes [29]. Interestingly, about 60% of metastatic breast cancers that are classified as HER2-negative by immunohistochemistry (IHC)—specifically those with an IHC score of 1+ or 2+ with negative in situ hybridization (ISH)—actually exhibit low levels of HER2 expression [30, 31].

Before the results of the DESTINY-Breast04 study, cases with low HER2 expression were generally treated according to protocols for HER2-negative breast cancer. However, following the approval of trastuzumab deruxtecan, a significant improvement in progression-free survival and overall survival was observed in patients with HER2-low metastatic breast cancer compared to those receiving physician's choice of chemotherapy [32].

Another emerging therapy is trastuzumab deruxtecan (DS-8201), an antibody-drug conjugate comprising a humanized monoclonal antibody that specifically targets HER2, linked to a potent topoisomerase I inhibitor as its cytotoxic agent. It was first approved by the FDA as a second-line treatment for HER2-overexpressing metastatic breast cancer.

Additionally, various tyrosine kinase inhibitors (TKIs) have been developed to treat patients with HER2-positive breast cancer, including afatinib, lapatinib, neratinib, tucatinib, and pyrotinib. These agents are designed as HER2-targeted therapies.

4.2 Gastric adenocarcinoma

Gastric cancer is the fourth most commonly diagnosed cancer and the second leading cause of cancer-related mortality worldwide, often presenting with a challenging prognosis [33, 34]. The five-year survival rate for advanced or metastatic gastric cancer ranges from approximately 5–20%, with a median overall survival of less than 1 year [35–37].

HER2 amplification or overexpression is observed in 7–34% of gastric tumors and serves as a significant biomarker and a key driver of tumor development. Some studies indicate that HER2-positive gastric cancers tend to be more aggressive and are associated with poorer clinical outcomes [38, 39].

The TOGA trial demonstrated that adding trastuzumab to chemotherapy significantly improved overall survival compared to chemotherapy alone in patients with advanced gastric or gastro-esophageal junction cancers exhibiting HER2 overexpression, defined as immunohistochemistry (IHC) 3+ or IHC 2+ with fluorescence *in situ* hybridization (FISH) positivity [40].

4.3 Colorectal cancer

Colorectal cancer (CRC) is the third most common malignancy diagnosed in men and the second in women worldwide with nearly 9% of all cancer-related death [41].

It is estimated that around 3–5% of CRC cases exhibit amplification of the human epidermal growth factor receptor 2 (HER2) or overexpression of the HER2 protein.

Genomic studies on CRC tumors have revealed that gene alterations are distributed along a continuum throughout the colorectal tract. These alterations are more frequently observed in left-sided tumors distal to the splenic flexure [42, 43]. In colorectal cancer (CRC), HER2 amplifications are primarily found in KRAS/BRAF wild-type tumors, with an incidence ranging from 2.1 to 5.2%. In contrast, these amplifications occur in KRAS/BRAF-mutant tumors with a much lower incidence, between 0.2 and 2.1% [44].

These tumors appear to exhibit worse outcomes and are associated with a higher incidence of metastatic disease in the central nervous system, lower overall survival (OS), and poor response to anti-EGFR therapy in RAS/RAF wild-type

HER2-overexpressed metastatic setting, also is associated with a shorter disease free survival in the early stages of disease following resection [45–47].

As mentioned the role of HER2 in CRCs above and evidence supports the therapeutic benefit of HER2 blockade therapies in patients with metastatic CRC overexpressing HER2 (IHC HER2 3+ or HER2 2+ and FISH positive).

4.4 Endometrial carcinoma

Endometrial cancer is the most prevalent gynecological malignancy in the developed countries. In the United States, it was estimated that in 2022 there were 65,950 new diagnoses and 12,550 deaths attributed to this disease [48, 49]. Among the various subtypes of endometrial cancer, uterine serous carcinoma (USC) is recognized as a high-grade histologic variant, associated with a relatively poor prognosis because of its aggressive biological behavior and high rates of recurrence.

Five-year survival is estimated to be 37% in advanced diseases (i.e., stages III–IV) [50]. Endometrial cancer mortality is up to 10% with USC-related endometrial cancer-associated deaths is up to 40% [51]. About 30–35% USC harbor HER2 amplification [9, 10], while rates of HER2 expression in UCS according to the literature are variable, estimated to be between 6 and 56% [52]. As seen in many cancers, HER2 has been demonstrated to be a poor prognostic biomarker, which can be a potential target for novel anti-HER2 therapies [53, 54].

National Comprehensive Cancer Network (NCCN) guidelines have been recommended HER2 assessment for advanced or recurrent uterine serous carcinoma as a prognostic biomarker [55].

Assessment of HER2 in USC can be evaluated by IHC, FIH, or Next Generation Sequencing. According to studies, there have been some coordination or incoordination between HER2 results with the two methods, which could significantly impact patients' qualification for HER2-directed therapy [56].

Currently, there are no recommendations to perform FISH in lieu of IHC testing [57].

A review of the literature reveals a scarcity of studies focused on NGS in USC. However, available studies suggest that NGS is highly specific for detecting HER2 gene amplification. Nonetheless, it demonstrates lower sensitivity compared to immunohistochemistry (IHC) or fluorescence *in situ* hybridization (FISH) when assessing tumors with focal expression or low levels of HER2 [58].

While progression-free survival has improved in patients with homozygous HER2 protein expression treated with targeted chemotherapy, the overall response rate remains low. Additionally, uterine serous carcinomas often exhibit heterogeneous HER2 expression, which may have significant implications for treatment strategies. Furthermore, negative HER2 results from small tissue samples could lead to the erroneous exclusion of patients from HER2-targeted therapies [59].

5. Conclusion

Human epidermal growth factor receptor 2 (HER2) is a key member of the tyrosine kinase receptor family and plays a significant role in carcinogenesis. Its overexpression or amplification is recognized as a negative prognostic factor across various cancer types. HER2 is expressed in subsets of cancers, including breast,

gastroesophageal, pulmonary, and endometrial serous carcinomas. HER2-amplified cancers tend to be invasive, possess metastatic potential, and are associated with decreased overall survival.

Accurate assessment of HER2 status through diagnostic testing by an experienced pathologist and, if necessary, a genetic expert is essential for appropriate treatment planning. Detection of HER2 expression in tumors should follow established guidelines to identify candidates for targeted therapy. Such targeted treatments can markedly improve therapeutic outcomes in patients with these aggressive cancers.

Conflict of interest

The authors declare no conflict of interest.

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Section 2

HER2 and Cancer

The Role of HER2 in Cancer and Its Influence on the Tumor Microenvironment

Sieun Choi, Minseop Kim and Minsuh Kim

Abstract

HER2 (human epidermal growth factor receptor 2) is a transmembrane receptor tyrosine kinase that plays a pivotal role in cancer progression. Overexpressed in cancers such as breast, gastric, and lung cancers, HER2 contributes to aggressive tumor growth, metastasis, and therapy resistance. This chapter explores HER2's molecular functions, including its activation of key signaling pathways like PI3K/AKT and MAPK, and its role in shaping the tumor microenvironment (TME). A unique focus is placed on HER2's ability to reprogram the TME by modulating immune suppression, activating cancer-associated fibroblasts (CAFs), and enhancing angiogenesis. These interactions establish a permissive environment for tumor progression and therapeutic resistance. The chapter also discusses HER2-targeted therapies, such as trastuzumab, pertuzumab, and antibody-drug conjugates like T-DM1 and T-DXd, alongside emerging strategies to overcome resistance. In addition, advanced research platforms, including organoids and microphysiological systems (MPS), are highlighted as transformative tools for studying HER2-TME interactions. These systems enable dynamic modeling of the tumor ecosystem, offering unprecedented insights into HER2-driven cancer biology and precision medicine approaches. This chapter emphasizes the integration of organoids and MPS as innovative technologies for enhancing translational research and overcoming therapeutic challenges in HER2-positive cancers.

Keywords: HER2, tumor microenvironment (TME), cancer progression, drug resistance, HER2-targeted therapies, organoids, microphysiological systems (MPS)

1. Introduction

HER2 (human epidermal growth factor receptor 2) is a transmembrane receptor tyrosine kinase and a member of the ERBB family, which includes EGFR (ERBB1), HER3 (ERBB3), and HER4 (ERBB4). Unlike other ERBB receptors, HER2 does not have a known ligand and remains in a constitutively active conformation [1]. This unique feature makes HER2 the preferred partner for heterodimerization with other receptors, such as HER3, significantly amplifying downstream signaling pathways that regulate cell proliferation, survival, and differentiation. While HER2 expression

is tightly controlled in normal cells, its overexpression or gene amplification in cancers such as breast, gastric, and lung cancers leads to dysregulated signaling, promoting aggressive tumor growth, metastasis, and therapy resistance [2].

HER2 overexpression is most commonly found in breast (20–30%) and gastric cancers (10–20%), with lower frequencies in lung, ovarian, and colorectal cancers [3]. These cancers exhibit distinctive biological features driven by HER2 amplification, including rapid cell division, invasion, and metastasis. HER2 activation triggers key signaling pathways, such as the PI3K/AKT/mTOR and MAPK/ERK cascades, which promote cancer cell survival, proliferation, and resistance to apoptosis. These pathways also influence other hallmarks of cancer, such as sustained angiogenesis, immune evasion, and metabolic reprogramming, making HER2 a central player in oncogenesis.

In addition to its role in intrinsic tumor cell signaling, HER2 exerts profound effects on the tumor microenvironment (TME). HER2-positive tumors actively reshape their surrounding environment to support growth and metastasis. For example, HER2 overexpression can enhance the recruitment and activation of cancer-associated fibroblasts (CAFs), which remodel the extracellular matrix (ECM) to facilitate tumor invasion. It also promotes angiogenesis by increasing vascular endothelial growth factor (VEGF) signaling, ensuring an adequate blood supply for tumor growth. Furthermore, HER2-driven tumors create an immunosuppressive TME by upregulating PD-L1 expression and recruiting immune-suppressive cells, such as regulatory T cells (Tregs) and M2 macrophages. These interactions not only sustain tumor progression but also contribute to resistance against HER2-targeted therapies.

Clinically, HER2 serves as both a prognostic biomarker and a therapeutic target, revolutionizing cancer treatment. HER2-positive cancers are often associated with poor prognosis due to their aggressive nature and frequent resistance to conventional therapies [4]. However, the development of HER2-targeted therapies, such as trastuzumab, pertuzumab, and antibody-drug conjugates (ADCs) like T-DM1 and T-DXd, has significantly improved survival outcomes for patients with HER2-positive tumors. Despite these advancements, resistance to therapy remains a major challenge, highlighting the need for further research into HER2 biology and its interactions with the TME.

Emerging research platforms, such as organoids and microphysiological systems (MPS), are providing new insights into HER2-driven cancer biology. These innovative models replicate the complex interplay between cancer cells and the TME, enabling precise studies of HER2's role in tumor progression and therapeutic resistance. By integrating these advanced tools, researchers can uncover novel therapeutic strategies to address the limitations of current treatments and improve outcomes for patients with HER2-positive cancers.

In summary, HER2 is a critical driver of tumor growth and progression, with far-reaching implications for cancer biology and therapy. Understanding its molecular mechanisms and its dynamic interactions within the TME is essential for developing innovative therapeutic approaches and advancing precision medicine.

2. HER2: An oncogenic driver in cancer progression

HER2 (human epidermal growth factor receptor 2) is a critical driver of tumorigenesis, metastasis, and therapy resistance. Its amplification or overexpression is frequently observed in aggressive tumors and strongly correlates with poor prognosis and resistance

to conventional therapies. Unlike other members of the HER family, HER2 does not require ligand binding to initiate signaling [5]. Instead, it forms ligand-independent homodimers or heterodimers with other HER family receptors, such as HER3 [6]. This dimerization triggers persistent autophosphorylation and activation of downstream pathways, including PI3K/AKT/mTOR and MAPK, which regulate cellular proliferation, survival, and migration. Mutations in critical domains such as the tyrosine kinase domain (TKD) or extracellular domain (ECD) further stabilize receptor dimerization, amplifying oncogenic signaling and accelerating tumor progression.

2.1 HER2 structure and mutations

HER2 protein is composed of four key regions: the extracellular domain (ECD), the transmembrane domain (TMD), the juxtamembrane domain (JMD), and the intracellular tyrosine kinase domain (TKD). The ECD is subdivided into four subdomains (I-IV), where domains II and IV play pivotal roles in dimerization and ligand-independent activation [7]. The intracellular TKD regulates autophosphorylation and initiates downstream signaling cascades (**Figure 1a**).

Mutations in critical HER2 domains, such as the TKD or ECD, can further enhance dimerization stability and signaling activity. For instance, mutations in the ECD (e.g., S310 in the dimerization domain) or TKD (e.g., L755, V777, and D759Y) are commonly associated with heightened oncogenic activity, amplifying signaling through PI3K/AKT/mTOR and MAPK pathways. Such alterations accelerate tumor progression by enhancing cell survival, proliferation, and migration [8–10].

2.2 HER2 signaling pathways

HER2-driven signaling plays a central role in cancer progression by upregulating pathways that sustain cellular homeostasis and promote resistance to apoptosis. Upon

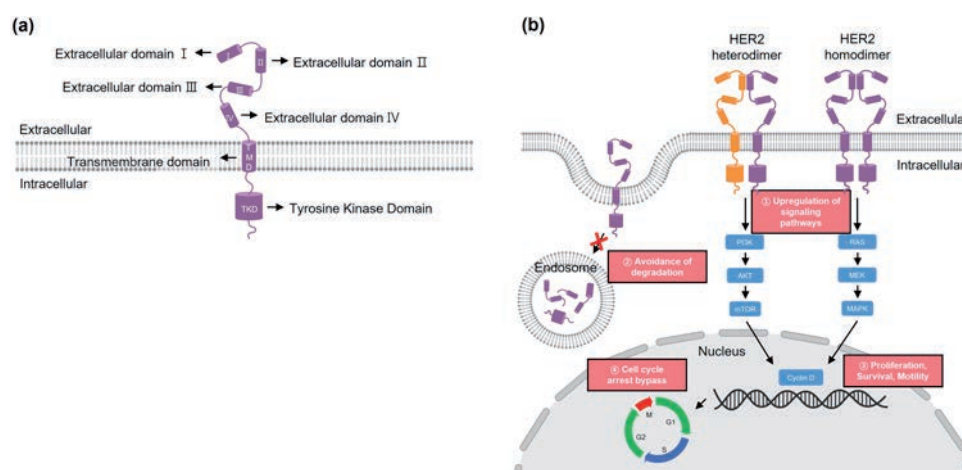


Figure 1.
Structure and Mechanisms of HER2 Receptor on Cancer Cells. (a) The HER2 receptor consists of four extracellular domains (I-IV), a transmembrane domain (TMD), and an intracellular tyrosine kinase domain (TKD). Domains II and IV of the extracellular regions play key roles in receptor dimerization and activation. (b) HER2 dimerization at the cell membrane activates several key pathways: (1) Upregulation of signaling pathways (PI3K/AKT/mTOR, MAPK), (2) Avoidance of degradation through impaired endosomal trafficking, (3) Bypass of cell cycle arrest, (4) Promotion of proliferation, survival, and motility.

dimerization, HER2 activates the PI3K/AKT/mTOR pathway, which promotes cell survival by inhibiting apoptotic signals and enhancing growth-related gene expression [11, 12]. Additionally, this pathway supports metabolic adaptation, enabling tumor cells to thrive under hypoxic or nutrient-deprived conditions (**Figure 1b**). Simultaneously, activation of the MAPK pathway facilitates tumor invasion and metastasis. This cascade modulates cytoskeletal dynamics, cell adhesion, and extracellular matrix remodeling, which are essential for metastatic dissemination [13, 14]. Aberrations in HER2 recycling and degradation pathways lead to prolonged receptor activity, amplifying downstream signaling and contributing to therapy resistance (**Figure 1b**) [15, 16].

HER2-positive cancers also exhibit mechanisms to bypass degradation. Impaired endosomal trafficking prevents receptor degradation, maintaining sustained activation of HER2 at the plasma membrane (**Figure 1b**). This evasion of degradation amplifies downstream signaling, further supporting uncontrolled proliferation and therapy resistance.

2.3 Diagnostic criteria and HER2-low classification

Amplification of the HER2 gene leads to its overexpression at both the protein and mRNA levels. In breast cancer, approximately 15–20% of patients exhibit HER2 amplification, making it a significant biomarker for clinical assessment [9, 10]. Techniques such as immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), and chromogenic in situ hybridization (CISH) are widely utilized to evaluate HER2 expression. ASCO/CAP guidelines classify HER2 expression as follows: IHC 3+ (positive) represents circumferential membrane staining that is complete, intense, and observed in >10% of tumor cells; IHC 2+ (equivocal) indicates weak to moderate membrane staining in >10% of tumor cells; IHC 1+ and IHC 0 are classified as negative, with faint or no staining observed. These classifications are critical for determining eligibility for HER2-targeted therapies [17, 18].

Recent findings have introduced the concept of HER2-low cancers, characterized by IHC 1+ or 2+ expression without gene amplification. HER2-low tumors account for a significant proportion of cancers, including 47% of breast cancers and similar rates in gastric, salivary gland, lung, endometrial, and urothelial cancers [19]. Despite their lower expression levels, HER2-low tumors exhibit distinct biological and clinical characteristics, underscoring the need for tailored therapeutic approaches [20].

2.4 HER2 and cancer stem cells

HER2 overexpression also plays a significant role in regulating cancer stem cells (CSCs), a subpopulation of tumor cells responsible for initiation, progression, and resistance to therapy. CSCs are characterized by their self-renewal capacity and plasticity, which are enhanced by HER2-driven signaling pathways such as Wnt and Notch. These pathways upregulate stemness markers, including Oct-4 and Sox-2, further promoting tumor growth and resistance to conventional treatments [21, 22]. HER2-positive cancers exhibit an increased CSC population, which interacts with the tumor microenvironment (TME) to create a niche supportive of sustained tumor progression and immune evasion [23].

2.5 Transition to tumor microenvironment

While the focus of this section has been on HER2's intrinsic cellular roles, its broader impact on the tumor microenvironment (TME) plays a crucial role in cancer progression. HER2's influence on stromal and immune components of the TME, as well as its modulation of CSC dynamics, is explored in detail in Section 4. Understanding this dual role is essential for developing comprehensive therapeutic strategies.

In conclusion, HER2's oncogenic role extends far beyond its influence on tumor cells, encompassing a wide range of interactions with the TME and associated resistance mechanisms. A comprehensive understanding of these complex networks is critical for advancing therapeutic development and achieving long-term control of HER2-driven malignancies. By addressing the multifaceted nature of HER2's impact, researchers and clinicians can pave the way for innovative treatments that improve patient outcomes.

3. HER2-targeted therapies

The pivotal role of HER2 in cancer progression has catalyzed the development of a range of targeted therapies designed to inhibit its oncogenic signaling. **Figure 2** summarizes the diverse therapeutic strategies targeting HER2, illustrating mechanisms of action for monoclonal antibodies, Fc-engineered antibodies, antibody-drug conjugates, tyrosine kinase inhibitors, nanoparticles, and mRNA vaccines. These strategies

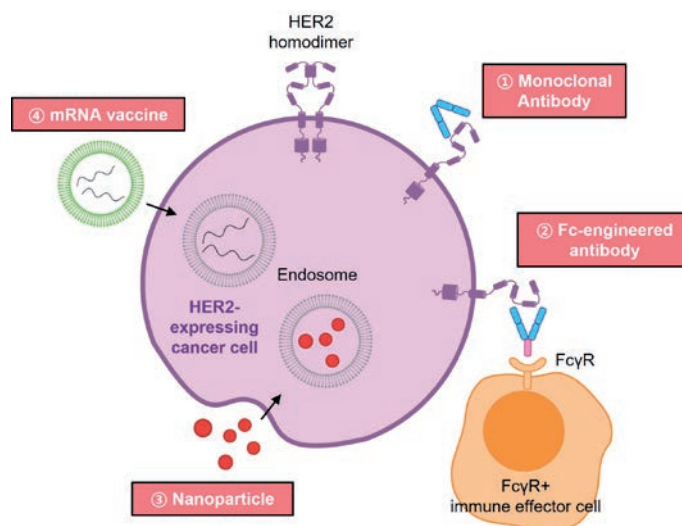


Figure 2. *Therapeutic Approaches Targeting HER2.* This diagram illustrates various therapeutic strategies targeting HER2-expressing cancer cells. Monoclonal antibodies [1] bind to HER2, preventing receptor dimerization and inhibiting downstream signaling. Fc-engineered antibodies [2] enhance immune cell-mediated cytotoxicity by binding to Fcγ receptors on immune effector cells, promoting the elimination of HER2-positive cells. Nanoparticles [3] are used to deliver therapeutic agents specifically to HER2-expressing cells, improving treatment efficacy and reducing systemic toxicity. mRNA vaccines [4] stimulate the immune system to target and destroy HER2-positive cancer cells through the production of tumor-specific antigens.

highlight the advancements in understanding HER2 biology and the development of innovative treatments to combat HER2-positive cancers.

Monoclonal antibodies (mAbs) were the first therapeutic agents developed to specifically target HER2-positive cancers. MAbs are laboratory-engineered antibodies that selectively bind to specific antigens, such as the extracellular domain (ECD) or tyrosine kinase domain (TKD) of HER2 [24]. By binding to HER2, mAbs prevent the receptor from forming ligand-independent homodimers or heterodimers with other HER family receptors, such as HER3. This inhibition effectively disrupts downstream signaling pathways, including PI3K/AKT and MAPK/ERK, which are critical for cancer cell proliferation, survival, and migration. Moreover, HER2-bound mAbs initiate antibody-dependent cell-mediated cytotoxicity (ADCC), wherein the Fc region of the antibody interacts with Fc receptors on immune effector cells, such as natural killer (NK) cells, macrophages, and neutrophils. These immune cells then induce cancer cell death through cytotoxicity, phagocytosis, and apoptosis [25, 26].

Among the notable mAbs are trastuzumab (Herceptin) and pertuzumab. Trastuzumab, a humanized IgG1 monoclonal antibody, was first approved by the FDA in 1998 for HER2-positive breast cancer. Its efficacy has been demonstrated through multiple mechanisms, including enhancement of ADCC, promotion of dendritic cell-mediated HER2 antigen uptake, and activation of macrophages [27–29]. Additionally, trastuzumab inhibits the activation of intracellular signaling pathways, such as PI3K/AKT and MAPK, through modulation of phosphorylation [30]. Pertuzumab, approved by the FDA in 2012, binds to a different site on HER2 (ECD2) and inhibits its heterodimerization with HER3, further disrupting downstream signaling. When used in combination, trastuzumab and pertuzumab exert synergistic effects, enhancing the therapeutic efficacy by targeting distinct functional regions of HER2 [31].

To overcome limitations of mAb monotherapy, researchers have developed additional strategies. Margetuximab, a next-generation anti-HER2 mAb, shares the same binding epitope as trastuzumab but is engineered to enhance Fc receptor binding, thereby improving ADCC. Margetuximab received FDA approval in 2020 and represents a step forward in optimizing immune-mediated responses [32, 33]. Another innovative approach involves antibody-drug conjugates (ADCs), which couple mAbs with cytotoxic agents. For example, T-DM1 (trastuzumab emtansine) combines trastuzumab with the cytotoxic agent emtansine (DM1), delivering the cytotoxic payload directly to HER2-positive cancer cells and inducing apoptosis [25, 34]. Similarly, trastuzumab deruxtecan (T-DXd) links trastuzumab to a potent cytotoxic agent via a peptide linker. Once internalized into the cancer cell, the linker is cleaved, releasing the cytotoxic agent to induce DNA damage and cell death [35]. ADCs have demonstrated significant efficacy in resistant HER2-positive cancers, expanding treatment options for patients who no longer respond to standard therapies.

Another class of HER2-targeted therapies is tyrosine kinase inhibitors (TKIs). TKIs block the intracellular tyrosine kinase activity of HER2 by binding to the ATP-binding site, thereby preventing receptor autophosphorylation and subsequent activation of downstream signaling pathways [36]. FDA-approved TKIs, including lapatinib, neratinib, and tucatinib, have shown efficacy in treating HER2-positive cancers, particularly in cases of resistance to mAb-based therapies. Lapatinib, for instance, inhibits both HER2 and EGFR, offering dual inhibition of oncogenic signaling. Tucatinib, on the other hand, demonstrates high selectivity for HER2, minimizing off-target effects and reducing toxicity. Ongoing research is exploring newer TKIs

with improved potency and reduced side effects, such as zongertinib and pyrotinib [37, 38]. **Table 1** summarizes the characteristics of key HER2-targeted TKIs, including their generation, receptor targets, tumor indications, and FDA approval status.

Despite the remarkable success of HER2-targeted therapies, resistance remains a significant clinical challenge. Cancer immunotherapy is emerging as a complementary approach to address this issue [39]. Active immunotherapies, such as immune checkpoint inhibitors and adoptive T-cell therapies, aim to stimulate the patient's immune system to recognize and attack HER2-positive tumor cells [40]. Chimeric antigen receptor (CAR) T-cell therapy, for instance, involves engineering T cells to express receptors that specifically target HER2, thereby enhancing the immune system's ability to eliminate cancer cells. Additionally, tumor vaccines designed to elicit HER2-specific immune responses are being investigated in clinical trials, with promising preliminary results [41].

Emerging technologies are also contributing to the advancement of HER2-targeted therapies. Nanotechnology, for example, offers innovative solutions for drug delivery. Nanoparticles (NPs) can encapsulate therapeutic agents, such as nanobodies, peptides, or small molecules, providing targeted delivery to HER2-positive tumors. HER2-targeted nanoparticles have been shown to enhance drug stability and bio-availability, reduce systemic toxicity, and improve therapeutic efficacy [42, 43]. Self-assembling nanopeptides, which form nanofibrils upon binding to HER2, have demonstrated the ability to inhibit HER2 dimerization and induce cancer cell death [44]. RNA-based therapies, including small interfering RNA (siRNA) and messenger RNA (mRNA), represent another frontier in targeting HER2-driven cancers. These

Treatments	Generation	Target	Receptor binding	Tumor types	Administration	FDA approval
Lapatinib	1	HER2, EGFR	Reversible	Breast cancer, Gastric cancer	Oral	2007
Neratinib	2	HER2, EGFR, HER4	Irreversible	Breast cancer, Gastric cancer	Oral	2017
Tucatinib	2	HER2, HER3	Reversible	Metastatic Breast cancer	Oral	2020
Afatinib	2	HER2, EGFR	Irreversible	NSCLC, Breast cancer	Oral	2013
Pozotinib	3	HER2, EGFR, HER4	Irreversible	NSCLC, Breast cancer	Oral	—
Zongertinib	3	HER2, EGFR	Irreversible	NSCLC, Breast cancer	Oral	—
Pyrotinib	3	HER2, EGFR, HER4	Irreversible	Metastatic Breast cancer, gastric cancer	Oral	—
ZN-A-1041	3	HER2	Irreversible	NSCLC, Breast cancer	Oral	—
ORIC-114	3	HER2, EGFR	Irreversible	NSCLC, Breast cancer	Oral	—

Table 1.
HER2-targeted tyrosine kinase inhibitors.

approaches aim to downregulate HER2 expression or modulate its signaling pathways, providing a novel avenue for therapeutic intervention [45, 46].

Precision medicine remains a cornerstone of HER2-targeted therapy. The heterogeneity of HER2-positive cancers necessitates individualized treatment strategies that incorporate genetic profiling, biomarker analysis, and tumor microenvironment characteristics. Advances in molecular diagnostics are enabling the identification of HER2-low and HER2-mutated tumors, broadening the scope of targeted therapies. By tailoring treatment plans to the unique molecular features of each patient's tumor, clinicians can optimize therapeutic outcomes while minimizing adverse effects [47, 48].

In conclusion, HER2-targeted therapies have revolutionized the management of HER2-positive cancers, offering improved survival and quality of life for many patients. However, the complexity of resistance mechanisms and tumor heterogeneity underscores the need for continued innovation. Future research should focus on integrating novel therapeutic approaches, such as immunotherapy and nanotechnology, into existing treatment paradigms to overcome resistance and achieve durable clinical responses. As our understanding of HER2 biology deepens, the potential for transformative advancements in cancer treatment continues to grow.

4. The impact of HER2 on the tumor microenvironment and immune modulation

TME is an essential factor influencing cancer progression, metastasis, and therapeutic resistance. HER2-positive tumors are particularly adept at reshaping their TME to promote tumor growth, immune evasion, and resistance to therapy. **Figure 3** illustrates the multifaceted interactions between HER2 signaling and various TME components, including endothelial cells, fibroblasts, immune cells, and the extracellular matrix (ECM), which collectively contribute to tumor progression and therapy resistance. These interactions highlight the complexity of HER2-positive tumors and underscore the need for innovative therapeutic strategies targeting the TME.

4.1 Angiogenesis and vascular remodeling in HER2-positive tumors

Angiogenesis is a hallmark of cancer, driven by the tumor's demand for oxygen and nutrients. HER2-positive tumors exhibit heightened angiogenic activity compared to HER2-negative tumors, primarily due to HER2-mediated activation of the PI3K/AKT and mTOR pathways [49–52]. These pathways stimulate hypoxia-inducible factors (HIF- α), leading to increased secretion of vascular endothelial growth factor (VEGF), a key driver of angiogenesis [52, 53]. Additionally, HER2-positive tumors secrete other pro-angiogenic factors such as fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF), which further enhance endothelial cell proliferation and migration [54, 55].

HER2 overexpression also upregulates COX-2 expression, which drives prostaglandin E2 (PGE2) production, activating HIF-1 α and nuclear factor kappa B (NF- κ B) to further increase VEGF expression [54, 56]. These mechanisms collectively enhance angiogenesis and promote tumor progression. Additionally, HER2-overexpressing cancer cells can mimic endothelial cells by overexpressing VE-cadherin, a process known as vasculogenic mimicry [57]. This allows cancer cells to create vessel-like structures, bypassing the need for traditional vasculature, and supports tumor survival in hypoxic conditions.

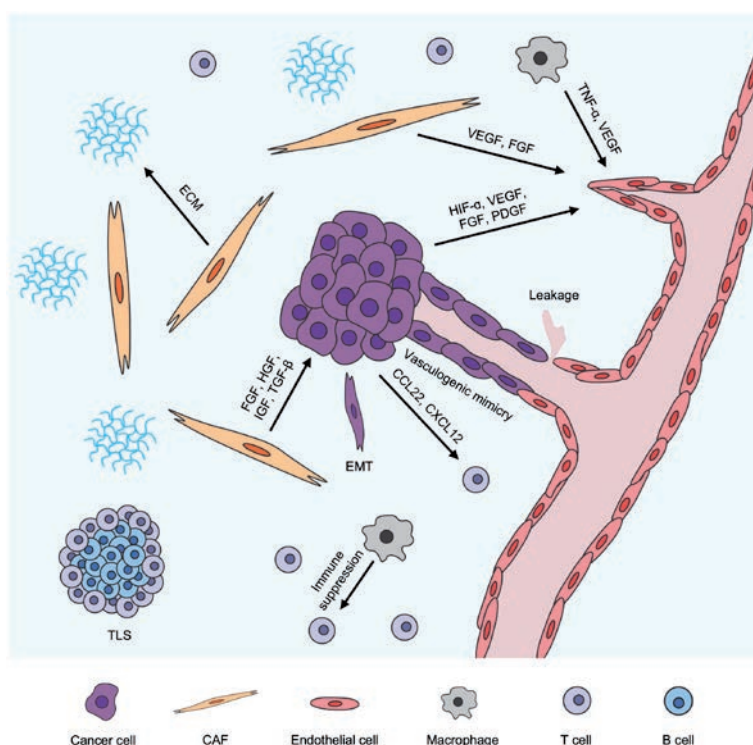


Figure 3.
Impact of HER2 on Tumor Microenvironment and Immune Modulation. This diagram illustrates the complex interactions between HER2 signaling and various components of TME. HER2-positive tumors remodel the TME by influencing key elements such as endothelial cells, cancer-associated fibroblasts (CAFs), immune cells, and the extracellular matrix (ECM). HER2 signaling promotes angiogenesis through factors like VEGF and FGF, while also facilitating vasculogenic mimicry in cancer cells. Additionally, tumor-secreted factors like HGF, IGF, and TGF- β contribute to ECM remodeling, immune suppression, and epithelial-mesenchymal transition (EMT), further supporting tumor progression. The diagram highlights how HER2 signaling induces immune suppression through interactions with immune cells such as macrophages, T cells, and B cells, creating a microenvironment conducive to cancer cell survival, migration, and resistance to therapy.

The vasculature in HER2-positive tumors, like many cancers, is often abnormal, characterized by disorganized and leaky vessels [50, 52, 54]. These vascular abnormalities lead to hypoxia, which exacerbates angiogenesis by upregulating HIF- α and VEGF in a feedback loop [58, 59]. Hypoxia also promotes epithelial-mesenchymal transition (EMT), a process that enhances metastasis by enabling cancer cells to acquire migratory and invasive capabilities [58, 60]. EMT in HER2-positive tumors disrupts cell-cell adhesion, reorganizes the cytoskeleton, and enhances motility, all of which contributes to systemic tumor dissemination. In addition, hypoxia-induced EMT increases resistance to anti-cancer therapies by impairing drug delivery and creating a sanctuary for cancer cells.

In addition to VEGF-driven angiogenesis, HER2-positive tumors may utilize alternative mechanisms such as vasculogenic mimicry [57]. In this process, tumor cells adopt endothelial-like properties to form vessel-like structures, bypassing the need for traditional blood vessels [57]. These structures contribute to tumor survival in hypoxic environments and represent a significant challenge for anti-angiogenic therapies. Current research is focused on combining HER2-targeted therapies with angiogenesis inhibitors to address these challenges and enhance therapeutic efficacy [50, 53, 55].

4.2 Fibroblasts, EMT, and cancer stem cells in HER2-positive tumors

Fibroblasts are critical cellular components of TME, and in certain cancers, they can constitute up to 90% of the tumor mass [61]. These fibroblasts undergo persistent activation under the influence of tumor-secreted factors such as transforming growth factor-beta (TGF- β), transforming into cancer-associated fibroblasts (CAFs) [62]. Unlike normal fibroblasts, CAFs exhibit distinct phenotypes, including matrix-remodeling myfibroblastic CAFs (myCAFs), immune-regulatory CAFs (iCAFs), and vascular CAFs (vCAFs) [63]. Each subtype plays a specialized role in supporting tumor progression, remodeling the extracellular matrix (ECM), and modulating the immune response [63].

In HER2-positive tumors, CAFs are activated through HER2-driven signaling pathways, including the PI3K/AKT/mTOR and TGF- β pathways [64, 65]. These activated CAFs secrete a range of growth factors, such as FGFs, hepatocyte growth factor (HGF), and insulin-like growth factor (IGF), which enhance cancer cell proliferation, motility, and invasion [62, 66]. Additionally, chemokines like CXCL12 contribute to cancer cell migration by creating chemotactic gradients within the TME [67, 68].

A key function of CAFs is ECM remodeling. HER2-driven CAFs upregulate the production of ECM components, including fibronectin, collagen, and biglycan, increasing ECM stiffness and density [67, 69]. This stiffened ECM creates a mechanical barrier that not only facilitates cancer cell migration and invasion but also impedes the infiltration of therapeutic agents and immune cells [68, 70]. Furthermore, fibrosis-related factors, such as connective tissue growth factor (CTGF) and lysyl oxidase (LOX), are secreted by HER2-activated fibroblasts, promoting collagen cross-linking and ECM remodeling [71, 72]. These changes exacerbate the immunosuppressive nature of the TME by restricting immune cell infiltration and polarizing macrophages toward the tumor-promoting M2 phenotype [63, 73].

HER2 signaling, mediated by CAF-secreted factors like TGF- β , drives EMT, enabling cancer cells to acquire mesenchymal traits such as enhanced motility and invasiveness [62, 66, 67]. EMT is further supported by ECM remodeling, as increased stiffness and altered alignment provide physical cues that promote cytoskeletal reorganization in cancer cells. This process not only facilitates metastatic dissemination but also fosters the plasticity of cancer cells, enabling their transition into CSCs. HER2-positive cancers exhibit high levels of CSC activity, partly due to HER2-driven EMT and CAF interactions. CSCs thrive in the CAF-modulated microenvironment, which provides both structural and biochemical support. In turn, CSCs interact with CAFs in a reciprocal feedback loop, reinforcing a tumor-supportive niche that sustains tumor progression and immune evasion.

Moreover, HER2-driven CAF activity promotes angiogenesis by interacting with endothelial cells and releasing pro-angiogenic factors such as VEGF and FGF. This angiogenic support sustains tumor growth under hypoxic conditions, often seen in dense, ECM-rich tumors. Hypoxia also contributes to the polarization of macrophages and the recruitment of Tregs, enhancing immune suppression [74, 75].

HER2-driven ECM remodeling has additional consequences for the TME. The stiffened ECM influences integrin signaling in cancer cells, further driving their migratory and invasive behavior [76, 77]. Additionally, ECM remodeling alters the biochemical properties of the TME, creating chemokine gradients that regulate the infiltration of neutrophils and other immune cells [63]. This intricate network of interactions underscores the multifaceted role of CAFs in HER2-positive tumors.

To counter these tumor-promoting mechanisms, strategies targeting CAF activity, ECM remodeling, and the associated EMT and CSC plasticity are under active investigation. These approaches include inhibitors of TGF- β signaling, LOX inhibitors to reduce ECM stiffness, and agents targeting CAF subtypes. By disrupting the feedback loop between HER2 signaling, CAF activity, and ECM remodeling, researchers aim to enhance the efficacy of HER2-targeted therapies and improve patient outcomes.

4.3 Immune modulation and immunosuppression in HER2-positive tumors

HER2-positive tumors profoundly reshape the tumor immune microenvironment (TIME), promoting immune evasion and supporting tumor progression [78, 79]. Immune cells within TIME exhibit dual roles, acting as either anti-tumor or pro-tumor agents depending on their interactions with HER2-driven signaling pathways [80].

Anti-tumor immune cells, such as CD8⁺ memory T cells and CD4⁺ T helper 1 (TH1) cells, play crucial roles in cancer cell killing and are associated with favorable prognoses [81, 82]. Conversely, pro-tumor immune cells, including CD4⁺ regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), suppress cytotoxic T lymphocyte (CTL) and natural killer (NK) cell activity, enabling immune evasion [62, 83]. HER2-positive tumors secrete cytokines like TGF- β and chemokines such as CCL22 and CXCL12 to recruit Tregs and MDSCs, collectively suppressing anti-tumor immune responses and creating a permissive environment for tumor growth [75, 78, 84, 85].

TAMs are among the most abundant immune cells in TIME and exhibit polarization into two functional phenotypes: M1 macrophages, which are anti-tumorigenic, and M2 macrophages, which promote tumor growth and immune suppression [81]. HER2-positive tumors recruit M2 macrophages through hypoxia-related factors, stimulating the secretion of pro-angiogenic molecules such as VEGF and TNF- α [74, 81]. These macrophages not only support angiogenesis but also remodel the extracellular matrix (ECM), facilitating immune evasion and tumor progression [86, 87].

HER2 signaling further modulates immune checkpoint pathways by upregulating PD-L1 expression, directly inhibiting T-cell activation. Additionally, HER2 downregulates MHC class I expression on tumor cells, reducing their visibility to CTLs [88]. These mechanisms exacerbate immune evasion and therapeutic resistance, presenting significant challenges for cancer treatment.

A single tumor rarely contains only one functional group of immune cells. Instead, anti-tumor and pro-tumor immune cells coexist, with their interactions determining whether the TIME becomes predominantly pro-tumorigenic or anti-tumorigenic [89–91]. Understanding these interactions is critical for predicting prognosis and developing personalized therapeutic strategies.

Emerging immunotherapeutic strategies are being developed to counteract HER2-induced immune suppression. Immune checkpoint inhibitors targeting PD-1/PD-L1 and CTLA-4 pathways have shown promise in restoring T-cell activity in HER2-positive tumors. Additionally, adoptive cell therapies, such as CAR T cells engineered to target HER2, are under investigation to enhance anti-tumor immunity. These therapies, when combined with HER2-targeted treatments, offer a comprehensive approach to overcoming immune suppression and improving clinical outcomes.

In conclusion, HER2-positive tumors actively remodel the TME through mechanisms involving angiogenesis, ECM remodeling, immune modulation, and metabolic reprogramming. Understanding these complex interactions provides valuable insights for developing innovative therapies aimed at overcoming resistance and improving patient outcomes.

5. Advanced research models for HER2-positive cancer

Cancer research necessitates diverse and flexible models tailored to specific research goals. While high-throughput models are essential for drug screening, more sophisticated systems are required to investigate the complex mechanisms of cancer progression and the TME. This section explores the evolution of cancer research models—from animal models to cutting-edge microphysiological systems—highlighting their applications, limitations, and relevance to HER2-positive cancer studies (**Figure 4**).

5.1 Animal models

Animal models have long been foundational tools in cancer research. Their capacity to replicate complex in vivo interactions is invaluable for studying cancer initiation, progression, and therapeutic responses. Historically, animal models have significantly advanced our understanding of biology and disease.

In recent years, patient-derived xenograft (PDX) models have emerged as advanced tools for cancer research. In these models, patient tumor cells are implanted into immunodeficient animals, allowing for the preservation of the tumor's genetic and histological characteristics [92]. Compared to in vitro systems, PDX models more accurately reflect tumor behavior within a living organism, enabling researchers to study cancer biology in a physiologically relevant context. These models are particularly effective for exploring oncogene-driven pathways, such as those mediated by HER2, and for evaluating drug efficacy and resistance mechanisms [92]. By preserving patient tumor characteristics and leveraging the dynamic interactions of a living system, these models bridge the gap between preclinical findings and clinical applications [93].

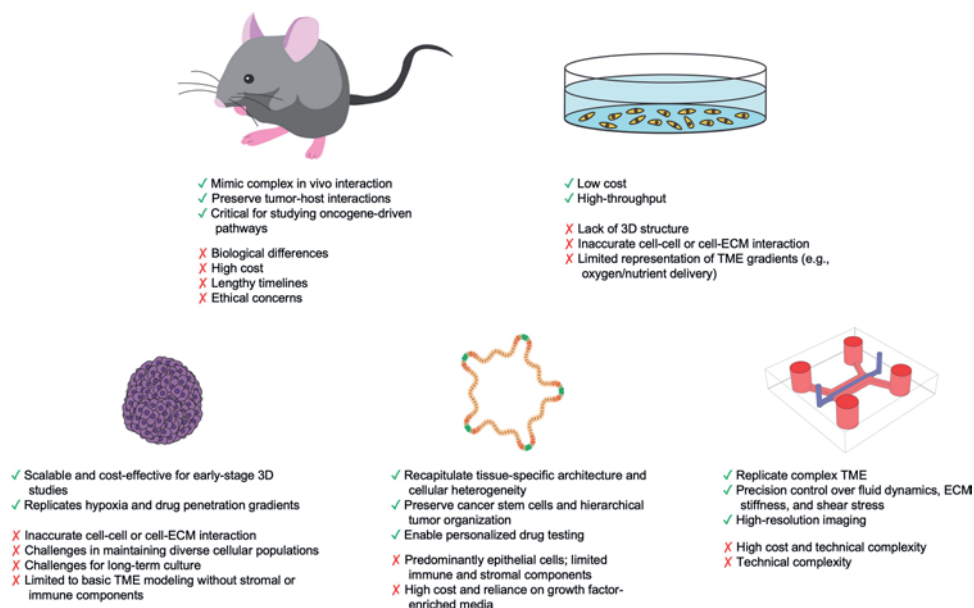


Figure 4.

Comparison of Different Tumor Models for Cancer Research. This diagram compares the advantages (green checkmarks) and limitations (red Xs) of five distinct tumor models: in vivo mouse models, 2D cell culture models, tumor spheroids, organoid model and microfluidic models.

Despite their advantages, animal models have inherent limitations. Biological differences between humans and animals, including disparities in TME composition, immune system function, and tumor-host interactions, reduce the translational potential of these studies. Even PDX models, which maintain patient tumor traits, cannot fully replicate the complexities of human physiology [94].

Moreover, the high costs, lengthy development timelines, and ethical concerns associated with animal models pose significant challenges. Nonetheless, animal models remain indispensable for validating findings from *in vitro* research and advancing our understanding of the intricate biology of cancer. They continue to serve as a vital bridge to clinical applications, providing critical insights that inform the development of more effective therapies [94].

5.2 2D cell culture models

The 2D cell culture model, introduced in the twentieth century, was the first *in vitro* system developed as an alternative to animal models. This foundational approach involves cultivating cells extracted from living tissues on glass or plastic surfaces, allowing them to grow in a monolayer. The simplicity and cost-effectiveness of 2D models make them highly scalable and ideal for high-throughput drug screening [95]. For these reasons, 2D culture systems remain widely used in cancer research today.

HER2-positive cancer research frequently employs 2D culture models, particularly HER2-overexpressing cell lines and genetically modified lines with enhanced HER2 expression. These models have been instrumental in elucidating molecular pathways, investigating the mechanisms of HER2 signaling, and assessing the efficacy of targeted therapies [96]. For instance, they allow for precise experimental control, enabling researchers to study the direct effects of HER2 on cell proliferation, survival, and therapeutic responses.

However, the 2D culture model is inherently limited in its ability to replicate the complexity of *in vivo* tumors. The lack of three-dimensional (3D) structure prevents accurate representation of cell-cell and cell-ECM interactions, key elements of the tumor microenvironment [97]. These deficiencies result in unnatural nutrient and oxygen delivery, as well as impaired signaling molecule gradients. Consequently, cellular behaviors such as differentiation, proliferation, and survival observed in 2D systems may differ significantly from those in living tissues [97]. These limitations hinder the translation of findings from 2D models to *in vivo* or clinical settings.

5.3 Spheroid models

Spheroid models address many limitations of 2D cultures by providing a 3D structure that better mimics the *in vivo* environment. These small, cell-aggregated structures can be cultured in suspension or embedded in ECM, enabling more natural cell-cell and cell-ECM interactions [98]. Spheroids are widely used in HER2 research to investigate signaling pathways, drug responsiveness, and resistance mechanisms [99].

The 3D architecture of spheroids allows for the establishment of nutrient and oxygen gradients, replicating conditions within solid tumors [100]. This feature makes spheroids particularly valuable for studying drug penetration and hypoxia-induced resistance. However, their compact structure can also restrict metabolism and drug delivery, posing challenges for long-term culture and modeling of diverse

cellular populations [98]. Despite these limitations, spheroids provide a cost-effective and scalable platform for bridging the gap between 2D cultures and more advanced models [100].

5.4 Organoid models

Organoids represent a transformative advancement in 3D culture technology, bridging the gap between traditional 2D models and the complexity of *in vivo* systems. Derived from embryonic or adult stem cells, organoids self-organize through processes of differentiation and self-renewal into tissue-like structures that mimic the architecture, cellular heterogeneity, and functionality of human organs [101, 102]. These *in vitro* mini-organs are guided by carefully controlled biochemical and biophysical cues, enabling the recapitulation of organ-specific hierarchies and functions [101, 102].

Patient-derived tumor organoids (PDOs), which are generated from cancer tissue biopsies, uniquely preserve the genetic, histological, and phenotypic features of the original tumor [103, 104]. These models excel in capturing the heterogeneity of cancer, including the coexistence of stem-like cancer cells and differentiated cancer cells, as well as variations in HER2 expression levels across cell populations, which is critical for studying therapeutic resistance and tumor evolution [103, 104]. By mirroring the hierarchical structure and architecture of human tumors, PDOs provide a robust platform for drug efficacy testing and resistance profiling within the context of personalized medicine.

Despite their significant advantages, organoids have notable limitations. Most organoids are predominantly composed of epithelial lineage cells, which limits their ability to fully replicate TME, including critical interactions with stromal, vascular, and immune components [105]. While recent advancements have incorporated immune cells and vascular networks into organoid systems, these approaches remain experimental and resource intensive. Furthermore, maintaining the balance between cellular differentiation and stemness requires growth factor-enriched media, which increases both the complexity and cost of culture. This reliance on specialized media and protocols demands skilled expertise, presenting barriers to widespread adoption. In addition, the lack of physiological mechanical forces, such as shear stress or stretching, limits organoids' ability to fully replicate dynamic tissue behaviors seen *in vivo* [106]. This is particularly relevant for HER2-positive cancers, where interactions with the ECM and surrounding stromal cells play a pivotal role in tumor progression and therapy resistance. Organoid models, while not without their challenges, have established themselves as indispensable tools for HER2-positive cancer research. By combining genetic fidelity with structural complexity, they offer unparalleled opportunities to study HER2-driven oncogenesis, evaluate therapeutic strategies, and explore resistance mechanisms in a patient-specific manner [103, 104]. As ongoing innovations address current limitations—such as integrating immune and stromal components—organoids are poised to further revolutionize cancer modeling and precision medicine.

5.5 Microphysiological systems (MPS)

Microphysiological systems (MPS), often referred to as organ-on-a-chip or lab-on-a-chip technology, have emerged as transformative tools in cancer research. Fabricated using biocompatible materials like polydimethylsiloxane (PDMS), these

microfluidic platforms replicate the architecture and functions of human tissues by incorporating organ-specific cells and ECM components [106, 107]. Depending on the tissue being modeled, these systems are adapted to mimic physiological conditions, earning names such as “tumor-on-a-chip.” By providing a controlled environment for cell growth and interaction, MPS overcomes many limitations of traditional 2D culture models and animal studies, including the inability to accurately recreate the complexity of TME [108, 109].

One of the key features of MPS is its ability to simulate physiological conditions with precision [106, 110, 111]. Materials such as PDMS and glass, commonly used in MPS fabrication, are transparent and thin, facilitating the acquisition of high-resolution images essential for detailed analyses and dynamic observations. These features enable researchers to monitor cellular behaviors, molecular interactions, and drug responses in real time with exceptional clarity. Additionally, the small-scale design of MPS systems supports rapid and precise analysis of localized regions, enhancing research efficiency and enabling comprehensive studies of complex biological processes and interactions [112, 113].

Furthermore, the fine control of fluid dynamics within MPS allows the replication of interstitial flow and shear stress, closely resembling the microenvironment of solid tumors [114]. By adjusting the composition and stiffness of ECM components, MPS can simulate the biomechanical properties unique to various tissues, offering valuable insights into the dynamics of cancer progression and the mechanisms underlying therapeutic responses [110, 114]. These capabilities make MPS a powerful tool for studying intricate tumor behaviors and interactions within the TME, advancing both basic and translational cancer research.

In the context of HER2-positive cancers, tumor-on-a-chip systems have shown promise in modeling the TME. By integrating patient-derived organoids, fibroblasts, and immune cells, these platforms enable the study of HER2 signaling pathways, therapeutic resistance mechanisms, and the influence of the TME on cancer progression. Although direct evidence for HER2-specific MPS studies remains limited, the versatility of MPS technology suggests its potential as a robust platform for advancing HER2-related research.

Despite their many advantages, MPS systems face notable challenges. Their complexity and reliance on advanced fabrication techniques increase costs and necessitate skilled operators, posing barriers to widespread adoption. Additionally, while MPS systems provide unparalleled precision in replicating physiological conditions, they are not yet suitable for high-throughput applications, limiting their scalability for large-scale drug screening [110, 113].

In conclusion, MPS represents a groundbreaking advancement in cancer modeling, offering unprecedented opportunities to study the intricacies of HER2-positive cancers and beyond. As technology continues to evolve, MPS platforms are poised to bridge the gap between *in vitro* and *in vivo* models, providing a critical tool for precision medicine and innovative cancer therapies.

6. Conclusion

HER2 plays a pivotal role in driving cancer progression, metastasis, and therapy resistance. Its overexpression in cancers such as breast, gastric, and lung cancers is associated with aggressive tumor behavior and poor prognosis. Through its ligand-independent dimerization and activation of downstream signaling pathways like

PI3K/AKT/mTOR and MAPK, HER2 not only promotes tumor cell proliferation and survival but also exerts profound effects on the TME. The dynamic interplay between HER2 signaling and the TME contributes to immune evasion, enhanced angiogenesis, extracellular matrix remodeling, and CSC plasticity, establishing a supportive niche for tumor growth and therapeutic resistance.

The development of HER2-targeted therapies, including monoclonal antibodies (e.g., trastuzumab and pertuzumab), antibody-drug conjugates (e.g., T-DM1 and T-DXd), and tyrosine kinase inhibitors (e.g., lapatinib and tucatinib), has significantly improved outcomes for patients with HER2-positive cancers. However, resistance mechanisms, including HER2 mutations, altered signaling pathways, TME-mediated immunosuppression, and EMT-driven invasiveness, remain major challenges. These limitations highlight the need for innovative therapeutic strategies that target both intrinsic tumor biology and the extrinsic influence of the TME.

Emerging research platforms, such as organoids and MPS, represent transformative tools for studying HER2-driven cancer biology and therapeutic responses. These advanced models offer unprecedented insights into the complex interactions between tumor cells and their microenvironment, enabling the development of precision medicine approaches tailored to the unique characteristics of each patient's cancer. By integrating these models with HER2-targeted therapies, researchers can uncover novel mechanisms of resistance and identify new therapeutic targets, paving the way for more effective and durable treatments.

In conclusion, understanding the multifaceted role of HER2 in cancer progression and its intricate relationship with the TME is critical for advancing cancer research and improving patient outcomes. Future efforts should focus on combining targeted therapies with approaches modulating CSC dynamics, EMT, and ECM remodeling to achieve comprehensive and sustained tumor control. By addressing these complexities, the integration of innovative research platforms with cutting-edge therapies offers a promising avenue for overcoming the challenges posed by HER2-positive cancers and transforming the landscape of their treatment.

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Conflict of interest

The authors declare no conflict of interest.

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The Role of HER2 in Cancer: Molecular Mechanisms, Clinical Impact, and Advances in Targeted Therapies

Hongting Wang

Abstract

Human Epidermal Growth Factor Receptor 2 (HER2) is a pivotal protein in cancer biology, primarily known for its role in breast cancer. As a receptor tyrosine kinase, HER2 is involved in regulating cell growth, differentiation, and survival. In many cancers, particularly breast cancer, HER2 is overexpressed or amplified, leading to more aggressive tumor growth and poorer patient outcomes. This chapter will explore the intricate molecular mechanisms by which HER2 contributes to oncogenesis, including its influence on signaling pathways that drive tumor progression. It will also examine the clinical significance of HER2 as both a biomarker and a therapeutic target. The impact of existing HER2-targeted treatments, such as trastuzumab and newer therapies, will be reviewed. Additionally, recent advancements in HER2 research will be discussed, along with future directions for overcoming resistance and improving treatment efficacy to enhance patient outcomes.

Keywords: molecular mechanisms, biomarker, therapeutic target, therapeutic approaches, prognostic implications

1. Introduction

The Epidermal Growth Factor Receptor (EGFR) family, also known as the ErbB receptor family, consists of four closely related transmembrane tyrosine kinase receptors: EGFR (ErbB1), ErbB2 (HER2), ErbB3, and ErbB4 [1]. These receptors play critical roles in regulating cellular processes such as growth, differentiation, survival, and repair (**Table 1**). They achieve this by mediating signal transduction pathways that are activated upon ligand binding, dimerization, and subsequent autophosphorylation of the receptor's intracellular tyrosine kinase domain [6]. Each member of the EGFR family has distinct and overlapping functions, dictated by their expression patterns and interactions with various ligands and co-receptors. Predominantly expressed in epithelial tissues, EGFR is a key regulator of cell proliferation and differentiation. Dysregulated EGFR signaling is associated with several cancers, including lung, colorectal, and head and neck cancers, where it

Receptor	Expression profile	Primary functions	Oncogenic dysregulation	Associated cancer types	Reference
EGFR (ErbB1)	Widely expressed in epithelial tissues	Regulates cell proliferation, differentiation, and repair	Overexpression, activating mutations (e.g., L858R, T790M)	Lung, colorectal, head and neck cancers	[2]
HER2 (ErbB2)	High in breast, gastric, and ovarian tissues	Acts as a co-receptor, amplifies signaling when dimerized	Gene amplification, overexpression	Breast, gastric, and ovarian cancers	[3]
ErbB3	Epithelial and neuronal cells	Signals via PI3K-AKT pathway, lacks intrinsic kinase activity	Heterodimerization with HER2	Breast cancer, therapy-resistant cancers	[4]
ErbB4	Neural and cardiac tissues	Involved in neurodevelopment and tissue differentiation	Dysregulated ligand binding or signaling	Breast cancer, neurodevelopmental disorders	[5]

Table 1.
EGFR family and associated oncogenic features.

promotes tumor growth, survival, and resistance to apoptosis [7]. Unlike other family members, HER2 does not directly bind ligands but acts as a preferred heterodimerization partner for other ErbB receptors, amplifying signaling potency [8]. Overexpression or gene amplification of HER2 is a hallmark of aggressive breast cancers and is associated with poor prognosis. This receptor lacks intrinsic kinase activity but forms heterodimers with other family members, particularly HER2 [9]. It is critical for signaling pathways like PI3K/AKT, which regulate cell survival and metabolism. ErbB3 dysregulation is implicated in resistance to targeted therapies in HER2-positive cancers. This receptor is unique in its ability to signal through both ligand-independent and ligand-dependent pathways. It is essential for neurodevelopment and tissue differentiation, with its dysregulation linked to certain cancers and neurological disorders [10]. The expression of these receptors is not restricted to epithelial tissues; they are also found in various other cell types, each contributing to distinct biological processes. ErbB2 and ErbB4 are involved in synaptic plasticity and neurodevelopment, influencing cognitive and sensory functions in neuronal cells [11]. EGFR and HER2 promote angiogenesis and vascular remodeling, processes that are co-opted in tumor progression in endothelial cells. EGFR expression in macrophages and lymphocytes modulates immune responses and inflammatory pathways in immune cells. ErbB receptors facilitate tissue repair and fibrosis, underscoring their role in wound healing and chronic inflammatory conditions in fibroblasts and mesenchymal cells [12]. HER2 stands out as a critical oncogenic driver in cancers, especially breast and gastric cancers [13]. Overexpression or gene amplification of HER2 leads to unchecked cellular proliferation, enhanced survival, and metastasis [14]. These characteristics underscore the necessity of targeting HER2 in cancer therapeutics. HER2-targeted therapies, including monoclonal antibodies (e.g., trastuzumab), tyrosine kinase inhibitors, and antibody-drug conjugates, have revolutionized the treatment landscape for HER2-positive cancers, significantly improving clinical outcomes [15]. This chapter delves into the molecular mechanisms underpinning HER2's role in cancer, its clinical significance, and the transformative advances in HER2-targeted therapies. By exploring these aspects, the chapter aims to provide a comprehensive understanding of HER2's multifaceted functions and its implications for cancer biology and therapy.

2. Functional biology of EGFR and its role in carcinogenesis

The EGFR family plays a central role in carcinogenesis, with its members regulating key cellular processes that, when dysregulated, contribute to tumor initiation, progression, and metastasis [16]. Ligand binding induces dimerization of EGFR family receptors, triggering intracellular signaling cascades such as the RAS-RAF-MEK-ERK pathway (promoting proliferation) and the PI3K-AKT-mTOR pathway (enhancing survival and growth) [17]. Dysregulation in these pathways, often due to mutations, overexpression, or gene amplification, underpins the oncogenic potential of EGFR family members. In normal cellular contexts, EGFR-mediated signaling is tightly regulated to ensure appropriate cellular responses. However, in cancer, aberrations such as EGFR mutations (e.g., EGFR exon 19 deletions or L858R mutations in non-small cell lung cancer) and HER2 amplification (commonly observed in breast and gastric cancers) lead to constitutive activation of these signaling networks [18]. This results in uncontrolled cell division, evasion of apoptosis, angiogenesis, and metastasis (**Figure 1**).

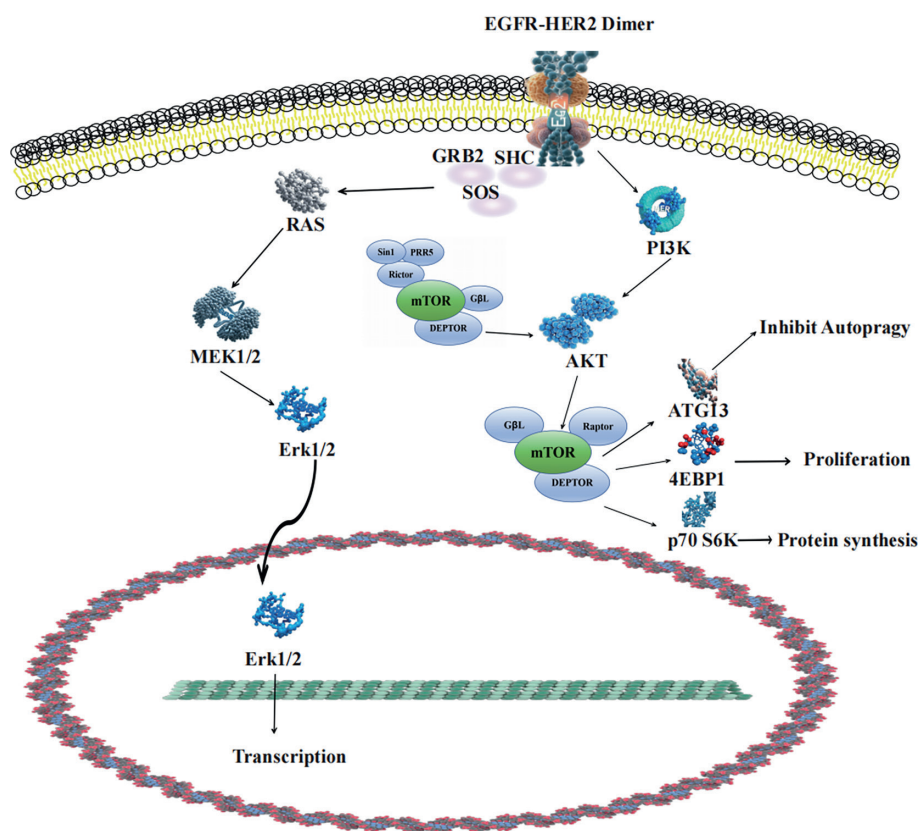


Figure 1. *EGFR-Mediated Signaling Pathways and Their Role in Carcinogenesis. The RAS-RAF-MEK-ERK pathway, emphasizing its role in promoting cell proliferation and migration. The PI3K-AKT-mTOR pathway, detailing its contribution to cell survival and growth.*

3. HER2's unique role in cancer biology and clinical significance

Human Epidermal Growth Factor Receptor 2 (HER2), a member of the EGFR family, distinguishes itself through its unique biological features and pivotal role in cancer progression [2]. Unlike other EGFR family members, HER2 lacks direct ligand-binding capability. Instead, it functions as a preferred heterodimerization partner, enhancing the signaling potency of other ErbB receptors [19]. This property amplifies critical pathways, such as PI3K-AKT and RAS-RAF-MEK-ERK, which regulate cell proliferation, survival, and metabolism [20]. The overexpression or gene amplification of HER2 is a hallmark of several aggressive cancers, including breast and gastric cancers [21]. This aberrant HER2 activity promotes uncontrolled cellular proliferation, enhanced survival, and increased metastasis, contributing to poor clinical outcomes. HER2's clinical importance is underscored by its dual role as a prognostic marker and a therapeutic target. In breast cancer, approximately 20–30% of cases exhibit HER2 overexpression or gene amplification, correlating with a more aggressive tumor phenotype characterized by rapid growth, higher metastatic potential, and worse prognosis if untreated [22]. Historically, HER2-positive breast cancers were associated with poor outcomes. However, the development of HER2-targeted therapies, including monoclonal antibodies (e.g., trastuzumab and pertuzumab),

tyrosine kinase inhibitors, and antibody-drug conjugates, has revolutionized treatment [23]. These therapies have significantly improved survival rates, transforming HER2-positive breast cancer from a highly aggressive disease to a manageable condition. Beyond breast cancer, HER2 plays a significant role in other malignancies. In gastric cancer, HER2 amplification or overexpression is observed in about 10–20% of cases [24]. Targeted therapies like trastuzumab have improved survival and treatment outcomes for these patients. HER2 involvement has also been identified in ovarian, endometrial, and non-small cell lung cancers (NSCLC), although the efficacy of HER2-targeted treatments in these cancers remains an active area of research [25]. The ability to identify HER2-positive tumors enables clinicians to tailor therapeutic strategies, improving patient outcomes and quality of life. HER2's broad relevance in oncology highlights its importance as both a biomarker and a therapeutic target across various cancer types.

4. The molecular architecture of HER2

HER2 is a tyrosine kinase receptor with a complex structure that consists of three major domains: the extracellular domain, the transmembrane region, and the intracellular tyrosine kinase domain (**Figure 2**). These components work together to mediate cell signaling.

4.1 Extracellular domain

The extracellular domain of HER2 is responsible for interacting with other ErbB family receptors (e.g., EGFR, HER3, and HER4) to form heterodimers [12]. Unlike other ErbB family receptors, HER2 does not bind a ligand directly but is always in a conformation ready to dimerize. Once HER2 forms a dimer with another receptor, this interaction triggers a conformational change that is transmitted through the transmembrane region to the intracellular tyrosine kinase domain [13].

4.2 Transmembrane region

The transmembrane region is a short hydrophobic sequence that anchors HER2 in the cell membrane [26]. It acts as a physical link between the extracellular domain and the intracellular tyrosine kinase domain. Upon dimerization at the

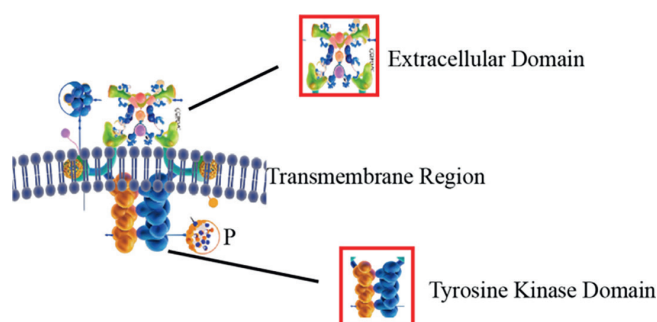


Figure 2.
 HER2-HER3 dimer with a consists of three major domains.

extracellular domain, the transmembrane region helps transmit the activation signal across the cell membrane, initiating the activation of the intracellular tyrosine kinase domain [20].

4.3 Intracellular tyrosine kinase domain

The intracellular domain contains the tyrosine kinase activity, which is responsible for phosphorylating specific tyrosine residues on itself (autophosphorylation) and on other substrates [27]. This phosphorylation activates downstream signaling pathways, such as the PI3K/Akt and MAPK/ERK pathways, which regulate cell growth, survival, and differentiation [28]. Dimerization and the conformational changes from the extracellular and transmembrane regions activate the tyrosine kinase domain. Upon activation, the kinase domain catalyzes the transfer of phosphate groups to tyrosine residues on both HER2 and its dimerization partner, initiating intracellular signaling [29].

5. The varieties of dimers and their signaling specificities

5.1 Homodimers

Homodimers refer to a molecular complex formed when two identical molecules (monomers) bind together through non-covalent interactions, such as hydrogen bonds, hydrophobic interactions, or ionic bonds [30]. Homodimers are formed by two identical receptor molecules, such as EGFR-EGFR. These dimers primarily activate the MAPK pathway, promoting cell proliferation, differentiation, and survival in response to external stimuli [20].

5.2 Heterodimers

Receptor dimerization occurs when two EGFR family members come together to form a dimer [31]. This process is triggered by ligand binding to the extracellular domain of most family members, such as EGFR (ErbB1), HER3 (ErbB3), and HER4 (ErbB4). HER2, however, does not require a ligand due to its constitutively active dimerization interface [32]. Heterodimers consist of different EGFR family members, such as HER2-HER3 or HER2-EGFR. Heterodimers exhibit stronger and more sustained signaling compared to homodimers, owing to the complementary properties of the partnered receptors [9]. The HER2-HER3 heterodimer is one of the most potent signaling complexes in the EGFR family. It strongly activates the PI3K-AKT pathway, which is crucial for cell survival, metabolism, and resistance to apoptosis [33]. The HER2-EGFR dimer contributes to both the PI3K-AKT and MAPK pathways, supporting cell growth, survival, and potentially therapeutic resistance. The HER2-HER4 heterodimer influences pathways involved in cell differentiation and tissue development [10].

6. The functional ramifications of dimerization

In healthy cells, HER2 (human epidermal growth factor receptor 2) plays a vital role in regulating normal cell growth, differentiation, survival, and repair. Unlike other members of the ErbB family, HER2 is constitutively active and does not require

ligand binding for activation [34]. It serves as a preferred partner for other ErbB receptors, such as EGFR (HER1), HER3, and HER4. The ability of HER2 to form heterodimers with these receptors leads to the activation of downstream signaling pathways that regulate key cellular processes. Heterodimers involving HER2 generate stronger and more sustained signaling compared to homodimers, ensuring a robust cellular response [35]. Upon dimerization, the intracellular tyrosine kinase domains of HER2 are activated, leading to autophosphorylation of specific tyrosine residues. This autophosphorylation of HER2 triggers several critical signaling pathways that regulate essential cellular functions. The PI3K/Akt pathway plays a central role in promoting cell survival by inhibiting apoptosis (programmed cell death) and is also involved in regulating metabolism, growth, and protein synthesis, ensuring that cells can survive under stressful conditions [36]. The MAPK pathway is crucial for cell proliferation, differentiation, and survival, driving appropriate cell division and growth in response to external signals and maintaining tissue integrity. Additionally, the JAK/STAT pathway, activated by HER2, is important for immune responses, cell division, and differentiation, and helps regulate the balance between cell proliferation and apoptosis in various tissues, contributing to cellular homeostasis [15]. Together, these pathways ensure that HER2 signaling plays a vital role in controlling cell growth, survival, and tissue integrity under normal conditions. In normal cells, HER2 signaling is tightly regulated to ensure that cell growth, differentiation, and repair occur in a controlled manner [37]. This regulation helps maintain tissue homeostasis, allowing tissues to repair and regenerate while preventing excessive or uncontrolled growth. During embryonic development and adult tissue maintenance, HER2 plays a key role in organ formation and maintaining tissue integrity, contributing to the development of the nervous system, heart, and skin [38]. In healthy cells, the expression and activity of HER2 are carefully regulated to balance cellular responses to growth factors and other external signals. This ensures appropriate cell growth, survival, and differentiation, facilitating tissue repair and adaptation to changing conditions [39].

However, in cancerous conditions, the regulatory mechanisms controlling HER2 activity are often disrupted. Overexpression or amplification of HER2 occurs in many cancers, including breast, gastric, and ovarian cancers, due to genetic alterations that increase HER2 receptor levels on the cell surface [3]. Elevated HER2 levels enhance the likelihood of dimerization even in the absence of ligands, leading to continuous activation of downstream signaling pathways. This sustained signaling drives tumorigenesis and cancer progression by promoting uncontrolled cell growth and survival [40]. The overactivation of key pathways, such as the MAPK and PI3K/Akt pathways, results in excessive cell proliferation and resistance to apoptosis. Cancer cells become more resistant to programmed cell death by continuously activating survival pathways and suppressing pro-apoptotic signals, enabling them to thrive in hostile environments, such as nutrient deprivation or immune attack [41]. Additionally, HER2 overexpression promotes cancer cell invasion and metastasis. It triggers the epithelial-mesenchymal transition (EMT), which alters cell adhesion and motility, allowing tumor cells to invade surrounding tissues and spread to distant organs [42]. HER2 also interacts with stromal cells, immune cells, and components of the extracellular matrix to create a pro-metastatic niche, supporting tumor growth and dissemination. Furthermore, HER2 dysregulation upregulates the production of pro-angiogenic factors, such as vascular endothelial growth factor (VEGF), which stimulate the formation of new blood vessels to supply the tumor with nutrients and oxygen, facilitating rapid tumor growth [43]. This angiogenesis further enhances the tumor's ability to expand and metastasize, creating a vicious cycle that drives cancer progression.

7. The progress in HER2-targeted therapies

The discovery of HER2 as a prognostic marker has revolutionized the treatment of various cancers, particularly HER2-positive breast cancer. HER2-positive tumors, which account for 15–20% of breast cancer cases, were historically associated with poor outcomes due to their aggressive nature, rapid progression, and high metastatic potential [44]. HER2 overexpression drives tumor growth by continuously activating key growth signaling pathways, such as PI3K/Akt and MAPK, which promote cell division, survival, and resistance to apoptosis [45]. These pathways contribute to the rapid proliferation and greater metastatic potential of HER2-positive tumors. Beyond breast cancer, HER2 amplification is found in 10–30% of gastric and esophageal cancers, particularly in gastroesophageal junction adenocarcinomas, where it similarly contributes to aggressive disease and a poor prognosis [46]. Although less frequently observed, HER2 amplification is also present in other cancers, such as ovarian, bladder, and non-small cell lung cancer (NSCLC), where it correlates with more aggressive disease and unfavorable clinical outcomes. However, the advent of HER2-targeted therapies has transformed the landscape for HER2-positive cancers, improving patient outcomes and providing new treatment options [47]. Trastuzumab (Herceptin), the first major breakthrough in HER2-targeted therapy, specifically binds to the extracellular domain of the HER2 receptor, blocking its signaling and slowing tumor growth. Trastuzumab marks tumor cells for destruction by the immune system through antibody-dependent cellular cytotoxicity (ADCC) [48]. It has become the standard of care for HER2-positive metastatic gastric cancer and gastroesophageal junction adenocarcinoma, as well as HER2-positive breast cancer. Other HER2-targeted therapies have since emerged, including pertuzumab (Perjeta), ado-trastuzumab emtansine (Kadcyla), trastuzumab deruxtecan (Enhertu), margetuximab (Margenza), and fam-trastuzumab deruxtecan-nxki (Enhertu) [49]. These monoclonal antibodies function by binding to HER2, preventing receptor dimerization, and activating ADCC, ultimately inhibiting tumor growth. Each of these therapies represents a significant step forward in cancer treatment, enabling more targeted interventions that specifically block HER2 signaling while reducing off-target effects.

The development of these therapies has dramatically improved the prognosis for patients with HER2-positive cancers, shifting them from a once-dismal outlook to a more manageable condition with the promise of personalized treatment options. As a result, HER2 status has become a critical factor in guiding therapeutic decisions, optimizing treatment strategies, and improving patient outcomes [50]. These HER2-targeted therapies are often used in combination with other treatments, such as, to maximize their effectiveness. For example, trastuzumab is commonly used alongside chemotherapy in HER2-positive breast cancer, while newer treatments like trastuzumab deruxtecan (Enhertu) and pertuzumab are incorporated into combination regimens to overcome resistance and improve efficacy [51]. The success of HER2-targeted therapies has expanded the treatment options available for HER2-positive cancers, particularly in breast, gastric, and other HER2-overexpressing tumors [23]. The continuous development and refinement of these therapies, supported by ongoing clinical research and collaboration between biotechnology companies, have transformed the therapeutic landscape, offering hope to patients and improving survival rates. **Table 2** below organizes these therapies based on their class (monoclonal antibodies vs. small molecule inhibitors), outlining their mechanisms of action, indications, and manufacturers, providing a comprehensive overview of the current and emerging treatments for HER2-positive cancers.

Therapy	Class	Mechanism of Action	Indications	Manufacturer	Reference
Trastuzumab (Herceptin)	Monoclonal Antibody	Binds to the extracellular domain of HER2, inhibiting dimerization and signaling; promotes ADCC	HER2-positive breast cancer, gastric cancer, others	Genentech (Roche)	[21]
Pertuzumab (Perjeta)	Monoclonal Antibody	Binds to a different site on HER2, preventing receptor dimerization with HER3	HER2-positive breast cancer, neoadjuvant and metastatic	Genentech (Roche)	[23]
Ado-trastuzumab emtansine (Kadcyla)	Antibody-Drug Conjugate (ADC)	Trastuzumab conjugated to emtansine (DM1), delivering cytotoxic chemotherapy directly to HER2-positive cells	HER2-positive breast cancer, metastatic	Genentech (Roche)	[52]
Trastuzumab deruxtecan (Enhertu)	Antibody-Drug Conjugate (ADC)	Trastuzumab linked to deruxtecan (topoisomerase inhibitor), targeting HER2-positive cells and delivering cytotoxic agent	HER2-positive breast cancer, gastric cancer, others	Daiichi Sankyo, AstraZeneca	[53]
Margetuximab (Margenza)	Monoclonal Antibody	Engineered antibody with enhanced Fc receptor binding, improving immune response against HER2-positive cells	HER2-positive breast cancer (advanced, refractory)	MacroGenics	[54]
Fam-trastuzumab deruxtecan-nxki (Enhertu)	Antibody-Drug Conjugate (ADC)	Delivers topoisomerase inhibitor (deruxtecan) directly to HER2-positive cells	HER2-positive breast cancer, gastric cancer, others	Daiichi Sankyo, AstraZeneca	[55]
Lapatinib (Tykerb)	Small Molecule Inhibitor	Dual inhibitor of HER2 and EGFR tyrosine kinases, preventing receptor activation and downstream signaling	HER2-positive breast cancer (with chemotherapy)	GlaxoSmith Kline (GSK)	[56]
Neratinib (Nerlynx)	Small Molecule Inhibitor	Irreversible pan-HER inhibitor targeting HER1, HER2, and HER4, inhibiting signaling pathways	Extended adjuvant treatment of HER2-positive breast cancer	Puma Biotechnology	[57]
Afatinib (Gilotrif)	Small Molecule Inhibitor	Irreversible inhibitor of EGFR family receptors, including HER2, blocking tumor growth signals	HER2-mutated NSCLC	Boehringer Ingelheim	[58]
Tucatinib (Tukysa)	Small Molecule Inhibitor	Selective HER2 inhibitor, prevents HER2 signaling and tumor cell proliferation	HER2-positive breast cancer (including brain metastasis)	Seattle Genetics (Seagen)	[59]

Table 2.
HER2-Targeted Therapies.

8. The resistance to HER2-targeted therapies

HER2 amplification can lead to resistance to HER2-targeted therapies, presenting a significant challenge in cancer treatment. Resistance mechanisms are multifaceted and often involve alterations at the molecular level that enable tumor cells to evade the effects of these therapies [2]. One common mechanism is the development of mutations in the HER2 receptor itself, which can alter the binding site for drugs like trastuzumab, reducing their efficacy. Additionally, tumors may activate alternative growth signaling pathways, such as those mediated by the PI3K/Akt, MAPK, or MET pathways, which bypass HER2 dependency and sustain tumor proliferation and survival [60]. Changes in the tumor microenvironment can also contribute to resistance, including alterations in stromal interactions, immune evasion, or the production of growth factors that diminish the effectiveness of HER2-targeted agents. For example, increased expression of ligands that activate HER3 or EGFR can enhance compensatory signaling, while upregulation of efflux pumps may reduce intracellular drug concentrations, particularly for antibody-drug conjugates [61]. In gastric and esophageal cancers, resistance to HER2-targeted therapies is similarly observed, driven by mechanisms such as HER2 receptor truncation, which eliminates the binding site for monoclonal antibodies, or a switch in tumor phenotype, such as epithelial-to-mesenchymal transition (EMT), which reduces HER2 expression [25].

9. The approaches to overcome resistance to HER2-targeted therapies

To overcome this resistance, various approaches are being explored. Combination therapies that target multiple pathways simultaneously, for example, pairing HER2 inhibitors with drugs that block other relevant kinases, are being investigated [62]. Lapatinib, a HER2 and EGFR dual inhibitor, has been combined with mTOR inhibitors like everolimus in clinical trials to target both HER2 and the activated PI3K/AKT/mTOR pathway [63]. Another strategy is the development of novel HER2-targeted agents with enhanced binding affinity or the ability to overcome specific resistance mutations. ADCs (antibody-drug conjugates) like ado-trastuzumab emtansine (T-DM1) have shown promise [59]. T-DM1 combines the HER2-targeting antibody trastuzumab with a cytotoxic agent, allowing for more effective delivery of the drug to HER2-expressing cancer cells [64]. Moreover, research is focused on understanding the role of the tumor microenvironment in promoting resistance and devising ways to modulate it to enhance the efficacy of HER2-targeted therapies. For example, studies have shown that fibroblasts in the tumor stroma can secrete factors that activate HER2-independent survival pathways in cancer cells [65]. Strategies to target these stromal cells or block the secreted factors are being explored. Overall, continuous efforts in deciphering the molecular mechanisms and devising innovative approaches are essential to improve the outcomes of patients receiving HER2-targeted therapies.

10. Conclusion

While the advent of HER2-targeted therapies has significantly improved outcomes for patients with HER2-positive cancers, ongoing research seeks to address challenges such as resistance and disease recurrence. Emerging strategies include bispecific antibodies, which simultaneously target HER2 and other receptors, and the use of

immune checkpoint inhibitors in combination with HER2 therapies to harness the immune system's ability to fight cancer. Additionally, liquid biopsy techniques are being developed to monitor HER2 expression dynamically throughout treatment, providing a less invasive method for detecting resistance or disease progression. As more is learned about the complex biology of HER2, these advances will likely lead to further refinement of therapeutic approaches, improving patient outcomes even more. In conclusion, HER2 plays a central role in the pathogenesis of various cancers. Its discovery as a targetable oncogene has transformed cancer treatment, particularly in breast cancer, where HER2-targeted therapies have become the standard of care. While challenges such as resistance remain, the ongoing development of new therapies and treatment strategies continues to push the boundaries of cancer care, offering hope for improved survival and quality of life for patients with HER2-positive cancers.

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HER2 and Epigenetic Modifications in Tumorigenesis: Mechanisms and Therapeutic Implications

Zhoujie Ye, Haile Yu, Liping Zhu, Xiaolu Fan, Aizhu Lin and Xinrui Wang

Abstract

Human epidermal growth factor receptor 2 (HER2) is a transmembrane tyrosine kinase receptor that plays a pivotal role in the development and progression of cancers, particularly in breast and gastric cancers. While HER2 overexpression is commonly attributed to gene amplification, recent studies indicate that epigenetic modifications, such as DNA methylation, histone modification, and non-coding RNA interference, are also critical in regulating HER2 expression and activity. This article will focus on the relationship between HER2 and epigenetic modification.

Keywords: human epidermal growth factor receptor 2, tumor, DNA methylation, histone modifications, phosphorylation, ubiquitination modification, non-coding RNA

1. Introduction

Early cancer research usually focuses on genomic variation during tumorigenesis, including gene mutation, copy number variation, and chromosome rearrangement [1]. Later, more and more studies have shown that epigenetic modification is closely related to the occurrence and development of cancer [2–4]. Epigenetic abnormalities have important effects on chromatin structure, gene expression and basic cell life activities and are the key factors inducing cancer and other diseases [5, 6]. The lack of methylation in the promoter region of the gene causes the gene to be in an abnormal state of activity, produce abnormal proteins, interfere with the composition of normal cells, cause the function and identity of cells to be destroyed on a large scale, and cell variation leads to cancer and the spread of cancer cells. Different tumor cells also have the specific expression of miRNAs, and the change of miRNAs expression profile is involved in the whole process of the occurrence and development of various cancers, including the origin, proliferation, invasion, metastasis and spread of tumor cells [7]. The imbalance of histone modification can affect cell life activities and also lead to the occurrence of many cancers.

Human epidermal growth factor receptor 2 (HER2) is a cell membrane receptor that belongs to the epidermal growth factor receptor (EGFR) family. HER2 plays an important role in a variety of cancers, especially breast cancer. Overexpression

of HER2 leads to cancer cell proliferation, migration and drug resistance. Overexpression or amplification of HER2 is considered to be an important factor in malignant transformation of tumors. HER2-targeted therapy has become a new strategy for the treatment of tumors, and HER2-targeted monoclonal antibodies, tyrosine kinase inhibitors, antibody-drug conjugates, bispecific antibodies and CAR-T-cell immunotherapy have become tumor treatment strategies. Variable variants of ERBB2, resulting in this diversity of HER2 expression, can lead to varying degrees of dependence on HER2 as a driver of carcinogenesis, resulting in different levels of response to treatment and the emergence of drug resistance.

The relationship between HER2 and epigenetic modification is mainly reflected in the expression level of the HER2 gene, while epigenetic modification mainly includes DNA methylation, histone modification and other mechanisms which can affect the expression and function of HER2. These epigenetic mechanisms can alter chromatin structure and gene expression, triggering aberrant HER2 signaling pathways that promote tumor proliferation, invasion, and resistance to targeted therapies. Therefore, in-depth study of the epigenetic modification of HER2 in tumors and the potential regulatory mechanism of HER2 expression will provide a new direction and treatment strategy for tumor-targeted therapy and HER2 drug resistance. This chapter will discuss in depth the influence of different epigenetic modifications on HER2 expression and the malignant progression of tumors.

2. Function of HER2 in tumors

2.1 Function of HER2

The ERBB2 is a proto-oncogene that encodes a 185 kDa transmembrane protein consisting of 1255 amino acids, commonly referred to as the HER2. The HER2 comprises an extracellular ligand-binding domain, a single transmembrane domain, and an intracellular tyrosine kinase domain responsible for signal transduction [8, 9]. Upon forming homodimers or heterodimers with other members of the Her family, HER2 activates key intracellular signaling pathways, including PI3K/AKT and RAS/MAPK, which regulate tumor cell proliferation, migration and invasion (**Figure 1**) [10–12]. Under normal physiological conditions, the HER2 provides cells with signals to regulate growth and division. HER2 plays an important role in biology. The main biological functions of HER2 are as follows: (1) cell proliferation and differentiation: HER2 activates PI3K/AKT and MAPK signaling pathways by forming heterodimers or heterodimers with other HER family proteins to promote cell proliferation and differentiation [10]. (2) Inhibiting apoptosis: Overexpression of HER2 can inhibit apoptosis, thereby helping tumor cells escape the apoptosis mechanism and promoting tumor growth and spread [11, 12]. (3) Enhanced migration and invasion ability: Overexpression of HER2 increases the mobility and invasion rate of tumor cells *in vitro*, making it easier for tumor cells to spread *in vivo* [12]. (4) Angiogenesis: HER2 also participates in the process of angiogenesis, helping tumor cells obtain necessary nutrients and oxygen and promoting tumor growth [9]. (5) Immune escape: In HER2-positive tumors, the interaction between tumor cells and immune cells plays an important role in tumor growth and metastasis, and HER2 can help tumor cells escape the attack of the immune system [13]. Targeting HER2 overexpression has thus become a critical clinical strategy for treating HER2-positive tumors.

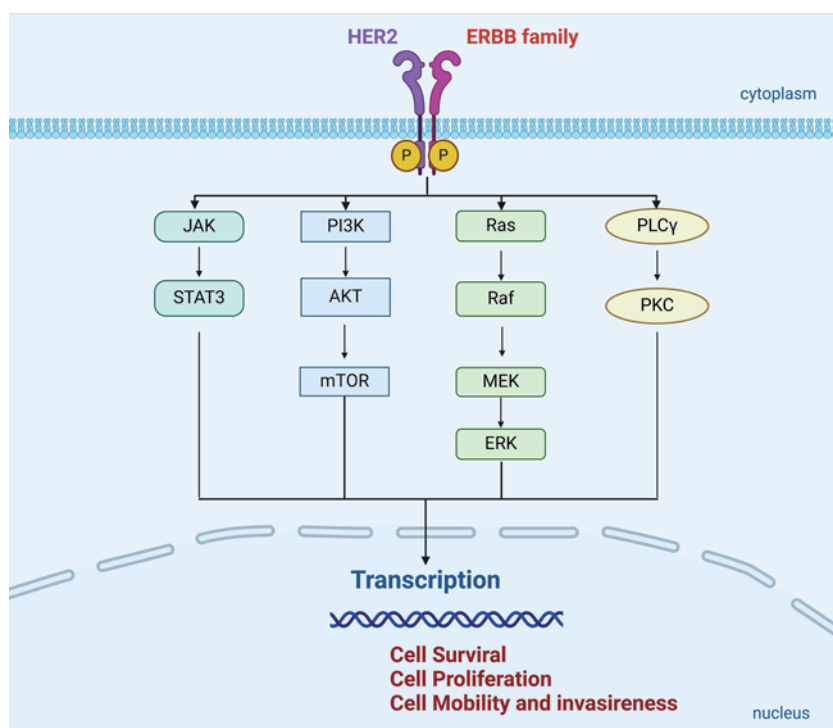


Figure 1.
 HER2 protein domain and downstream signal transduction of HER family.

2.2 HER2 expression in tumors

The mechanisms underlying HER2 protein overexpression primarily include HER2 protein overexpression, ERBB2 gene amplification, and ERBB2 gene mutations, all of which lead to the upregulation of HER2 expression [14]. According to the guidelines provided by the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP), HER2 overexpression is defined by an immunohistochemical (IHC) score of 3+ or an IHC2+ combined with *in situ* hybridization (ISH) [15]. Determination of staining intensity: The whole field of view of the tissue site was observed under a low-power microscope, and it was divided into weak positive, medium positive and strong positive. Weak positive is light yellow (+ or 1), medium positive is brownish yellow (++ or 2), and strong positive is tan (+++ or 3), as previously described by Bollag et al. [16].

HER2-positive breast cancer is a significant molecular subtype of breast cancer, accounting for approximately 15–20% of all breast cancer cases [17]. This subtype is associated with poorer patient response to treatment, increased disease invasion, and worse clinical outcomes [18]. In gastric cancer, HER2 overexpression is found in about 10–20% of all cases, with higher frequencies in specific subtypes: 30% of intestinal-type tumors, 15% of mixed tumors, and around 5% of diffuse-type tumors. Proximal gastric tumors also exhibit a higher frequency of HER2 overexpression, at approximately 30% [19]. In lung cancer, the incidence of HER2 mutations ranges from 1–4%, while HER2 amplification occurs in about 1.4–22% of cases [20]. HER2 amplification can be classified into two categories based on its occurrence: primary amplification

Species	Amplification	Overexpression	Mutation
Salivary gland	12–52%	17–44%	1%
Breast	20%	15–20%	2%
Stomach	11–16%	20%	3%
Ovary	7%	27%	1%
Uterus	4–69%	18–80%	2%
Cervix	0.5–14%	21%	<1%
Lung	2–3%	2.5%	3%
Biliary tract	5–15%	20%	1–3%
Pancreas	2%	26%	2%
Colorectum	5.8%	5%	2%
Bladder	8.6%	12.4%	9%
Prostate	5.8–6%	10%	<1%

Table 1.
HER2 mutation, amplification and overexpression frequency in each cancer species [9].

and acquired amplification in the context of resistance to EGFR-tyrosine kinase inhibitors (TKI), with the latter observed in 10–15% of cases [21]. In non-small cell lung cancer (NSCLC), the frequencies of HER2 mutations, amplification, and overexpression are 1–4%, 2–5%, and 2–30%, respectively [22]. Beyond breast, gastric, and lung cancers, HER2 gene amplification or overexpression has also been observed in several other cancers, including ovarian, prostate, colorectal, and bladder cancers [23–26]. The incidence of HER2 mutations in these tumors is summarized in **Table 1**.

3. HER2 and epigenetic modification in tumors

Epigenetics provides valuable insights into phenomena that cannot be fully explained by HER2 gene amplification alone. Through the study of DNA methylation, histone modifications, and non-coding RNAs, we propose that these mechanisms play a crucial role in regulating HER2 expression. Unlike genetic mutations, epigenetic changes are reversible, offering potential new intervention points for cancer therapy. In this section, we will discuss the roles of DNA methylation, histone modifications, and non-coding RNAs in the regulation of HER2.

3.1 DNA methylation and HER2 expression

DNA methylation involves the addition of methyl groups to DNA molecules, typically at CpG islands, which inhibits gene transcription. For HER2, studies have shown that promoter methylation status is closely correlated with gene expression [27]. In HER2-negative breast cancer tissues, the methylation rate of the HER2 promoter CpG islands is higher. This suggests that hypomethylation of HER2 CpG islands may be one of the mechanisms driving the high expression of HER2 mRNA in tissues adjacent to breast cancer [28]. Furthermore, demethylation of HER2 inhibits protein degradation and promotes the progression of breast cancer, indicating that DNA methylation may regulate HER2 expression by affecting protein stability [29].

The HER2 gene enhancer (HGE) is known to carry enhancer histone modification markers in specific cells, which enhance the transcriptional activity of the HER2 promoter [30]. Studies have demonstrated that DNA methylation in the HGE region is inversely correlated with HER2 expression in breast cancer samples, suggesting that methylation may reduce HER2 expression by suppressing enhancer activity [30]. These findings highlight the critical role of epigenetic mechanisms, particularly DNA methylation, in regulating HER2 transcription and enhancer function.

Clinically, DNA methylation status is emerging as a predictive biomarker for HER2-targeted therapies [31]. Evidence suggests that altering methylation states may restore sensitivity to HER2-targeted drugs, presenting new treatment opportunities for resistant tumors [32]. This has spurred the development of DNA methyltransferase (DNMT) inhibitors, such as azacitidine, designed to modulate methylation status and optimize therapeutic outcomes [33, 34].

3.2 Histone modifications: Mechanisms and influence on HER2

Histone modifications, which involve chemical alterations to histone proteins, play a critical role in influencing chromatin structure and gene expression [35]. Common modifications, including acetylation, methylation, and phosphorylation, respectively regulate chromatin structure by opening or closing it, thereby controlling gene activity [36–38]. Specific histone modification patterns in HER2-positive tumors are believed to impact HER2 gene transcription [39, 40]. For instance, Histone methyltransferase 2 (EZH2) promotes the downregulation of PPP2R2B expression, resulting in sustained phosphorylation of the PP2A targets p70S6K and 4EBP1. This cascade mediates resistance to HER2-targeted therapies. Interestingly, EZH2 inhibitors have been shown to restore PPP2R2B expression, re-sensitizing HER2-positive breast cancer cells to HER2-targeted treatments [41].

Histone deacetylation is often associated with gene silencing [42]. By inhibiting histone deacetylases (HDACs), chromatin de-condensation is promoted, facilitating the activation of HER2 transcription [43]. Furthermore, restoration and maintenance of PHLDA1 levels in cancer cells represent a potential strategy to overcome resistance to receptor tyrosine kinase inhibitors. HDAC inhibitors can restore PHLDA1 expression, thereby re-sensitizing HER2-positive cancer cells to HER2-targeted therapies [44]. This mechanism underscores the therapeutic potential of HDAC inhibitors, with clinical trials currently underway to assess their efficacy in enhancing HER2-targeted treatments [45].

In gastric cancer, HDAC inhibitors modify chromatin structure and gene expression by regulating histone acetylation levels. This alteration enhances the sensitivity of HER2-positive gastric cancer cells to targeted therapies such as trastuzumab, offering a promising approach to improve the therapeutic outcomes for HER2-positive gastric cancer patients [46].

3.3 Phosphorylation of HER2

HER2 is a receptor tyrosine kinase belonging to the EGFR family. It consists of an extracellular domain that does not bind ligands, a transmembrane domain, and an intracellular domain containing an active kinase and a C-terminal tail with multiple tyrosine phosphorylation sites [47]. It has been reported that after dissociation of heat shock protein 90 (HSP90) from ERBB2, SRC-family kinases, such as SRC, FYN, and YES1, can mediate the phosphorylation of ERBB2 at the tyrosine residue Y877 [48].

Phosphorylation at Y877 is not essential for the catalytic activity of ERBB2, but it significantly enhances its kinase activity [49].

Recently, HSP90 inhibitors such as CNT-547 and CNT-58 have been shown to effectively reduce trastuzumab resistance by inhibiting heterodimerization and disrupting the trastuzumab-mediated synergistic survival signaling in HER2-positive breast cancer [50, 51]. Phosphorylation of HER2 enhances signal transduction, leading to increased cell survival and proliferation. However, sustained phosphorylation can disrupt normal negative feedback mechanisms, thereby conferring resistance to treatment.

3.4 Ubiquitination modification of HER2

HER2 stability and trastuzumab sensitivity are also regulated by the ubiquitin-proteasome system (UPS). Cullin5, a ubiquitin ligase for HER2, can be induced by interferon- γ (IFN- γ) to degrade HER2, synergistically enhancing the efficacy of trastuzumab [52]. Additionally, HER2 has been identified as a substrate for the SMAD-specific E3 ubiquitin protein ligase 2 (SMURF2), which binds to its cytoplasmic domains and mediates ubiquitin-dependent degradation of HER2, thereby increasing trastuzumab sensitivity [53]. Two key proteins in the neddylation pathway, NEDD8 and the NEDD8-activating enzyme E1 subunit 1 (NAE1), have been detected in human breast cancer samples and are significantly positively correlated with HER2 expression levels [29]. Neddylation, a novel post-translational modification mechanism, regulates HER2 expression and contributes to the malignant progression of breast cancer [29].

Moreover, emodin azide methylantraone derivatives have been shown to reduce HER2 protein levels, an effect that is independent of mRNA expression, primarily due to its binding with Hsp90, leading to HER2 proteasomal degradation. Interestingly, the proteasome inhibitor MG132 can restore HER2 levels following treatment with emodin azide methylantraone derivatives, providing a promising new strategy for treating HER2-overexpressing tumors [54]. These regulatory mechanisms shed light on the role of HER2 expression, stability, and degradation in tumor progression, underscoring their importance in the development of targeted therapeutic strategies against HER2.

4. Regulatory role of non-coding RNA in HER2

Non-coding RNAs regulate gene expression through complex mechanisms, enabling precise control of cellular processes. They play crucial roles in development, disease progression, and normal physiological functions. Increasing evidence has demonstrated that non-coding RNAs significantly regulate HER2 expression. This paper will further explore the regulatory roles of miRNAs, lncRNAs, and circRNAs in modulating HER2 expression.

4.1 Regulation of HER2 expression by microRNA

MicroRNAs (miRNAs) are non-coding RNAs that regulate gene expression post-transcriptionally. Merja et al. characterized miRNAs that directly target HER2 and identified seven novel miRNAs (miR-552, miR-541, miR-193a-5p, miR-453, miR-134, miR-498, and miR-331-3p) as direct regulators of the HER2 3' UTR [55]. Furthermore, the authors found that miR-342-5p was associated with better survival

in breast cancer patients and specifically inhibited the growth of HER2-positive cells without affecting the growth of HER2-negative controls.

MiR-21, a widely studied miRNA, is frequently upregulated in various cancers [56–58]. It indirectly regulates HER2 and other receptor tyrosine kinase-related signaling pathways, thereby promoting tumor growth and invasion [59, 60]. Specific mechanisms of miR-21 include the inhibition of tumor suppressor genes such as PTEN and PDCD4. Overexpression of miR-21 reduces the sensitivity of gastric cancer cells to trastuzumab, while inhibiting miR-21 expression restores their sensitivity. Furthermore, overexpression of miR-21 can significantly inhibit trastuzumab-induced apoptosis [61]. In HER2-positive breast cancer cells, miR-21 downregulates the tumor suppressor protein PDCD4 (programmed cell death 4), promoting cell invasion and metastasis [62].

MiR-125a/b has been confirmed to directly target the 3' UTR of HER2, reducing mRNA stability and translation efficiency, thereby lowering HER2 protein expression. In HER2-positive breast cancer, miR-125 expression is often downregulated, which is associated with tumor progression and resistance to targeted therapies [63].

An increasing number of miRNAs have been shown to play a crucial role in the occurrence and development of HER2-positive breast cancer by regulating the HER2 signaling pathway [64–66]. This provides new insights and strategies for the diagnosis and treatment of HER2-positive breast cancer.

4.2 LncRNA and HER2

LncRNAs (long non-coding RNAs) are a class of non-coding RNAs longer than 200 nucleotides, which are widely distributed across cells. LncRNAs are less conserved than other RNA types and exhibit spatial and temporal expression specificity. They play diverse roles in cellular processes and can interact with DNA, RNA, or proteins. LncRNAs are essential in regulating gene expression, chromatin modification, and the cell cycle [67–69].

HOTAIR is a commonly studied lncRNA that acts as a sponge for miR-331-3p, thereby regulating HER2 expression. When HOTAIR expression is low, miR-331-3p and AGO2 bind to the 3' UTR of HER2 mRNA, inhibiting its translation. However, when HOTAIR is highly expressed, it competes with miR-331-3p, preventing miR-331-3p from binding to HER2 mRNA, which leads to increased translation of HER2 and subsequently higher expression of HER2 protein [70].

Dong et al. demonstrated that exosome-mediated lncRNA AFAP1-AS1 promotes ERBB2 translation without affecting ERBB2 mRNA expression. This occurs through the binding of AFAP1-AS1 to AUF1, contributing to trastuzumab resistance in breast cancer [71]. This suggests that lncRNA AFAP1-AS1 may directly regulate HER2 expression. Additionally, lncRNAs can regulate HER2 expression by sponging miRNAs. In breast cancer, lncBCLIN25 increases ERBB2 expression by enhancing CpG methylation of the miR-125b promoter, which leads to the downregulation of miR-125b. This reduction in miR-125b expression decreases its binding to the 3' UTR of ERBB2, thereby preventing ERBB2 mRNA degradation [72].

Furthermore, lncTMPO-AS1 has been shown to function as a “competing endogenous RNA” (ceRNA) that regulates ERBB2 expression by sponging miR-204-3p in non-small cell lung cancer (NSCLC) [73].

These studies on lncRNAs and HER2 reveal the complex interactions between lncRNAs and HER2, providing new insights and potential therapeutic targets for treating HER2-positive breast cancer.

4.3 CircRNA and HER2

Circular RNAs (circRNAs) are a unique class of non-coding RNA molecules characterized by a closed, continuous ring structure. These RNAs exhibit greater stability and reduced degradation compared to linear RNAs [74]. CircRNAs are abundant in miRNA binding sites and function as miRNA sponges, relieving the inhibitory effects of miRNAs on their target genes, thereby enhancing the expression of these target genes [75, 76]. This mechanism is referred to as the competitive endogenous RNA (ceRNA) mechanism [77, 78]. By interacting with disease-associated miRNAs, circRNAs play crucial roles in the regulation of various diseases [79–81].

CircERBB2 is upregulated in HER2-positive breast cancer tissues, and its interference has been shown to inhibit proliferation, migration, invasion, and accelerate apoptosis in HER2-positive breast cancer cells. Mechanistically, circ-ERBB2 functions as a ceRNA for miR-136-5p or miR-198, thereby relieving the inhibitory effects of these miRNAs on their target, the transcription factor activator protein 2C (TFAP2C) [82]. In gastric cancer cells, overexpression of circMAP7D1 significantly increases the stability of HER2 mRNA, while knocking down circMAP7D1 results in a marked reduction in HER2 stability [83]. In breast cancer, circ- β -TrCP regulates NRF2-mediated antioxidant pathways in a Keap1-independent manner. The β -TrCP protein isoforms encoded by circ- β -TrCP drive HER2-targeted therapeutic resistance in an NRF2-dependent manner, offering a potential therapeutic target for overcoming trastuzumab resistance [84].

A novel HER2-derived circular RNA, circ-HER2, has been identified and is expressed in approximately 30% of triple-negative breast cancer (TNBC) cells. Circ-HER2 is capable of translating a polypeptide, HER2-103, which promotes the proliferation and invasion of breast cancer cells [85]. Additionally, HER2-103 serves as a potential target for the anti-HER2 drug pertuzumab, providing a promising therapeutic target for patients with triple-negative breast cancer [85].

Overall, the intricate network of non-coding RNAs plays a pivotal role in regulating HER2 expression through both direct and indirect mechanisms. These findings not only illuminate the molecular regulatory mechanisms involved in HER2-positive cancers but also open new avenues for discovering diagnostic markers and therapeutic targets. Further research is required to explore the role of these non-coding RNAs in HER2-related signaling and their effects on drug resistance and cancer progression.

5. Conclusion

In the past few decades, significant progress has been made in the treatment of HER2-positive tumors. However, despite the notable improvements in progression-free survival (PFS) and overall survival (OS) rates achieved by HER2-targeted therapies such as trastuzumab [86], pertuzumab [87], and neratinib [88], acquired resistance to these therapies remains a major challenge [89, 90]. This resistance is not confined to HER2-targeted therapies alone; it is also linked to complex networks of cancer-related genes and molecular pathways [91].

Although the development of anti-HER2-targeted therapies has significantly improved the prognosis of patients with HER2-positive breast cancer, many patients still develop new or acquired resistance to anti-HER2-targeted therapies, leading to cancer recurrence or progression. Structural modification of the binding site of HER2 monoclonal antibody [92]. Activating mutation of HER2/ERBB2 gene [93]; Crosstalk between HER2 and estrogen receptors in breast cancer, thus keeping tumors alive [94].

The increased expression of EGFR and HER3 leads to anti-tumor therapy resistance and other problems [95], which will lead to the problem of drug resistance of clinically targeted HER2 therapy, resulting in the impairment of the life outcome of patients. Exploring the epigenetic modification of HER2 in tumors and elaborating the potential regulatory mode of HER2 protein in tumor tissues has become a new breakthrough in studying the regulation of HER2 in tumor nausea progression and targeting HER2 resistance. In this context, research into HER2 epigenetic modifications offers a potential strategy for developing new therapies to overcome resistance in HER2-positive tumors.

Epigenetics offers a new perspective on phenomena not fully explained by HER2 gene amplification. Through studies on DNA methylation, histone modifications, and non-coding RNAs, scientists have identified these mechanisms as essential in regulating HER2 expression. Unlike genetic mutations, epigenetic changes are reversible, providing novel intervention points for treatment. Abnormal DNA methylation patterns and histone modifications not only drive cancer progression but also contribute to resistance to HER2-targeted therapies. For example, aberrant methylation of specific gene promoter regions can silence tumor suppressor genes, thereby promoting cell proliferation and metastasis [96–98]. In this regard, epigenetic drugs, including histone deacetylase inhibitors (HDAC inhibitors) and DNA methyltransferase inhibitors (DNMT inhibitors), have been explored as potential solutions to combat resistance to HER2-targeted therapies [43, 99]. These drugs modulate the epigenetic state of cancer cells and restore the expression of key tumor suppressor genes, potentially re-sensitizing resistant cells to HER2-targeted therapies; some epigenetic mechanisms regulating HER2 expression are shown in **Table 2**.

The advantage of combination therapy strategies lies in their ability to target multiple levels and pathways in tumor cells. Firstly, epigenetic drugs can modify the tumor microenvironment and immune response, restoring the sensitivity of tumor cells to targeted therapies [104]. Secondly, in synergy with HER2-targeted drugs,

Name	Action mechanism	Related research drugs and genes
DNA Methyltransferase Inhibitors (DNMT inhibitors)	Inhibition of DNA methyltransferase reverses abnormal methylation in the ERBB2 promoter region, thereby regulating the expression of HER2.	Decitabine [99]
Histone deacetylase inhibitors (HDAC inhibitors)	Inhibit histone deacetylase, increase histone acetylation level, promote chromatin relaxation and gene transcription. In HER2- positive cancers, HDAC inhibitors down-regulate the expression of HER2 or enhance the sensitivity of their targeted drugs.	Vorinostat [100]
Histone methyltransferase inhibitors (HMT inhibitors)	HMT inhibitors (such as EZH2 inhibitors) reverse inhibitory histone markers such as H3K27me3 and activate the expression of tumor suppressor genes by inhibiting histone methyltransferase (such as EZH2).	MS1943 [101]
Noncoding RNA	The expression of HER2 is indirectly inhibited by targeting and regulating HER2-related mirnas (such as miR-125a, miR- 205) or lncrnas.	miR-125a/b [63], miR-205 [102], HOTAIR [70], MALAT1 [103], circHER2 [85]

Table 2.
The main mechanism of epigenetic modification regulating HER2 expression [100].

combination therapy can not only enhance efficacy but also delay or overcome resistance by modulating different cancer-related pathways [105]. Additionally, epigenetic drugs may exert multiple effects, such as regulating the cell cycle of tumor cells and promoting programmed cell death (apoptosis), thereby adding synergistic effects to the treatment regimen [106].

Preclinical studies and early-stage clinical trials have shown promising results for the combination of epigenetic drugs and HER2-targeted therapies. For example, some studies have indicated that this combination therapy can effectively inhibit the growth of HER2-positive breast cancer cells and reduce tumor burden in animal models [107]. However, further clinical trials are required to validate these findings and optimize dosage and treatment regimens to maximize therapeutic efficacy and safety.

Based on existing research on genetic modifications of HER2 expression in tumor tissues, it is necessary to continue to focus on the following areas in the future: first, to identify and validate more epigenetic biomarkers related to HER2 expression and function; The second is to develop more specific and efficient epigenetic regulators; Finally, its efficacy and safety are verified through clinical trials, accelerating the translation of laboratory findings into clinical applications.

In summary, the combined application of epigenetic drugs and HER2-targeted therapies presents a promising approach to overcoming resistance in HER2-positive tumors. This multimodal treatment strategy is expected to not only enhance therapeutic efficacy but also improve the survival prognosis and quality of life for patients by reducing drug resistance and offering new opportunities for personalized treatment. Future research should focus on identifying specific epigenetic targets, developing biomarkers for combination therapy, and assessing the safety of these treatments in clinical settings to advance this field further.

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Abbreviations

HER2	human epidermal growth factor receptor 2
CAR-T	chimeric antigen receptor T-cell immunotherapy
ERBB2	erb-b2 receptor tyrosine kinase 2
EGFR	epidermal growth factor receptor
ASCO	American society of clinical oncology
CAP	College of American Pathologists
TKI	tyrosine kinase inhibitors
NSCLC	non-small cell lung cancer

CpG	cytidyl phosphate guanosine
EZH2	histone methyltransferase 2
PPP2R2B	protein phosphatase 2 regulatory subunit B beta
PP2A	protein phosphatase 2A
p70S6K	p70 ribosomal protein s6 kinase
4EBP1	Eukaryotic translation initiation factor 4E-binding protein
HDACs	inhibiting histone deacetylases
PHLDA1	Pleckstrin homology like domain family A member 1
HSP90	heat shock protein 90
SRC	SRC proto-oncogene, non-receptor tyrosine kinase
FYN	FYN proto-oncogene, Src-family tyrosine kinase
YES1	YES proto-oncogene 1, Src-family tyrosine kinase
UPS	ubiquitin-proteasome system
NEDD8	neural precursor cell expressed developmentally downregulated 8
NAE1	enzyme E1 subunit 1
PTEN	phosphatase and tensin homolog deleted on chromosome ten
	PDCC4: programmed cell death 4
AFAP1-AS1	actin filament-associated protein1 antisense RNA1
ceRNA	competing endogenous RNA

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This book explores the crucial role that Human Epidermal Growth Factor Receptor 2 (HER2) plays in the initiation and progression of cancer, as well as cutting-edge molecular mechanisms, precision medicine, and novel targeted treatments, including lapatinib, pertuzumab, and trastuzumab. HER2 overexpression, especially for breast cancer and beyond, in combination with other development therapies, antibody-drug conjugates, and overcomes resistance mechanisms. This book provides comprehensive coverage of the PI3K/AKT and MAPK signaling pathways, up-to-date information on next-generation HER2 inhibitors, including neratinib and tucatinib, and offers helpful advice for researchers and clinicians managing HER2-positive tumors. This book, which links laboratory findings with clinical applications and offers hope for better outcomes in HER2-driven cancers, is an essential resource for oncologists, molecular biologists, and pharmaceutical scientists. It does so clearly and understandably.

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