The function of human epidermal growth factor receptor-3 and its role in tumors (Review)

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Abstract. Human epidermal growth factor receptor-3 (HER-3) is the third member of the HER family. It was previously considered not to contain tyrosine kinase activity and catalytic activity and the intracellular region of HER-3 could not bind ATP and be auto-phosphorylated. Thus, the clinical value of HER-3 was ignored. Currently, biochemical analysis has confirmed that the kinase domain of HER-3 is a specific allosteric activator; it acts as a functional activator to activate the recipient kinase (HER-1, HER-2, HER-4). With the in-depth knowledge of its structure and function, studies on the relationship of HER-3 and human tumors are rapidly increasing. HER-3 is closely related to tumorigenesis, progression and metastasis. HER-3 is involved in resistance to targeted therapy, and may serve as a new therapeutic target. The expression of HER-3 helps to predict prognosis and treatment efficacy. HER-3 has become a focus of concern in the HER family and has gained significant attention in the search for cancer treatment.

Contents

1. Introduction
2. In-depth understanding of the structure and function of HER-3
3. The close relationship between HER-3 and human tumor
4. Conclusion

1. Introduction

The human epidermal growth factor receptor (HER or ErbB) belongs to the tyrosine kinase receptor superfamily. It includes 4 highly homologous members, HER-1 (ErbB1), HER-2 (ErbB2), HER-3 (ErbB3) and HER-4 (ErbB4). The distinguishing characteristics of the HER family are interdependent and functional complementation between members. After the ligands bind to the receptor, it promotes the formation of HER/ErbB receptor homodimer or heterodimer which leads to activation of the tyrosine kinase domain (1,2) and downstream signaling pathways (3,4). Signal transduction networks control cellular activities such as gene expression, mitosis, cell differentiation, cell proliferation, cell survival and apoptosis (1,5).

HER-3 is a distinctive member of the HER family as its kinase domain lacks certain residues that are known to be essential for catalytic activity in other kinases. The function of HER-3 was previously thought to be entirely dependent on other members of the family, the role of HER-3 was considered to be passive and the clinical value of HER-3 was greatly underestimated. Currently, biochemical analysis has confirmed that the kinase domain of HER-3 is a specific allosteric activator, it acts as a functional activator to activate the recipient kinase. Accompanied by an in-depth understanding of the structure and function of HER-3, recent studies have also found HER-3 is involved in the tumorigenesis, progression, new target exploration, target therapy resistance of several types of cancer. In the critical search of a cure for cancer, HER-3 provides insight into the better understanding of tumors and targeted therapy.

2. In-depth understanding of the structure and function of HER-3

HER-3 was initially isolated by MH Kraus in 1989. The gene of HER-3 is located on chromosome 12q13, and its 6.2 kb transcript is expressed in normal epithelial tissues (6). Subsequently, HER-3 cDNA was isolated from human tumor cell lines (7). HER-3 possesses 40-50% sequence homology with HER-1 and 40-45% homology with HER-2 (7-9). The structure of HER-3 is typical in receptor tyrosine kinase family (Fig. 1). It includes an extracellular domain (ECD) with 612 amino acid residues, a transmembrane helix domain with 32 hydrophobic amino acids, and an intracellular tyrosine kinase domain (TKD) with 677 amino acids (7). Determination of the 2.6-angstrom crystal structure of the entire extracellular region of HER-3 revealed 4 type I insulin-like growth factor receptor homologous domains, 2 specific ligand binding flanking regions (district I and III) and 2 cysteine-rich regions (district II and IV). The interaction between district II

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and IV limits the relative direction of ligand binding domain and provides a structural basis for understanding the varied affinity and conformational changes of HER-3 upon ligand binding (10). The transmembrane region confers receptor internalization and ligand-dependent calcium influx (11). ErbB binding protein 1 (EBP-1) interacts with HER-3 and prevents the premature formation of dimers, which prevents inappropriate activation of molecular partners by HER-3 (12). The intracellular domain is a continuation of the transmembrane region and has a conserved ATP binding site (Gly-Xaa-Gly-Xaa-Gly-Xaa-Lys) that shares homology with other members of the tyrosine kinase family. The intracellular region is divided into a juxtamembrane region, a kinase domain and C-terminal tail. The juxtamembrane region is divided into N-terminal [juxtamembrane-A, (JM-A)] and C-terminal [juxtamembrane-B, (JM-B)] (13). The kinase domain includes N-lobe, helix αC, activation loop and C-lobe (13). The analysis of HER-3 dimers crystal structure shows that recipient protein kinase (HER-1, HER-2 and HER-4) interacts with the JM-A region of HER-3 via a conserved amino acid sequence, and the JM-B region of recipient protein kinase interacts with C-lobe of HER-3 by forming a stabilizing latch (14). C-lobe of HER-3 can combine and activate other members of the HER family, which is consistent with the role of HER-3 as a functional activator but not a recipient kinase. Helix αC of the kinase domain anchors activator kinase domain to recipient kinase domain (13). In general, HER-3 is very similar to inactive HER-1/HER-4. Conformational changes in helix αC sequence are highly important and may explain the difference in function of HER-3 compared with other members of the family. For example, Leu736 in helix αC of HER-1 is replaced by Thr738 in HER-3, and this change stabilizes the inactivation state of HER-3. Ile735 in hydrophobic core of HER-1 is replaced by Val737 in HER-3, and this change weakens the ability of HER-3 to form hydrophobic subunits. The structure of HER-3 is similar to that of an integrase kinase, but locked in an inactive conformation similar to that of Src/CDK. When the HER-3 sequence is activated, helix αC turns to the active site, the activation ring center is opened and bound the substrate peptide. There are 14 tyrosine residues in HER-3 C-terminal signal tail, including six PI3K binding sites that have been confirmed through phosphorylation, which mediate interactions between three regulatory subunits of PI3K and lead to activation of downstream AKT signaling pathways (15).

At present, our understanding of the function of HER-3 is very limited. In the 1990s, the kinase activity of HER-3 was not detected by recombinant protein technique. Therefore, researchers believed that the kinase domain of HER-3 may be non-functional (16,17). HER-3 kinase domain lacks several key residues required for catalytic activity, such as Asp813 which is present in HER-1; thus HER-3 was thought not to contain tyrosine kinase activity and catalytic activity. The intracellular region of HER-3 does not bind ATP and is not auto-phosphorylated (18,19). HER-3 was considered to be functional merely as a signaling substrate for other HER members, similar to the function of insulin receptors, IRS1 and IRS2. However, Korner and Taylor's (20) study in 2009 demonstrated that HER-3 was not completely inactive; its activity was very low and was not comparable to that of HER-1, but the kinase activity of HER-3 was sufficient to mediate auto-phosphorylation of its intracellular region. Shi et al (21), using molecular mechanics simulation in 2010, revealed that the phosphorylation catalyzed by HER-3 was mediated via the 'inactive-like' structure rather than the conserved catalytic subunit, suggesting that the cytoplasmic region of HER-3 within the receptor dimers was capable of binding ATP and promoting auto-phosphorylation. Jura et al (13) confirmed, using biochemical analysis in 2009, that the kinase domain of HER-3 was a specific allosteric activator to activate the recipient protein kinase. Although these studies challenged the traditional understanding of HER-3 function, the exact mechanism is not fully understood and further studies should be carried out. The function of HER-3 should be re-inspected, the role of HER-3 in cell signaling transduction and human cancer is becoming increasingly important. Findings with regard to the function of HER-3 may provide insight into the pathogenesis and therapy of human cancer.

Following ligand binding, HER-3 forms a receptor dimer via a unique mechanism by which monomeric inactive state changes to active state upon homo- or heterodimerization and the tyrosine kinase and its downstream signaling pathways are activated (22). HER-3 interacts with other members of the HER family. First, HER-3 interacts with HER-1 directly. EGF can activate the tyrosine kinase of HER-1, and can also cross-activate HER-3 at the same time (22). Tyrosine kinase inhibitor (TKI) blocks downstream signaling pathways by inhibiting the interaction of HER-1 and HER-3 (23). Second, HER-3 interacts with HER-2 directly. Heregulin (HRG) ligand binding causes prolonged activation of HER-3, but this process is strongly dependent on HER-2 expression. In the HER family, HER-3 mainly interacts with HER-2. Since HER-2 lacks ligand-binding activity and HER-3 lacks catalytic kinase activity, both the receptors are functionally interdependent. The relationship between HER-2 and HER-3 has been described as 'deaf' and 'dumb' (18,24,25). The cooperation between HER-2 and HER-3 is unique, but the underlying molecular mechanism is poorly understood. Third, HER-3 and HER-4 can form heterodimer, but few studies have explored the relationship between them (26).

There are two relevant downstream signaling pathways of HER-3 (Fig. 2). The first one is the phosphatidylinositol 3-kinase (PI3K)/3-phosphoinositide-dependent protein kinase (PDK) l/protein kinase B (AKT) pathway. Activation of PI3K is induced by the formation of dimer between HER-3 and HER-1/2. PI3K is a dimeric protein kinase composed of P110 catalytic subunit and P85 regulatory subunit (27). The P85 subunit binds to HER-specific anchor sites via its SH2 domain, and the P110 subunit catalyzes the phosphorylation of phosphatidylinositol 4,5-bisphosphate (PIP2) to 3,4,5-triphosphate phosphatidylinositol (PIP3). The level of PIP3 is regulated by phosphatase and tensin homologue deleted on chromosome 10 (PTEN) (28). PI3K accumulates PDK1/AKT in the cell membrane and activates it via phosphorylation, thus stimulating downstream signaling. The PI3K pathway regulates cell growth, cell apoptosis, tumor cell invasion, as well as metastasis and chemotherapy resistance. The second pathway is the Ras/Raf/MEK/mitogen-activated protein kinase (MAPK) pathway. Activation of HER-3 and subsequent phosphorylation of tyrosine kinase induce Grb2-SOS complex binding to phosphorylation anchor sites. Then, the three-dimensional
structure of SOS is altered which enables the formation of Ras-GTP from aggregated Ras-GDP (29,30), leading to the activation of Raf, MEK and MAPK (31,32). Activated MAPK transduces extracellular stimuli into the cell to regulate transcription factors in the nucleus and induces cell migration and proliferation (33).

3. The close relationship between HER-3 and human tumor

The studies on HER-1 and HER-2 in tumor targeted therapy and efficacy prediction have developed. For example, small molecule HER-1 TKI, gefitinib, has been used in the first-line treatment of advanced non-small cell lung cancer (NSCLC) with HER-1 mutation (34). Anti-HER-1 monoclonal antibody, cetuximab, has been used in targeted therapy for head and neck squamous cell carcinoma, colorectal cancer and advanced NSCLC (35-37). Anti-HER-2 monoclonal antibody, trastuzumab, has been used in targeted therapy for HER-2 positive advanced breast cancer and gastric cancer (38,39). In view of the significant contribution of HER-1 and HER-2, researchers began looking into the role of HER-3. With the new understanding of the structure and function of HER-3, studies on the
relationship of HER-3 with tumorigenesis, progression, new target exploration, target therapy resistance, prognosis and efficacy prediction are increasing. Some studies have confirmed that HER-3 plays an important role in the occurrence and progression of lung cancer, breast cancer, colorectal cancer as well as other types of cancer (26,40-42). The HER-3/Pi3K/AKT signal pathway plays a key role in the target therapy resistance of NSCLC, breast cancer, head and neck squamous cell carcinoma, prostate cancer and hepatocellular carcinoma and other types of cancer (43-48). Inhibition of HER-3 and HER-1/HER-2 is very important for tumor treatment (49,50) and it may be a new therapeutic target. HER-3 is also beneficial in predicting the prognosis and treatment efficacy. In the search for tumor treatment, HER-3 has become a focus of concern in the HER family. The following describes the role of HER-3 in different tumors.

Overexpression of HER-3 in NSCLC cell lines accelerated growth and metastasis of tumor cells, and promoted tumorigenicity of allografts in a kinase-dependent manner. By contrast, downregulation of HER-3 inhibited proliferation and migration of tumor cells, tumor growth and metastasis in vivo. HER-3 silencing inhibited tumor cell growth by reducing DNA synthesis and caspase-8-mediated apoptosis, and tumor cell migration by increasing accumulation of focal adhesion components (40). Lung adenocarcinoma cells were markedly suppressed in culture by siRNAs to the receptor HER-3 or its downstream signaling partner AKT2 (51). The above studies suggest that HER-3 and its downstream signaling pathway play a crucial role in occurrence and metastasis of lung cancer. HER-1 TKI such as gefitinib/erlotinib is very effective treatment for NSCLC with HER-1 mutation, but the emergence of drug resistance is difficult to overcome. The sensitivity of HER-1 TKI is associated with inhibition of the HER-3/Pi3K/AKT signaling pathway, i.e., this pathway will lead to TKI resistance if not effectively inhibited (43). Gefitinib temporarily inhibits HER-3/Pi3K/AKT signaling, but in the process of subsequent sustained inhibition of HER-1 and HER-2, recovery of HER-3 activity and reactivation of the Pi3K/AKT pathway will lead to drug resistance. Downregulation of HER-3 led to reduction of AKT phosphorylation level and growth inhibition in an NSCLC mutant cell line that was sensitive to gefitinib. However, downregulation of HER-3 did not alter the activity of AKT in resistant tumor cell lines, suggesting that the separation of HER-3 from downstream AKT signaling pathway was one of the important aspects of the drug resistance (52). HER-3 and Pi3K/AKT pathways may enable tumor cells to escape TKI inhibition through a compensatory offset of the equilibrium between HER-3 phosphorylation and dephosphorylation (43). Amplification of MET proto-oncogene promoted HER-3-dependent Pi3K activation and led to drug resistance in gefitinib-sensitive lung cancer cell lines, inhibition of MET proto-oncogene restored the sensitivity to gefitinib (48). In addition to HER-1 mutation, a second mutation, T790M, is also associated with acquired drug resistance. Introduction of exogenous HER-1 with T790M mutation effectively blocked gefitinib activity and maintained HER-3/Pi3K/AKT signal activation in lung cancer cells (53). In addition, oncogenic mutation of PI3KCA, p110αE545K, activated Pi3K signaling and eliminated gefitinib-induced apoptosis (54). These studies demonstrated that HER-3 and/or Pi3K/AKT signal may be intermediate links of acquired gefitinib resistance. While irreversible tyrosine kinase agents inhibited HER-1 in resistant cells, they re-inhibited HER-3 and Pi3K signaling at the same time, which further highlighted the central role of HER-3 in adjusting drug sensitivity or resistance (55). miR-22 in lung cancer cell lines played a good antitumor effect through inhibition of HER-3 transcriptional regulation (56). Thus, HER-3 is a potential therapeutic target and simultaneous inhibition of HER-3 and HER-1 will bring considerable benefit to the clinic. Due to the complexity of signaling networks, whether the HER-3/Pi3K/AKT pathway alone can induce TKI resistance in NSCLC merits further study. The positive expression rates of HER-3 in NSCLC are 18-67%. Study results on the response to TKI, survival and prognosis of patients with HER-3 high expression are inconsistent. A study including 192 surgically removed NSCLC cases showed the expression of HER-3 mRNA was higher in patients with highly-differentiated, adenocarcinoma, mutant HER-1 than in patients with poorly-differentiated, non-adenocarcinoma, wild-type HER-1, and the expression was higher in females than in males (57). Large sample studies and more uniform and accurate research methods are required to further clarify whether high HER-3 expression is an indicator of TKI benefit.

The role of the HER family in tumorigenesis is most aptly understood in breast cancer subtypes with HER-2 gene amplification. HER-3 is required for HER-2-induced preneoplastic changes to breast tumor formation (58). HER-2 must dimerize with HER-3 to promote breast cancer cell proliferation; deletion of HER-3 in HER-2 positive breast cancer cell lines produces strong anti-proliferative effects (59). HER-2/HER-3 heterodimer is the most powerful carcinogenic unit, the phosphorylation state of HER-3 is critical for HER-2 positive breast cancer cell motility and metastasis (41). A significant increase of HER-3 phosphorylation in HER-2 positive breast cancer was accompanied by activation of downstream signaling pathways, and knockdown of HER-3 was always accompanied by tumor shrinkage in vitro (60). Dephosphorylation of HER-3 and decoupling with Pi3K lead to downregulation of AKT signaling and it is directly related to the anti-proliferative effect of trastuzumab. HER-3-specific affibody molecules (Z05416, Z05417) blocked cancer cell growth by inhibiting HRG-induced HER-3 phosphorylation in the MCF-7 and SKBR-3 breast cancer cell lines (61). The above studies clarify that the phosphorylation state of HER-3 and downstream signaling play a central role in the occurrence of HER-2 positive breast cancer, and HER-3 may be a drug target. Since the process of TKI inhibiting HER-2/HER-3 transphosphorylation and Pi3K/AKT signaling pathway activation in HER-2 positive breast cancer are transient, the antitumor efficacy of TKI is weakened (43). The kinase function of HER-2 is essential during tumorigenesis (62), therefore, inhibition of the catalytic kinase activity is a key mechanism for anticancer drugs. The buffering effect of incomplete inhibition of HER-2 kinase activity by HER-3 may be a highly important mechanism by which HER-2 positive breast cancer cells escape TKI treatment (43,63). miR-205 downregulates HER-3 and recovers the sensitivity to TKI in human breast cancer cells (64). pHER-3 upregulation in a fulvestrant resistant cell line was mostly accompanied by an
increase of pAKT activity. However, highly specific inhibition by HER-3 antibody (A5) significantly downregulated pHER-3 without affecting downstream ERK/AKT phosphorylation, suggesting that the resistant cells may produce endogenous ligand that reactivated pHER-3. Exogenous ligands binding to HER-3 affect AKT downstream signals, but the underlying mechanism remains unclear (47). Bispecific antibody (MM-111) formed trimer with HER-2/HER-3, which effectively inhibited proliferation of HER-3 and HER-2 positive tumor cells (50). A new selective PI3K inhibitor (GDC-0941) combined with trastuzumab and pertuzumab inhibited the growth of tumor cells, and led to morphological changes of gland cells and inhibition of the HER-3/PI3K/AKT signal pathway (65). GDC-0941 is also effective for the treatment of trastuzumab-resistant tumor cells (66). XL147, which is also a PI3K inhibitor, inhibits tumor cell growth in a dose-dependent manner. In HER-2 positive breast cancer cells, knockdown of HER-3 by siRNA enhanced the effect of XL147 (67). Thus, multi-target treatment provides an increase of clinical benefit for patients with breast cancer, inhibition of HER-2, HER-3 and PI3K simultaneously may be the future treatment direction of HER-2 positive breast cancer. The positive expression rates of HER-3 in breast cancer are 18–75%. The expression of HER-3 was positively correlated with high organizational classification and lymphatic vessel invasion, suggesting it was significantly associated with tumor progression and metastasis, and may serve as a useful prognostic biomarker (68). Tissue microarray analysis demonstrated that normal expression of HER-1/HER-2 and overexpression of HER-3 in invasive breast cancer indicated poor prognosis (69,77). Multivariate analysis showed that HER-2 and HER-3 were independent prognostic markers, while clustering analysis showed that coexpression of HER-1 and HER-3 suggested poor prognosis, with a 10-year survival rate of 42% (70). However, in HER-2 negative/low expression cases or HER-2 positive breast cancer patients treated with trastuzumab, there was no correlation between the expression of HRG, HER-3 and survival or known clinical prognostic factors (71,72).

There is almost no HER-3 expression in normal colon tissue, but the positive expression rates of HER-3 in colorectal cancer tissue are 50–89%. Knockdown of HER-3 by siRNA in colon cancer cell lines was accompanied by absence of HER-4 expression and elevation of tumor cell apoptosis; HER-3/HER-4 heterodimer may be one of the precipitating factors of colon cancer (26). HRG expression was detected in colon metastatic liver cancer cells, knockdown of integrin αv and HER-3 by siRNA significantly inhibited HRG-induced tumor cell migration as well as liver metastasis in vivo, marked phosphorylation of AKT was found in the process, cell migration was suppressed by specific inhibitors of PI3K. The study indicated that HRG/HER-3/PI3K/AKT may participate in colon cancer liver metastasis (73). The median progression-free survival time and the median overall survival time of the patients with wild-type K-RAS advanced colorectal cancer receiving cetuximab combining irinotecan treatment in the HER-3 negative group were significantly higher than in the HER-3 positive group, suggesting that HER-3 may be a predictor of cetuximab efficacy in patients with wild-type K-RAS advanced colorectal cancer (74). Comprehensive analysis of HER-3 and K-RAS may aid in identifying the most appropriate colorectal cancer patients for cetuximab treatment and may provide an effective treatment strategy. Studies on HER-3 and other digestive system tumors are limited. The positive expression rate of HER-3 in gastric cancer is 13.7%, and it correlates with late stage and poor prognosis (75). DARPP-32 promotes resistance of gastric cancer cells to gefitinib by stimulating interaction between HER-1 and HER-3 and activating PI3K/AKT signaling (76). The results of the ToGA trial are encouraging; it is expected that routine detection of HER-2 will be included in the diagnosis of advanced gastric cancer (39,77). The trial investigates whether HER-3 will be of value for guiding the treatment of gastric cancer. HER-1/2 expression is absent in normal pancreatic tissue, but HER-3/4 are expressed (78). The positive expression rates of HER-3 in pancreatic cancer tissues are 27–47%. Generally, HER-3 positive was prone to cause targeted therapy drug resistance, but HER-3 increases the sensitivity of pancreatic cancer cells to erlotinib. Knockdown of HER-3 in ER-3 sensitive pancreatic cancer cell lines resulted in AKT level reduction and pancreatic cancer cell proliferation, suggesting that HER-3 may be a sensitive biomarker for erlotinib in pancreatic cancer (79). The median survival time in HER-3 overexpression patients with resectable pancreatic cancer was 37.2 months, but in HER-3-negative patients it was 58.6 months, therefore, HER-3 overexpression may be an independent indicator of poor prognosis for patients with curatively resected pancreatic cancer (80). A study found HER-3 (isomers) was more accurate than AFP in identifying early liver cancer from chronic hepatitis; the plasma high-level was closely related to portal venous invasion and extrahepatic metastasis (81). HER-3 restricted cell response to sorafenib or IGFIR inhibitor in hepatocellular carcinoma cells (46,82).

HER-3 is activated in multiple ovarian cancer cell lines. Activation of NRG1/HER-3 autocrine loop pathway promotes the proliferation of human ovarian cancer cells. In the mouse xenograft model, deletion of HER-3 inhibited proliferation of OVCAR8 cells and slowed down tumor progression, suggesting that HER-3 and/or NRG1 play a key role in the pathogenesis of ovarian cancer and are potential therapeutic targets for advanced ovarian cancer (83). The positive expression rates of HER-3 in ovarian cancer are 3–53%, and some studies reported that HER-3 expression was negatively correlated to overall survival (84,85). Regardless of whether the corresponding ligand NRG existed or not, HER-3 promoted prostate cancer cells mobile in vitro and tumor formation in vivo (86). HER-2/HER-3 heterodimer promoted aberrant activation of androgen and led to the formation of hormone-resistant prostate cancer (45). Further studies are required to elucidate the role of HER-3 and other HER members in reductive system tumors.

High expression of HER-3 and absence of HER-2 expression in melanoma indicated that HER-3 may be an allosteric activator of HER-1 or HER-4. Disorders of NRG1/HER-3 and HRG/HER-3 signaling are correlated with development and metastasis of melanoma (87,88). Anti-human HER-3 monoclonal antibody promoted HER-3 receptor internalization and degradation, and inhibited growth and migration of human melanoma cells (89). The pan-HER receptor TK1 (canertinitib) inhibits HER-1, HER-2 and HER-3 receptor phosphorylation and promotes apoptosis of malignant melanoma in vitro; it also displays antitumor activity in vivo (90).
4. Conclusion

With protein crystallization, molecular biology has begun to reveal the structure of HER-3. At the same time, the kinase domain of HER-3 acting as a functional activator to activate the recipient kinase was confirmed. Insights into the activation mechanism of the HER family were also gradually elucidated. In the critical search of a cure for cancer, HER-3, as a member recognized step by step in the HER family, seems to provide some insight into tumor therapy. Although people have known about HER-3 for several years, the value of HER-3 was formerly ignored. Currently, research results demonstrate that HER-3 is closely related to tumorigenesis, progression and metastasis, which helps to clarify the mechanisms of tumor biological behavior. HER-3 is involved in targeted therapy resistance and may be a new therapeutic target. A further in-depth understanding of HER-3 will play a fueling role in HER-3 associated targeted therapies. Analyzing the relationship between the expression of HER-3 and the effects of targeted therapy may help to identify the most appropriate patient sub-groups for HER-3 targeted treatment. In the search for a breakthrough in cancer treatment, HER-3 has become an emerging protagonist in the HER family.

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