

Application of HER2-targeted Therapy in Tumors

Ruihua Song

*Clinical Pathology, Kyungwoon National University, Daegu, South Korea
songruihua577@gmail.com*

Abstract. Human epidermal growth factor receptor 2 (HER2) is a significant component of the epidermal growth factor receptor family. Its overexpression, gene amplification, or activating mutations play a crucial role in the occurrence and progression of various malignant tumors and often indicate poor prognosis. HER2 has become a key target for precision oncology due to the development of molecular targeted therapy. Numerous clinical studies have shown that tyrosine kinase inhibitors, monoclonal antibodies and antibody-drug conjugates targeting HER2 can significantly improve patient prognosis and prolong overall survival in tumors, including gastric cancer and breast cancer. However, challenges remain in treatment, such as drug resistance and individual variability in efficacy. This article systematically reviews the biological role of HER2 in tumors and the latest research progress in its targeted therapy, and explores its application prospects in precision medicine, aiming to provide a theoretical basis for optimizing clinical treatment strategies.

Keywords: HER2, targeted therapy, tumor, molecular mechanism, drug resistance

1. Introduction

With the advancement of precision medicine and molecular biology, tumor research has gradually shifted from traditional morphological analysis to molecular mechanism research. Human epidermal growth factor receptor 2 (HER2), a critical member of the epidermal growth factor receptor (EGFR) family, belongs to the transmembrane glycoprotein receptor with tyrosine kinase activity. Through the activation of several signaling pathways, including PI3K/AKT and MAPK, HER2 can take part in biological processes such as cell proliferation, differentiation, migration, and apoptosis [1, 2]. When HER2 undergoes gene amplification, protein overexpression or activating mutation, it can lead to abnormal cell proliferation and malignant transformation, thereby promoting the occurrence and development of tumors [2]. Therefore, HER2 has become an important target in tumor molecular biology research and precision treatment. Studies have shown that HER2 abnormalities are widely present in a variety of solid tumors and are closely related to increased tumor invasiveness, increased risk of metastasis and poor patient prognosis [2, 3]. In breast cancer, HER2 overexpression accounts for about 15% to 20%, which usually indicates a high degree of malignancy and recurrence risk [3]. HER2 abnormality is also closely related to tumor progression in gastric cancer and gastroesophageal junction cancer. Besides, HER2 abnormality has been found in various tumors like colorectal cancer, non-small cell lung cancer, biliary tract cancer and bladder cancer, and its tumorigenic role has gradually attracted attention. The occurrence of HER2 abnormality varies in

different tumors, including gene amplification, protein overexpression and somatic mutation, etc. These differences not only affect the biological behavior of tumors, but are also closely related to clinical treatment response. Currently, abnormal activation and drug resistance mechanisms of HER2-related signaling pathways have emerged as a critical research direction in precision oncology.

Based on this, this article reviews the research progress, drug resistance mechanisms and clinical application prospects of HER2-targeted therapy. It focuses on the biological characteristics and molecular mechanism of HER2 in tumors, providing theoretical reference for the precision treatment of HER2-related tumors.

2. Structure and biological function of HER2

HER2, a transmembrane receptor tyrosine kinase, is crucial in signal transmission and cell proliferation. HER2 is mainly composed of a transmembrane domain, an extracellular domain and an intracellular tyrosine kinase domain. The extracellular domain is involved in receptor recognition and dimerization, while the intracellular kinase domain is responsible for signal transduction [1]. Although HER2 lacks a specific ligand, it has a strong dimerization ability, especially with HER1 and HER3 to form heterodimers, thereby activating classical signaling pathways, including PI3K/Akt/mTOR and MAPK, and participating in the regulation of biological processes, which is of great significance for maintaining normal tissue homeostasis [1, 2]. Under normal conditions, HER2 signaling is strictly regulated; however, when the ERBB2 gene is amplified, HER2 protein is overexpressed, or activating mutations occur, HER2 signaling can be continuously and abnormally activated, thereby enhancing cell proliferation, invasion, and metastasis, and promoting tumor development. Research has found that HER2 abnormalities are widely present in various solid tumors; they are also associated with treatment resistance, tumor invasiveness and poor prognosis [2, 3]. Therefore, HER2 is a vital driving factor for various tumors and a key biomarker in clinical subtyping, prognostic assessment, and precision treatment.

3. Clinical significance of HER2 and advances in targeted therapy

3.1. Clinical progress of HER2 in breast cancer

In breast cancer, approximately 15%–20% of patients have HER2 overexpression or ERBB2 gene amplification. This subtype typically exhibits greater invasiveness, a poorer prognosis and a higher risk of recurrence [3]. HER2 abnormalities can facilitate tumor cell proliferation, invasion, survival and metastasis by continuously triggering classic signaling pathways like PI3K/Akt/mTOR and MAPK [2]. In addition to HER2 amplification, some HER2 activating mutations can also drive continuous HER2 signal activation, potentially promoting tumor progression and distant metastasis even if HER2 is negative in immunohistochemical tests. Studies have shown that about 20% of all cases of breast cancer are HER2-positive and has a high degree of malignancy. However, patient prognosis has significantly promoted as HER2-targeted therapy develops [4]. Currently, the clinical treatment of HER2-positive breast cancer has formed a comprehensive treatment model centered on HER2-targeted therapy. Commonly used drugs include tyrosine kinase inhibitor neratinib, monoclonal antibodies trastuzumab and pertuzumab, etc. Trastuzumab mainly exerts its anti-tumor effect by preventing downstream signaling pathways, inhibiting HER2 receptor dimerization and mediating antibody-dependent cytotoxicity (ADCC) [5]. Pertuzumab can further inhibit the formation of HER2/HER3 heterodimers, thereby enhancing the HER2 blocking effect [6]. Novel

antibody-drug conjugates represented by T-DXd have shown strong anti-tumor action in both HER2-positive and HER2-low-expressing breast cancer. They deliver highly effective cytotoxic drugs through HER2 targeting and have a "bystander effect," which can further improve the treatment effect. Related studies have shown that T-DXd is substantially more effective than T-DM1 in treating advanced HER2-positive breast cancer. It is gradually becoming an important treatment option for HER2-positive advanced breast cancer [7]. Although HER2-targeted therapy has significantly improved the survival outcome of patients with HER2-positive breast cancer, primary and acquired resistance remains the main challenge in current treatment. Studies have found that alterations in HER2 structure, abnormal activation of the PI3K signaling route, loss of HER2 expression, activation of bypass signals, and changes in the tumor microenvironment can all lead to drug resistance [4]. In addition, the HER2 mutation spectrum is complex, and different mutation types have different drug sensitivities, which further increases the difficulty of individualized treatment. Therefore, in-depth research on HER2 drug resistance mechanisms and the development of novel multi-target or bispecific HER2-targeting drugs have become an important research direction for the precision treatment.

3.2. Clinical progress of HER2 in gastric cancer (gastrointestinal tract)

About 20% of gastric cancer cases have HER2 abnormalities; intestinal type gastric cancer is more common than diffuse type, and gastroesophageal junction cancer has a higher HER2 positive rate than regular gastric cancer. HER2 positive gastric cancer has strong biological heterogeneity, and its HER2 expression pattern is different from that of breast cancer, often showing incomplete basolateral membrane staining. The ToGA study conducted a phase III clinical trial of trastuzumab integrated with chemotherapy for HER2 positive advanced gastroesophageal junction cancer and gastric cancer. The results showed that the median overall survival of patients increased from 11.1 months to 13.8 months. Trastuzumab plus chemotherapy is now the first-line standard treatment for HER2-positive gastric cancer due to the notable improvements in progression-free survival and objective response rate [8]. Trastuzumab primarily works against tumors by inducing ADCC, blocking downstream signaling pathways like PI3K/AKT, and preventing HER2 receptor dimerization. However, the efficacy of some HER2-targeting drugs such as lapatinib and T-DM1 in gastric cancer is limited, suggesting that gastric cancer has high HER2 heterogeneity and is prone to acquired resistance. For patients with gastric cancer who are HER2 IHC 3+ or IHC 2+ and ISH/FISH positive, trastuzumab with chemotherapy is currently the primary treatment recommendation.

Biliary tract cancer includes various types such as gallbladder cancer, bile duct cancer and ampullary cancer, and is a highly heterogeneous malignant tumor. Studies have shown that about 5% to 15% of biliary tract cancer patients have ERBB2 gene amplification, with gallbladder cancer having a relatively higher HER2 positivity rate. Preclinical studies have found that HER2-targeted drugs such as T-DM1, trastuzumab, pertuzumab can inhibit the growth of HER2-positive biliary tract cancer cells. In patients with HER2-positive advanced biliary tract cancer, the MyPathway study also reveals that some patients achieved sustained disease control, suggesting that HER2-targeted therapy has potential application value in biliary tract cancer [8]. Studies have confirmed that dual HER2 blockade can inhibit tumor progression by inhibiting HER2/HER3 dimerization and blocking downstream signal transduction. Although HER2-targeted therapy is a crucial area of research for the precise treatment of HER2-abnormal biliary tract cancer, it is still not a conventional treatment.

The incidence of HER2 overexpression and ERBB2 gene amplification in colorectal cancer is about 5%, and some patients also have HER2 activating mutations. HER2 abnormalities can not only promote the proliferation of colorectal cancer cells, but are also closely related to resistance to EGFR-targeted therapy. Studies have found that HER2 mutations can continuously activate signaling pathways such as MAPK, declining the sensitivity of tumor cells to EGFR inhibitors such as cetuximab, thereby affecting the prognosis of patients. The HERACLES study's findings demonstrated that HER2 is a crucial therapeutic target for colorectal cancer, with an objective response rate of 30%, a disease control rate of 74%, and a median progression-free survival of 5.2 months [9]. The study holds that trastuzumab combined with lapatinib mainly reduces the continuous proliferation of tumor cells and reverses EGFR-targeted therapy resistance by inhibiting the HER2-mediated PI3K/AKT and MAPK signaling pathways. Currently, HER2-targeted therapy is mainly suitable for patients with HER2-positive, RAS/BRAF wild-type metastatic colorectal cancer who have failed standard treatment.

3.3. Clinical progress of HER2 in other tumors

HER2 abnormalities are widely present in various solid tumors, including biliary tract cancer, colorectal cancer, non-small cell lung cancer, ovarian cancer and bladder cancer. Among them, HER2 mutations are of great significance in non-small cell lung cancer (NSCLC), especially ERBB2 exon 20 insertion mutations, which can lead to continuous activation of the HER2 receptor and drive tumor development and progression [10]. In NSCLC, HER2 overexpression, gene amplification, and ERBB2 mutations can all occur, with HER2 mutations mainly seen in lung adenocarcinoma. By triggering signaling pathways including PI3K/Akt and MAPK, HER2 alterations can encourage the growth and spread of tumor cells. In recent years, new HER2-targeted drugs have made great progress, and small molecule tyrosine kinase inhibitors have exhibited good efficacy in HER2-mutant NSCLC. The phase I study of T-DXd treatment for HER2-mutant NSCLC conducted by Li et al. showed that the median progression-free survival was 14.1 months, and the objective response rate reached 72.7%, suggesting that T-DXd has strong anti-tumor activity [10]. Currently, HER2-targeted therapy is mainly applicable to patients with advanced NSCLC who have ERBB2 mutations, especially exon 20 insertion mutations.

HER2 abnormalities are also common in bladder cancer, with an overexpression rate of over 10%, and are linked with increased tumor invasiveness and poor prognosis. HER2 abnormalities can improve the invasion, proliferation, and metastasis of bladder cancer cells. A phase II study found that when trastuzumab was related to carboplatin, gemcitabine, and paclitaxel to treat patients with metastatic bladder cancer or HER2-positive locally advanced, the objective response rate reached 70%, and the median overall survival was 14.1 months, suggesting that HER2 may become an important therapeutic target for bladder cancer [11]. Although there is no unified standard for HER2-targeted therapy in bladder cancer, patients with HER2 overexpression are increasingly being studied for precision treatment.

Overall, HER2-targeted therapy is gradually expanding to various solid tumors. Studies have shown that pan-HER tyrosine kinase inhibitors such as neratinib and new-generation antibody-drug conjugates have shown certain anti-tumor activity in various HER2-mutant tumors. However, due to the complex HER2 mutation profile and significant tumor heterogeneity, there are still large differences in treatment response among different patients. Further improvements to the HER2 molecular subtyping system and combination therapy strategies are needed in the future.

4. Conclusion

The development and spread of many malignant cancers are significantly influenced by HER2. Its abnormal forms, including gene amplification, protein overexpression and somatic mutations, can promote survival, tumor cell proliferation, and invasion/metastasis by activating signaling routes such as MAPK and PI3K/Akt/mTOR. Furthermore, the types and distribution of HER2 abnormalities vary significantly among different tumors, leading to strong heterogeneity in their biological behavior and treatment response. HER2-targeted therapy has gradually evolved from single-antibody therapy to a multi-strategy combination approach, achieving good efficacy in various solid tumors. Among these, novel antibody-drug conjugates have demonstrated strong anti-tumor activity. However, the treatment of HER2-related tumors still faces challenges such as complex mutation profiles, individual differences in treatment response, and acquired resistance. The mechanisms involved include bypass signaling activation, receptor structural alterations, and tumor microenvironment regulation. Future research should further combine high-throughput sequencing technology to improve the HER2 molecular typing system, explore HER2-related signaling pathways and drug resistance mechanisms in depth, and develop novel multi-target or bispecific drugs to improve the precision treatment of HER2-related tumors.

References

- [1] Cheng, X. (2024). A comprehensive review of HER2 in cancer biology and therapeutics. *Genes*, 15(7), 903. <https://doi.org/10.3390/genes15070903>
- [2] Pan, L., Li, J., Xu, Q., Gao, Z., Yang, M., Wu, X., & Li, X. (2024). HER2/PI3K/AKT pathway in HER2-positive breast cancer: A review. *Medicine*, 103(24), e38508. <https://doi.org/10.1097/MD.00000000000038508>
- [3] Loibl, S., & Gianni, L. (2017). HER2-positive breast cancer. *Lancet*, 389(10087), 2415–2429. [https://doi.org/10.1016/S0140-6736\(16\)32417-5](https://doi.org/10.1016/S0140-6736(16)32417-5)
- [4] Shen, L., Xu, J. M., Feng, F. Y., et al. (2013). Trastuzumab in combination with chemotherapy versus chemotherapy alone for first-line treatment of HER2-positive advanced gastric or gastroesophageal junction cancer: A phase III, multi-center, randomized controlled trial, Chinese subreport. *Chinese Journal of Oncology*, 35(4), 295–300. <https://doi.org/10.3760/cma.j.issn.0253-3760.2013.04.012>
- [5] Petricevic, B., Laengle, J., Singer, J., Sachet, M., Fazekas, J., Steger, G., Bartsch, R., Jensen-Jarolim, E., & Bergmann, M. (2013). Trastuzumab mediates antibody-dependent cell-mediated cytotoxicity and phagocytosis to the same extent in both adjuvant and metastatic HER2/neu breast cancer patients. *Journal of Translational Medicine*, 11, 307. <https://doi.org/10.1186/1479-5876-11-307>
- [6] Yi, J. H., Kang, J. H., Hwang, I. G., Ahn, H. K., Baek, H. J., Lee, S. I., Lim, D. H., Won, Y. W., Ji, J. H., Kim, H. S., Rha, S. Y., Oh, S. Y., Lee, K. E., Lim, T., Maeng, C. H., Kim, M. J., Kim, S. T., Lee, J., Park, J. O., Park, Y. S., & Park, S. H. (2016). A retrospective analysis for patients with HER2-positive gastric cancer who were treated with trastuzumab-based chemotherapy: In the perspectives of ethnicity and histology. *Cancer Research and Treatment*, 48(2), 553–560. <https://doi.org/10.4143/crt.2015.155>
- [7] Wang, Z. H., Zheng, Z. Q., Jia, S. C., Liu, S. N., Xiao, X. F., Chen, G. Y., Liang, W. Q., & Lu, X. F. (2022). Trastuzumab resistance in HER2-positive breast cancer: Mechanisms, emerging biomarkers and targeting agents. *Frontiers in Oncology*, 12, 1006429. <https://doi.org/10.3389/fonc.2022.1006429>
- [8] Javle, M., Borad, M. J., Azad, N. S., Kurzrock, R., Abou-Alfa, G. K., George, B., Hainsworth, J., Meric-Bernstam, F., Swanton, C., Sweeney, C. J., Friedman, C. F., Bose, R., Spigel, D. R., Wang, Y., Levy, J., Schulze, K., Cuchelkar, V., Patel, A., & Burris, H. (2021). Pertuzumab and trastuzumab for HER2-positive, metastatic biliary tract cancer (MyPathway): A multicentre, open-label, phase 2a, multiple basket study. *Lancet Oncology*, 22(9), 1290–1300. [https://doi.org/10.1016/S1470-2045\(21\)00336-3](https://doi.org/10.1016/S1470-2045(21)00336-3)
- [9] Wang, Y., Jiang, T., Qin, Z., Jiang, J., Wang, Q., Yang, S., Rivard, C., Gao, G., Ng, T. L., Tu, M. M., Yu, H., Ji, H., Zhou, C., Ren, S., Zhang, J., Bunn, P., Doebele, R. C., Camidge, D. R., & Hirsch, F. R. (2019). HER2 exon 20 insertions in non-small-cell lung cancer are sensitive to the irreversible pan-HER receptor tyrosine kinase inhibitor pyrotinib. *Annals of Oncology*, 30(3), 447–455. <https://doi.org/10.1093/annonc/mdy542>

- [10] Li, B. T., Smit, E. F., Goto, Y., Nakagawa, K., Udagawa, H., Mazières, J., Nagasaka, M., Bazhenova, L., Saltos, A. N., Felip, E., Pacheco, J. M., Pérol, M., Paz-Ares, L., Saxena, K., Shiga, R., Cheng, Y., Acharyya, S., Vitazka, P., Shahidi, J., Planchard, D., & DESTINY-Lung01 Trial Investigators. (2022). Trastuzumab deruxtecan in HER2-mutant non-small-cell lung cancer. *New England Journal of Medicine*, 386(3), 241–251. <https://doi.org/10.1056/NEJMoa2112431>
- [11] Hussain, M. H., MacVicar, G. R., Petrylak, D. P., Dunn, R. L., Vaishampayan, U., Lara, P. N., Jr, Chatta, G. S., Nanus, D. M., Glode, L. M., Trump, D. L., Chen, H., Smith, D. C., & National Cancer Institute. (2007). Trastuzumab, paclitaxel, carboplatin, and gemcitabine in advanced human epidermal growth factor receptor-2/neu-positive urothelial carcinoma: Results of a multicenter phase II National Cancer Institute trial. *Journal of Clinical Oncology*, 25(16), 2218–2224. <https://doi.org/10.1200/JCO.2006.08.0994>