Proceedings of the 2nd International Conference on Biological Engineering and Medical Science (ICBioMed 2022), Part I
DOI: 10.54254/2753-8818/3/20220210

HER 2 Targeted Therapy and Its Potential Risk of Drug Resistance

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Abstract. HER2, human epidermal receptor 2(c-erbB-2 gene), is a hot targeted point in various cancer's targeted therapy. Breast cancer including HER2 positive or negative. HER2 is an oncogenic receptor tyrosine kinase. HER2 gene amplification occurs in some of breast cancers (BCS), resulting in overexpression of the HER2 protein. Compared to the trastuzumab or pertuzumab, the performance of trastuzumab deruxtecan is excellent. Drug resistance is known to be the main cause of failure of tumor chemotherapy. Tumor drug resistance involves various mechanisms, such as those involving decreased intracellular drug concentration, changes of drug target molecules, metabolic detoxification, and imbalance of DNA damage repair function. HER2-positive breast cancer becomes resistant to trastuzumab, thereby blocking effective binding and developing resistance. The significance of this review is to understand the mechanism of drug resistance from molecular and chemotherapy perspectives by studying the structure and overexpression of HER2 protein as predictors, so as to grasp the progress of current targeted drug therapy. Our review starting from HER2 and its targeted therapy gets to the deep insight into the antibody drug conjugates and explores the possible proteins which may become the potential targeted points in future research.

Keywords: HER2, targeted therapy, antibody-drug conjugates (ADC)

1. Introduction

In 2020, about 2.3 million women worldwide were diagnosed with breast cancer, and nearly 30 percent of them died. In recent years, people have begun to pay attention to the heterogeneity of breast cancer. Based on microarray-based gene expression studies, several subtypes of breast cancer have been identified, one of which is human epidermal growth factor receptor2 (HER2) overexpression type, characterized by increasing numbers of gene copies and receptors.

Clinically, HER2+ patients account for about 20% of breast cancer patients. These patients can be treated with trastuzumab, a humanized monoclonal antibody approved by FDA in 1998 to treat metastatic HER2+ breast cancer (BC) patients. Though trastuzumab based therapy has been shown to be effective in HER2-positive breast cancer, it shows week therapeutic efficiency in the low expression of HER2 in breast cancer.

Drug resistance is the tolerance of microorganisms, parasites and tumor cells on the effects of

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DOI: 10.54254/2753-8818/3/20220210

chemotherapy drugs. When drug resistance appears, the chemotherapy effects of drugs will dramatically decrease, and the emergence of drug resistance has a great impact on the long-term treatment effect of tumors. Among them, the influence of drug resistance in the treatment of breast cancer also appears from known studies, such as human breast cancer cells developing resistance to docetaxel, tamoxifen, paclitaxel, trastuzumab and so on. According to the DESTINT-BREAST04, DS-8201 in latest study in the field of ADC drugs became the leader even exceed the second generation of T-DM1, its excellent performance and amazing outcomes in clinic will make the progression much harder out of our anticipation because of its perfect efficiency.

The mechanism which induces the drug resistance after using the trastuzumab still need exploring. Focus on the HER2 itself, from the property of the protein and its structure, there are two situations discovered from the clinical scenario. One is the accumulation of the truncated mutant P95-HER2. P95-HER2 decreased the sensibility of the cancer cells when the patients were treated by trastuzumab in the past cases. TCB in some extent made the targeted more precisely which even can figure out the resistance occur in the ADCs and the other is the over expression of the MUC4(mucin 4), which occupies the sites and blocks the combination with the trastuzumab. MUC 4, one member in mucin family, both dependent and independently HER2 can also activate the PI3K-AKT-mTOR signal pathway. The ignorance of the trastuzumab directly causes the amplification of the cells and makes the worse situation.

Now as the DS-8201 taken the first, HER2 targeted therapy in ADC has been hardly to innovate any more. According the proportion of the patients from the past data, the drug resistance occurs more due to the unbind between the HER2 and the trastuzumab. This review focuses on the progression on HER2 targeted therapy and casts eyes on three main proteins including HER2, p95-HER2 and mucin-4. From the aspect of targeted therapy mainly in breast cancer and its common trastuzumab therapy, we found the extraordinary potential in such novel area like ADCs which give more possibility in the prognosis or even prediction in the early period on various cancers. Simultaneously, two proteins won our eyes when they have been identified in other reviews which may become instantly the next generation of ADCs' targeted aims to be explored. We hope that the updated research on the targeted drugs can be approved and make it possible to decrease the mortality of the cancer patient in the future.

2. HER2 biology

HER2 and Neu, human and rodent oncogenic growth factor receptors, were independently identified and named in rodent and human models as early as the early 1980s, but were quickly identified as homologous. The Neu oncogene is highly homologous with the ERBB gene encoding epidermal growth factor receptor (EGFR) [1].

2.1. HER2 receptor

The HER2 receptor, a 185kDa trans-membrane protein with tyrosine kinase activity, is encoded by ERBB2 (Erb-B2 Receptor Tyrosine Kinase 2) gene,which is generally referred as HER2 gene. Popescuetal located the erbB-2 gene at the long arm of chromosome 17 (17q12-q21.32) through in situ hybridization.HER2 are normally expressed in epithelial tissues of organs like the breast, the stomach, the small intestine and the liver. HER2 expressed low in normal mammary epithelial cells, while in HER2+ breast cancer(BC) patients , increased numbers of HER2 gene copies and HER2 receptors result in up to 2 million receptors being expressed on the tumor cell surface [2]. Approximately 20% of breast cancer patients have overexpression of the HER2 receptor, according to studies. ErbB2 is an essential therapeutic target since it is not only overexpressed in some tumor types including non-small cell lung cancer and ovarian cancer, but it is also amplified in breast cancer.

DOI: 10.54254/2753-8818/3/20220210

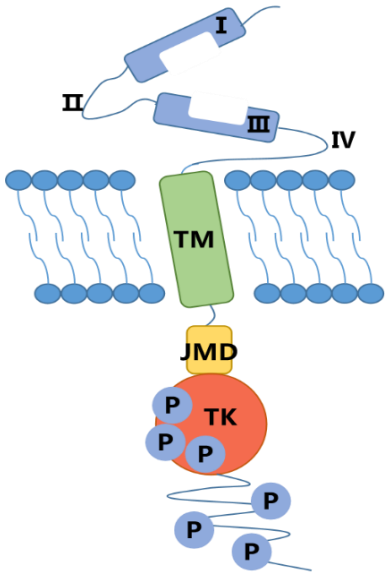


Figure 1. The transmembrane protein of the epidermal growth factor receptor (EGFR) has a basic structure. I and III are two ligand-binding domains that are repeated in the extracellular domain. There are two repeating cysteine-rich regions: II and IV. Short transmembrane sequence is referred to as TM. TK is a catalytic tyrosine kinase that functions inside cells. The phosphorylation site in the TK region is shown by a circled P.

2.2. Structure & function

HER2 is a member of the epidermal growth factor receptor (EGFR) family. This family concludes four HER receptors: HER1(ERBB1, EGFR), HER2(ERBB2, NEU), HER3(ERBB3) and HER4(ERBB4). The EGFR family belongs to tyrosine kinase family. Akiyama et al. (1986) synthesized antibodies to HER2 C-terminal peptide of 14 amino acids and used the antibodies to precipitate ERBB2 gene products, demonstrating that HER2 is a glycoprotein with tyrosine kinase activity.

The structure of the EGFR family members is very similar. The four ErbB receptors consist of a large extracellular domain, a hydrophobic transmembrane domain and an intracellular part containing the tyrosine kinase domain. (Figure 1)

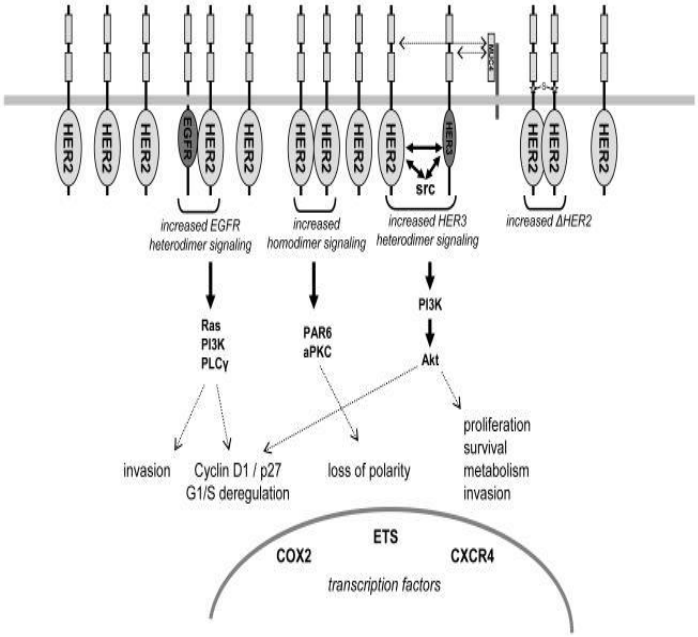


Figure 2. Image of abnormal signaling caused by HER2 overexpression, which is thought to contribute to the development of tumors. HER2 overexpression leads to an increase in dimers, especially those containing HER2.

The extracellular portion can be divided into four domains. I and III are two repeated domains rich in leucine, participating ligand binding. II and IV contain cysteine residues. The middle transmembrane portion consists of about 20 amino acid residues [2].

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In general, growth factors bind to members of the EFFR family as ligands, inducing dimerization and activating downstream pathways, but this activation form does not include HER2.As a orphan receptor, HER2 have no known ligands so far.Instead,HER2 remains an intrinsic activated conformation.HER1 receptor is activated by EGF, epigen ,transforming growth factor, and amphiregulin. ErbB3 and ErbB4 bind to Neuregulin-1 and Neuregulin-2, respectively.

Crystallographic studies have advanced the understanding of HER receptor dimerization. The dimerization of the extracellular domain of EGFR is mediated by a "dimerization arm" located in domain II. However, for HER1, HER3 and HER4, two different conformations can be observed, that is, the conformation without the ligand and the conformational change after the ligand binding. In the inactive state, where the ligand is not present, the dimerization arms are hidden, and the domain II bind to domain IV. Phosphorylation of the kinase receptor activates downstream signaling pathways. HER2 is mainly involved in the ras-Raf-MEK-ERK pathway of cell proliferation and the PI3K-Akt-MTOR pathway of cell survival [2,3].

2.3. HER2 signal transmission mechanism

HER family proteins are transmembrane growth factor receptors, which play a role in signaling between cells. This family of signal-activation systems is complex in mammals because its functions are performed by more ligand receptors. The molecular basis of its signal transduction has been well studied and confirmed. When a ligand binds to the extracellular domain of HER family, its intracellular domain receives the signal and dimerization and transphosphorylation occur. These phosphorylated tyrosine residues located in intracellular structures (seen in Figure 1) connect to a large number of intracellular signaling molecules, resulting in the activation of a large number of downstream signaling pathways.
HER2 is a member of the epidermal growth factor receptor (EGFR) family. This family concludes four HER receptors: HER1(ERBB1, EGFR), HER2(ERBB2, NEU), HER3(ERBB3) and HER4(ERBB4) [1]. EGFR family belongs to tyrosine kinase family. Akiyama et al. (1986) synthesized antibodies to HER2 C-terminal peptide of 14 amino acids and used the antibodies to precipitate ERBB2 gene products, demonstrating that HER2 is a glycoprotein with tyrosine kinase activity [2].

Among the four family members, the catalytic activity of HER2 kinase is stronger than that of the other three members, and the signal transduction ability of her2-containing heterodimers is also stronger than that of the other dimers. HER2 and HER3 are functionally incomplete receptors, which exemplifies that the expansion of HER family in mammalian systems is related to functional differentiation. The figure (Figure 2) shows the downstream cascade caused by HER2 overexpression.

Most members of the family rotate between active and inactive conformations (the inactive conformation shown in Figure 1), with the exception of the extracellular domain of HER2, which exists as an active conformation. HER2 itself has no ligand-binding ability and its signal transduction function depends on its partner in the formation of heterodimers. On the other hand, HER3 in particular has no catalytic activity because of the lack of ATP binding sites in its catalytic domain. HER3 lacks the ability of homologous dimerization and is an obligate heterodimerization partner [4].

2.4. Approach to identify the level of HER2 expression

To classify the type of the expression of HER2, IHC (immunohistochemistry) is now the most common approach, which can make the clear classification by dying the cancer cells or its tissue section and distinct the types through the depth of the colors manifested on them. The section will be named 3+ if the value of IHC is over 30%. It will be included by the group of positive breast cancer and treated by the strategies of HER2 positive breast cancer. Whether the IHC is under 20%, it will be named as 1+/0, respectively few HER2 expression or seemingly none of them, which means it will be hard to use the therapy on HER2 targeted.

IHC between 20% and 30%, the decision of it will rely the ISH (in situ hybridization), which means if the proliferation appears in the outcome, the therapy will be on going just as the HER2 over expression, if it is on contrast, the outcome will be identified to the low expression and the therapy will follow the rules of negative breast cancer (Figure 3).

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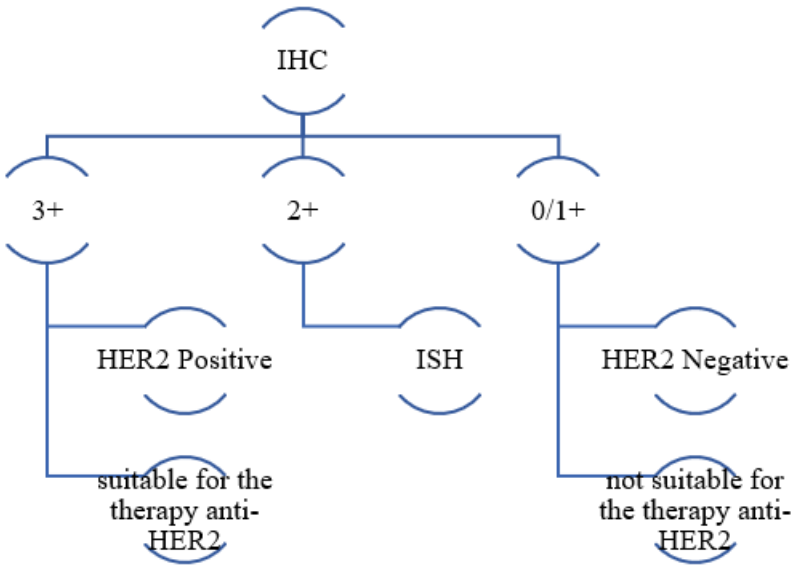


Figure 3. Approach to identify the level of HER2 expression.

2.5. HER2 targeted therapies in cancers

HER2 targeted therapy applies in various types of cancers in common cases. From the data published by the IARC (international agency for research on cancer) in 2020, breast cancer covered over 20% over the world, which instead the first status owned by the stomach cancer before 2020. HER2 targeted therapy has the potential possibility of the progression in different cancers. Besides Stomach cancer and breast cancer, the NSCLC, non-small cell lung cancer, has been expected some outbreaks on HER2 therapy on June in 2022. Despite the experimentally acquired mutations, human breast cancers always appear as wild-type HER2, suggesting that human HER2 appears to have tumorigenic potential through overexpression alone. Kallioniemi et al. 's study pointed out that HER2 protein expression increases 40-100 times in breast cancer, resulting in the expression of up to 2 million receptors on the surface of tumor cells About breast cancer, positive breast cancer has the proportion about 15% and the 85% is the negative breast cancer. Besides the positive breast cancer, the negative breast cancer has about 35%~45% patients related to the HER2 over expression and the left is the low expression.

3. Therapeutic strategies

3.1. The disadvantage of trastuzumab

Trastuzumab (TZB) is a molecular targeted drug which binds to the HER2 produced by the breast cancer cells after being injected into the body. It induces the antibody-dependent cell-mediated cytotoxicity (ADCC) and kills the cancer cells later in patients' body. HER2 is a protein which can stimulate the growth of the cancer cells and TZB can also block its conduction of the signaling pathway terminating the proliferation of the cancer cells. Nowadays, trastuzumab is still the main strategy among patients who are suffering from cancers caused by high positive HER2 over expression. Positive breast cancer has mature strategies compared to the negative breast cancer which is diagnosed by the machine. Some common drugs just like the trastuzumab and pertuzumab, which were considerably traditional drug targeted at the HER2 over expression since 20th century, typically the monoclonal drug. Laptinib and Neratinib are common small molecular tyrosine inhibitors. Laptinib showed its great performance in mutant breast cancer, and the Neratinib is an adjuvant which is applied after the trastuzumab, the patients still have the risk of some unknown factors. Both of them are effective to the survival of the advanced breast cancer. Ado-trastuzumab, T-DM1, was the first appearance of ADC (antibody-drug conjugates) drug, which had micro effect in the clinical trials leading no real profound in the past. Until the DS-2801

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appears in the market, just like a bomb beats the T-DM1 and occupy the first place of the ADC in HER2 targeted therapy. The appearance of DS-2801 finishes the classification of the positive and negative, which brings the bless to the negative breast cancer patients in some extent, especially the patients who suffered from triple negative breast cancer.

Whether the novel therapy flows as an endless stream or ceases to advance, the drug resistance is the considerably general headache problem while is in the clinical application. To investigate the detail mechanism is still a long way to go according to the studies. Novel drugs' efficiency wins much focus because of its high interests to both company and the patients, simultaneously, the resistance of the problems manifested is essential in a long term. Combined with the signaling pathway of HER2, some closed proteins win our eyes, especially the p95HER2 and protein of mucin family, MUC4 (mucin4). As the previous introduction, the main therapy of HER2 over expression is still the trastuzumab and pertuzumab, which covers most of the positive breast cancer. Both proteins play important roles in the resistance in binding to the drugs. Messages below will respectively narrative the details of the researches carried by scientists, and the targeted drugs which are used to avoid it or the research is still on the way. We hope that as the novel drugs produced to cure the patients which may not be covered before, at the same moment, put more eyes on the prognosis of the patients who are seem to cure but has the risk of the resistance to the drug if they carry the disease again.

3.2. The tendency of monopoly on ADC

Monoclonal antibodies that target certain antigens and small-molecule cytotoxic medications are combined to create antibody-coupled drugs (ADCs), which combine the potent killing ability of conventional small-molecule chemotherapy with the tumor-targeting capabilities of antibody therapeutics. a linker that joins the antibody to the payload, and a payload. The ADC enters the cell by the endocytic pathway after recognizing the antigen, and after being broken down by the lysosome, the payload is released in a biologically active form and functions to kill cancer cells. The number of antigens on each cell surface, the number of drug payload molecules per ADC (also known as the drug antibody ratio, or DAR), and the amount of time needed for the antigen to return to the cell surface all affect the amount of intracellular payload. After the decomposition and death of the cancer cell, the payload may escape, or it may leave the cytoplasm through the membrane.

3.2.1. The composition of ADC. Antibodies, payloads, and chemical connectors make up ADCs. The perfect ADC medication maintains stability in the bloodstream, precisely reaches its therapeutic target, and eventually releases its cytotoxic payload close to the target (e.g., cancer cells). Each element affects the ultimate efficacy and safety of an ADC, and overall, ADC development requires consideration of all of these key components, including target, antibody, cytotoxic payload, junction, and choice of coupling method.[5]

3.2.2. Pharmacokinetic complexity. The ADCs has been explored for three generation. The next generation of ADCs has improved cytotoxicity and specificity over earlier generations. Drug resistance, insufficient tumor targeting and payload release, and pharmacokinetic complexity are only a few of the difficulties still facing the development of ADCs. Main challenge on the pharmacokinetic complexity. Following ADC administration (often by intravenous infusion), the bodily circulation may contain intact ADC, naked antibody, and free payload, in that order. As ADC is internally metabolized and the antibody is eliminated, the quantities of linked ADC and bare antibody continue to fall in the normal pharmacokinetic profile of ADC.

The development of the HER2 targeted therapy undergoing three stages, including trastuzumab and pertuzumab above, the small molecular tyrosine inhibitors and the antibody-drug conjugates. As many new drugs produced by many biochemical companies, among of them are still about monoclonal antibody. As we cast our eyes on the market, the fields in ADC are most actively novel, attracting many young scientists' eyes. Early in 2010, the second generation of T-DM1 has been put onto the market. In addition to the humanised antibody for HER2, the conjugate alsocontains a topoisomerase l inhibitor in

DOI: 10.54254/2753-8818/3/20220210

addition to a novel enzyme-clearable linker. Latest studies according to the DESTINY-breast04 has proved that DS-8201 owns the best data from the feedback comparing with the T-DM1 on clinical trial. There is no doubt that in the field of ADC, DS-8201 will hardly be beaten by a totally new drug in a generable long term [6].

Side effects appeared in ADC. Hematologic toxicity, which includes neutropenia, thrombocytopenia, leukopenia, and anemia, is the most frequent significant adverse event (Grade 3 or higher). Several deaths associated with ILD have been documented in clinical studies of T-DM1 and DS-8201. ILD's precise method of action, however, is still unknown.

3.2.3. Drug resistance. Drug resistance is another difficulty in the development of ADCs. Escape mutations in the therapeutic target are frequently involved in tyrosine kinase inhibitor (TKI) resistance. ADC resistance is more complex and varied than ADC resistance, and the processes of ADC resistance have not yet been fully defined. According to the available data, tumors can acquire ADC resistance in a variety of mechanisms, including decreased antigen expression, modified intracellular transport pathways, and resistance to payloads [7].

4. P95HER2

P95HER2 is a truncated form of HER2 receptor [8], which lacks the domain out of the cells and fails to bind with the trastuzumab or pertuzumab. The entity of it is a family of HER2 CTFs (carboxy terminal fragments), which is uncommon in length and owns oncogenic activity. Now it is not weird to see that the carboxy terminal has been described. As the past study went by others, P95 is a critical biomarker which can precisely predict the poor outcomes in the prognosis in the HER2 positive metastatic breast cancer. And in the early breast cancer, it can also make difference on the trastuzumab treatment, just like the prediction. What has been overviewed is that there may be some relation between the P95 in tumors and the DDFS (distant disease-free of survival). P95 expression is capable to enhance the sensitivity to chemotherapy in vitro and in the xenograft models derived from the patients. There is a warrant to go further in the targeted biomarker of high expression in HER2 positive breast cancer.

Trastuzumab (T) and lapatinib (L) accompanied by paclitaxel led topathological complete response (pCR) according to Scaltriti et al. A study by Lipton et.al. aims to explore the potential of HER3 alone and in conjunction with p95HER2 (p95), a trastuzumab resistance marker, as biomarkers of trastuzumab resistance. The patients' underlying tumors provided an exceptional opportunity to find biomarkers that could forecast long-term clinical success with CT-free anti-HER2 therapy. On the other hand, high HER2 concentrations have been associated with a greater therapeutic benefit from anti-HER2 therapy. To determine whether the levels of p95HER2 and HER2 can predict a patient's response to anti-HER2 therapy in this study's topic, Scaltriti et al. and Kallergi et. al., p95HER2 expression on circulating tumor cells (CTCs) from breast cancer patients was examined. In Nishimura et al., In trastuzumab-refractory HER2-positive metastatic breast cancer, the aim was to investigate the association between HER2-related biomarkers and the outcomes of treatment with lapatinib plus capecitabine (LC) and to evaluate the influence of the ER status. Given that p95HER2 levels correlate with overall HER2 expression levels, which are associated with better outcomes, the North Central Cancer Treatment Group N0337 and N98-32-52 studies seek to evaluate the p95HER2/HER2 ratio [7]. P95 was looked into as a potential indicator of the therapeutic efficacy of trastuzumab in the FinHer adjuvant phase III study's HER2-positive subgroup. Other noteworthy works include Prudkin et. al. In breast cancer, over 40% HER2 over expression patients connected to the P95HER2. P95HER2 is the part of HER2, C terminal fragment truncated, which has no sites binding to the trastuzumab. HER2 binds with trastuzumab in IV domain of its extracellular part and after HER2 changing into P95HER2, the site lost, which affects the therapeutic efficiency of the trastuzumab in clinal treatment. Compare to the HER2, P95HER2 can easily combine to the HER3 and activate the down streams of the signaling path, which is also a main reason leads the resistance to trastuzumab.

DOI: 10.54254/2753-8818/3/20220210

4.1. Advanced targeted beat on HER2

TCB (T-cell bispecific antibody) [9], it is a novel therapy that depend on the immune system itself to kill the cancer cell. T cell is as a leader that induce the lymphocyte to the cancer cell and then undergo the ADCC (antibody-dependent cell cytotoxicity) to kill the targeted cell which achieve the goal that kill the tumor instead of killing healthy cell.

In 2018, Ruiz and colleagues reported that p95HER2-positive breast cancer and brain lesions can be treated with a powerful anti-cancer effect by increasing the levels of this protein. This finding suggests that the presence of this gene in the blood can influence the outcomes of patients with cancer. The next step is to establish the exact ratio of this gene to total human epidermal growth factor 2 (HER2) in the N0337 and N98-32 trials. In 2019, Gorbatenko and colleagues reported that the presence of p95HER2- in breast cancer cells has a significant effect on the regulation of the multiple factors that affect the development and maintenance of cancer. Their study also revealed that the role of this protein in the regulation of the motility of cancer cells is dependent on the interaction between the MYB family and the TIMP2. In 2020, Griessinger and colleagues reported that they used a radiolabeled minibody to monitor the movement of cancer cells. Li et al. examined 280 individuals with early TOP2A-normal stagell-lll breast cancer who participated in three studies to evaluate theeffects of the minibody, which is CD8 specific. They found that the minibody detected and monitored the presence of cancer cells infiltrates by positron emission tomography (PET). Exploring possible predictors and treatment targets based on clinical and genetic features is the focus of Wang et al. The bispecific CEA-CD3 T cell antibody cibisatamab (CEA-TCB) is undergoing clinical studies right now. using confocal time-lapse imaging By Teijeira et al, it is compared to a lower affinity CEACAM5-CD3 (CEACAM5-TCB) bispecific antibody for its efficacy against three-dimensional tumor organoids in cocultures with T cells [6]. At the Central Hospital of Zhuzhou, 80 patients with advanced epithelial ovarian cancer (stage IIIc or IV) who received NACT between February 2019 and October 2020 were enrolled. Another significant works including Kim et. al. The P95-HER2 takes about a third in the HER2, it influences the prognosis of the patients the TCB gives hope to the precisely attack by the T cells on gene. It is a totally novel therapy, temporarily on the stage of trail.Hence, it is still short of the clear data. The experiments are still on the way, but the novel treatment make the tumor targeted therapy more precisely.

Bispecific antibody technology developments have increased the potential for ADC innovation. These ADC designs can increase tumor selectivity and antibody internalization. These options have been investigated in developing therapies. Bispecific ADCs that target various locations on the same antigen can enhance receptor aggregation and hasten target site internalization. Additionally, in preclinical studies, bispecific ADCs with dual targeting of HER2 and LAMP-3 demonstrated improved lysosomal aggregation and load distribution.

5. Mucin-4 (MUC4)

Mucins are large, heavily glycosylated proteins which survives on the surface of cells. Mucin is the most abundant macromolecular protein in the gelatinous material, a family of high molecular weight proteins, which determines the biochemical and biophysical properties of mucus [10]. A wide range of organisms, such as parasites, fungi, and viruses, produce mucin-like molecules. In humans, mucin glycosylation has been associated with tumor development in epithelial tissues. It is expressed on the apical surface of epithelial cells in many tissues, and plays a barrier and lubrication role in the inner membrane of cells, as well as a conduction and adhesion function to cell growth signals. In the signaling pathway of Mucin4 protein, the signal directly interacts with the signal domain through HER2. Mucin4 can also signal through other EGFR families, such as HER3. In triple negative breast cancer, Mucin4 plays a role in increasing the expression of HER3 and EGFR, driving cell proliferation.

There are two aspects effecting the trastuzumab combination with HER2.Both can be classified into the steric hindrance, one of which causes by the receptor which is masked by the MUC4 and the other is the inaccessibility of the epitopeMUC4, a membrane-bound mucin, has undergone in-depth research in a wide range of normal tissues and malignancies.

Knowing the prevalence and clinical significance of a molecular mutation may help us choose the

DOI: 10.54254/2753-8818/3/20220210

best course of action and monitor patients. Previous research has demonstrated that MUC4 is pathobiologically significant in the disease process and is aberrantly expressed in many malignancies, supporting its usage as a potential target for cancer diagnosis, prognosis, and treatment. With further understanding of MUC4 expression, its pathological significance in cancer, and through the characterization of the mechanisms of MUC4 action, new approaches to cancer management can be devised.

6. Conclusion

Targeted therapy gives patients of cancers more possibility to have a longer life. ADCs could be extremely hard since the existence of the trastuzumab-deruxtecan, which has been show its perfect performance in this area. Although Chinese biochemical companies have aboard RX48, the main stream in the application of DS-8201 will hardly not to change in the next decade. From the perspective of P95HER2, the toxicity in current experiment to patients' heart is still a potential risk in the input for the universal therapy. Later in the next few days, the direction in bispecific antibody is waiting to be expanded, maybe in P95 or MUC4 targeted, ADC will continue to be a hot area and a bright light to those who gives in cancers.

References

[1] MM Moasser. The oncogene HER2: its signaling and transforming functions and its role in human cancer pathogenesis. *Oncogene*. 2007 Oct 4;**26(45)**:6469-87.

[2] V Hart, H Gautrey, J Kirby, A Tyson-Capper. HER2 splice variants in breast cancer: investigating their impact on diagnosis and treatment outcomes. *Oncotarget*. 2020 Nov 17;**11(46)**:4338-4357.

[3] A Appert-Collin, P Hubert, G Crémel, A Bennasroune. Role of ErbB Receptors in Cancer Cell Migration and Invasion. *Front Pharmacol*. 2015 Nov 24; **6**:283.

[4] Q Lv, Z Meng, Y Yu, F Jiang, D Guan, C Liang, J Zhou, A Lu, G. Zhang Molecular Mechanisms and Translational Therapies for Human Epidermal Receptor 2 Positive Breast Cancer. *Int J Mol Sci*. 2016 Dec 14;**17(12)**:2095.

[5] Z. Fu, S. Li, S. Han, C. Shi, &, Y. Zhang. Antibody drug conjugate: the "biological missile" for targeted cancer therapy. *Signal Transduction and Targeted Therapy*, **7(1)**, 93. (2022)

[6] S. Modi, W. Jacot, T. Yamashita, J. Sohn, M. Vidal, E. Tokunaga, J. Tsurutani, N. T. Ueno, A. Prat, Y. S. Chae, K. S. Lee, N. Niikura, Y. H. Park, B. Xu, X. Wang, M. Gil-Gil, W. Li, J. Y. Pierga, S. A. Im, H. Moore … DESTINY-Breast04 Trial Investigators. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. *The New England Journal of Medicine*, **387(1)**, 9–20. (2022)

[7] C. H. Chau, P. S. Steeg, & W. D. Figg, Antibody-drug conjugates for cancer. *Lancet* (London, England), **394(10200)**, 793–804. (2019)

[8] M. Scaltriti, F. Rojo, A. Ocana, J. Anido, M. Guzman, J. Cortes, S. Di Cosimo, X. Matias-Guiu, S. Ramon y Cajal, J. Arribas, & J. Baselga. Expression of p95HER2, a Truncated Form of the HER2 Receptor, and Response to Anti-HER2 Therapies in Breast Cancer. *JNCI Journal of the National Cancer Institute*, **99(8)**, 628–638. (2007)

[9] Rius Ruiz Irene, Vicario Rocio, Morancho Beatriz et al. p95HER2-T cell bispecific antibody for breast cancer treatment.[J] .*Sci Transl Med*, 2018.

[10] C. A. Dreyer, K. Vander Vorst, S. Free, A Rowson-Hodel, & K. L. Carraway.The role of membrane mucin MUC4 in breast cancer metastasis. *Endocrine-Related Cancer*, **29(1)**, R17–R32. (2022)