

Research Progress in Drug Application and Treatment of Breast Cancer Organoids

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Abstract. Background: In recent years, the incidence of breast cancer (BC) is high and on the rise. Organoids, as a new in vitro 3D culture model, play a huge role in BC treatment and drug development. Objective: To summarize the domestic and foreign research experience in BC organoids in drug screening, in order to provide new ideas for BC treatment. Summary: This article briefly summarized the mechanism of action of commonly used drugs for BC, including trastuzumab, tamoxifen, olaparib, paclitaxel, pembrolizumab, and the effects of HER-2 drugs and CDK4/6 inhibitors on BC organoids, clarified the importance of BC organoids, and drew the conclusion that more accurate treatment could be achieved by using this model. The successful establishment of papillary carcinoma organoids further demonstrated the feasibility of cultured 3D models in vitro. On this basis, drug sensitivity tests for different drugs were conducted, and it was concluded that fluvastatin had the best anticancer effect, thus proving that BC organoids played an important role in drug screening. In addition, organoid technology also has a good effect in the treatment of Triple-negative breast cancer (TNBC). Using this model for large-scale drug detection, four compounds including papirinestat, patinib, JIB-04 and TAK-901 showed effective activity on TNBC organoids, indicating that organoids can promote drug discovery. It is concluded that BC organoids are a potential therapeutic model, and the development of this technology provides an innovative approach to treating BC.

Keywords: Breast cancer organoids; drug screening; drug therapy.

1. Introduction

Breast cancer (BC) is the most common cancer, and also the main cause of cancer death for women all over the world. Its incidence is increasing year by year. There are two main types of BC: non-invasive carcinoma (i.e., carcinoma in situ) and invasive carcinoma. Carcinoma in situ can be further divided into DCIS and LCIS. Invasive cancers can be further subdivided into: invasive ductal carcinoma, invasive lobular carcinoma, and other less common invasive cancers such as tubular carcinoma, mucinous carcinoma (colloidal carcinoma), papillary carcinoma, and medullary carcinoma.

Common treatment methods for BC patients include surgery, chemotherapy, radiotherapy, endocrine therapy, targeted therapy, and immunotherapy are all options, but their therapeutic effects are not ideal. At this time the development and the use of organoid technology have brought new directions for the establishment and analysis of the etiology and drug treatment of BC. Organoids are tissue analogues with in vitro 3D culture formed by adult stem cells or pluripotent stem cells. Patient-derived organoids (PDOs) mainly use fresh tumor tissues from patients to conduct 3D culture in vitro under specific liquid culture conditions to form miniature tumor models, which the role of this tissue in the body is to mimic the biology of the tumor. It is often used for personalized treatment of various cancers and early drug screening. In the treatment of BC, drug therapy is an important component. BC organoids are derived from patients, retain the cellular characteristics of the primary tumor, and can be used for high-throughput screening, which is a very effective platform for drug development. It can also be used in clinical evaluation of anti-tumor activity, drug toxicity, determination of drug action targets and drug sensitivity screening.

By summarizing the mechanism of action of different anti-BC drugs and their effective activities on BC organoids, this article compares the therapeutic effects of drugs by listing experimental cases of cultured BC organoids in vitro, accelerates the transformation of basic experimental research into

clinical practice, makes it possible to achieve personalized treatment for BC patients, and provides new ideas for BC treatment.

2. Classification of Commonly Used Drugs for BC

In recent years, with the deepening of BC research, the treatment of BC is gradually enriched, and more and more anti-BC drugs are available in clinic, including HER2 drugs, endocrine drugs, targeted drugs, immune drugs, etc. The list of commonly used therapeutic drugs for BC and the corresponding mechanisms of action are shown in Table 1

Table 1 Commonly used therapeutic drugs for breast cancer and their mechanisms of action.

Representative drugs	Action target	Action mechanism	limitation	Reference
Trastuzumab	HER2	Interacts with HER2 and blocks tyrosine kinase signaling. Kill tumor cells through cytotoxic effects.	1) There is a high probability of drug resistance. 2) Increases the risk of heart problems. 3) Targeting a single target.	[1]
Tamoxifen	ER	Compete with E2 for endoplasmic reticulum binding and prevents LBD mediated co activation factor aggregation. Promotes activation of the AF1 domain, resulting in weaker transcriptional activation under hormone deprivation.	1) Endoplasmic reticulum transcriptional activity could not be completely inhibited. 2) The range of prohibited people is large.	[2]
Olaparib	BRCA-1/2, PARP, ATM or CHEK2	Inhibit PARP, block DNA repair pathway, lead to accumulation of DNA damage, and eventually induce apoptosis of cancer cells. Patients with BRCA1/BRCA2 germline mutations develop tumors that are sensitive to PARPi.	It may cause side effects such as anemia, decreased platelets, and decreased white blood cells.	[3]
Taxol	Intracellular tubulin	Inhibit microtubule assembly and prevent cell division. It prevented the progression of G2/M phase cells and eventually induced apoptosis.	The therapeutic effect is limited by the toxic side effects of anthracyclines.	[4]
Pembrolizumab	PD-1/PD-L1	PD-1 immunosuppressant. Blocking the interaction between PD-1 and PD-L1, PD-L2, restoring tumor specific T cell immunity, inhibiting tumor cell growth, and other processes.	Many patients With advanced malignant tumors are insensitive to, or even resistant to, single agent immunotherapy. Therefore, combination therapy is recommended.	[5]

It can be concluded from the above content that although many drugs can exert corresponding inhibitory effects on breast cancer in the process of breast cancer treatment, due to their different mechanisms of action and targets, as well as the individual differences of patients themselves, how to effectively improve treatment accuracy and give full play to drug activity is the key research object in breast cancer treatment.

3. Research Status of Commonly Used Drugs for BC in BC Organoids

3.1. HER2 Drugs and BC Organoids

Human epidermal growth factor 2(HER-2) plays a significant role in the treatment of BC. The development of HER-2 targeting drugs began with the monoclonal antibody trastuzumab, to pertuzumab, tyrosine kinase inhibitors (e.g., lapatinib, naratinib, and Tucatinib), and more recently, antibody drug couplers (which bind anticancer drugs to specific antibodies to deliver them directly to cancer cells). Benefit HER-2 positive BC patients. With the development of modern technology, researchers have also carried out relevant experiments on HER-2 low expression BC patients [6].

Sachs et al. found that in the case of HER2 overexpression, the HER2 signaling pathway is blocked by drugs that affect BC organoids. In addition, BC organoids with high BRCA1/2 expression are sensitive to ADP-ribose polymerase inhibitors, while BC organoids with low BRCA1/2 expression are resistant to ADP-ribose polymerase inhibitors, suggesting that gene expression at the transcriptomic level of organoids can also serve as an important basis for drug susceptibility screening [7]. The European Society of Medical Oncology IMMUNO-ONCOLOGY Congress (ESMO) announced a study based on the co-culture system of tumor organoids and T cells, which established a co-culture system of organoids and immune cells derived from BC patients with low HER2 expression. The research results revealed the synergistic effect of BC patients with low HER2 expression patient-derived organoids when treated with T-DXd and trastuzumab combined with durvalumab [8]. The results provide a basis for the application of antibody-coupled drug combined immunotherapy in BC patients with low HER2 expression, and also bring new inspiration for scientific research and clinical practice of BC with low HER2 expression.

3.2. CDK4/6 Inhibitors and BC Organoids

Overactivity of cyclin-dependent kinases 4 and 6 (CDK4/6) is a common phenomenon in HR+ BC. CDK4/6 inhibitors restore cell cycle control by selectively inhibiting CDK4/6, thereby blocking tumor cell proliferation. In recent years, researchers have achieved effective results in the research of CDK4/6 inhibitor targeted therapy combined with endocrine therapy in early and advanced HR+ BC, making it gradually become an important choice for the treatment of HR+ BC [9].

CDK4/6 inhibitors (CDK4/6i) and anti-estrogenic drugs have transformed the treatment of ER+.Survival is significantly extended by Advanced BC (MBC). However, tumors eventually grow despite this combination therapy being not a cure develop resistance.

Hanker et al. developed a platform for CDK4/6i resistant BC PDOs as a model for acquiring the ability to resist CDK4/6i + anti-estrogens and for discovering methods to overcome resistance. And 32 patients successfully received CDK4/6i (palbocinib or abesili) + anti-estrogenic (letrozole or fluevestrant). The mean response time to combination therapy was 9 months. Sixteen PDOs were established in metastatic biopsies of ER+ MBC patients who progressed to treatment (50% efficiency). After a series of controls and high-throughput screening, it was confirmed that tumors amplified by CCNE1 are susceptible to CDK2 inhibition. Thus, it is concluded that establishing PDOs from ER+ MBC biopsies, maintaining a resistant phenotype in culture, retaining driver changes consistent with their source tumors, and failing to inhibit E2F targets after CDK4/6i therapy are all possible. The PDOs are a valuable model for CDK4/6i resistance and therapeutic vulnerabilities [10].

These results demonstrate the feasibility of maintaining resistance in culture in organoids from patients with CDK4/6i progression and confirm the feasibility of CDK4/6i resistant BC organoids, through which these organoid models can better understand Identified therapies to overcome

resistance to CDK4/6i + anti-estrogen and acquired resistance. To provide more accurate treatment for ER+ advanced BC patients.

3.3. Screening of Drugs on BC Organoids

Papillary carcinoma is a rare form of BC. In addition, patients with giant adenocarcinoma are extremely rare in clinical practice [11]. The aim is to enhance the treatment efficacy of such patients, researchers conducted a series of experiments to explore pathological conditions and discovering effective therapeutic drugs requires clinically relevant models.

Li X et al. successfully constructed the organoid of papillary carcinoma, and confirmed that the phenotype of organoid matched the original histological type of BC [11]. Afterward, 9 concentrations of tamoxifen, fluvoxetine, pembroxili, everolimus, PI3K inhibitor (BKM120) (MedChemExpress, Monmouth Junction, NJ, USA), and DMSO control were added. The sensitivity of cultured organoids to various clinical endocrine therapy drugs and targeted therapies was evaluated. According to the findings, the organoid in breast papillary carcinoma was the most sensitive to fluvestrant monotherapy. It is suggested that the use of gene sequencing technology and drug sensitivity testing should be combined to achieve better therapeutic effect. The research also revealed that fluvestrant (IC₅₀ 0.275 μmol) had the best anti-cancer effect, but tamoxifen (IC₅₀ 19.13 μmol) had the worst anti-cancer effect. It concluded that the model could be a personalized way to predict potentially effective therapeutic drugs.

The findings of this study show that the response of cancer organoids is consistent with the patient's tumor tissue, thus revealing the feasibility of 3D culture of tumor-derived organoids from cancer in vitro, and further demonstrating that BC organoids can be used as a potential therapeutic prediction model. Through this model, the etiology and pathological process of BC can be studied, so as to promote the discovery of drugs, further explore the mechanism of drugs, and lay the foundation for improving the treatment rate.

3.4. 3D Organoid Drug Screening and TNBC

Triple-negative breast cancer (TNBC) is a subtype of BC, which is highly invasive, prone to recurrence and metastasis. Because it does not express ER, PR and HER-2, it cannot be treated by traditional endocrine therapy and targeted therapy. At present, the treatment of TNBC still faces many difficulties, including the lack of targeted treatment drugs, high risk of recurrence and metastasis, tumor heterogeneity and drug resistance, and the corresponding research aims to find more effective treatment strategies [12].

3D organoid culture has made drug screening more accurate and facilitated the screening of compounds that are effective in the treatment of TNBC. A drug screening system that is highly efficient was implemented by establishing Two patient-derived TNBC organoids and two TNBC cell lines were utilized. A total of 169 epigenetic compounds were screened and conclusions were concluded that organoid-based systems were significantly more accurate in evaluating drugs than cell-based models. Compounds that show the highest drug sensitivity in the initial screening and are in the top 30 it will be evaluated in a secondary screening. It was concluded that the four compounds of papirinestat, patinib, TAK-901 and JIB-04 targeted HDAC, JAK/STAT, histone demethylase and northern light kinase pathway, respectively, and showed effective antitumor activity in TNBC organoid. Demonstrated the value of patient-derived organoids in the advancement of drug discovery [13].

These findings lay the foundation for the success of establishing patient-derived TNBC organoids, demonstrating that TNBC organoids can perform high-throughput drug screening. Using this model, it was determined that these compounds exhibited drug activity beyond paclitaxel and showed significant antitumor effects on TNBC. The results of the research indicate that the development of this model can advance drug discovery and be used as a potential therapeutic model for further clinical trials.

4. Conclusion

This article summarizes the relevant targets, mechanisms of action and limitations of five commonly used drugs for BC: trastuzumab, tamoxifen, olaparib, paclitaxel and pembrolizumab. Therefore, it is necessary to continue to study more accurate treatment programs on the basis of drug treatment to help drug activity get full play. BC organoids are currently the best model for studying pathogenesis and customized treatment. It has the following characteristics: it can maintain the high heterogeneity of BC; Maintain the contact polarity between cancer cells and microenvironment matrix to better simulate the microenvironment in vivo; Organoid culture from clinical tissue is efficient and less time-consuming. At the same time, it has the advantage that cancer cell lines can be genetically manipulated. The effects of HER-2 drugs and CDK4/6 inhibitors on BC organoids indicate that BC organoids can improve the precision of treatment. The successful establishment of papillary carcinoma organoids further demonstrated the important role of in vitro culture 3D model in BC treatment. On this basis, drug sensitivity tests were carried out on different drugs, and it was concluded that flutemetamol had the best anti-cancer effect, proving that BC organoids can improve drug accuracy and provide personalized treatment in drug screening. Targeted to improve the survival rate of patients. For TNBC that is difficult to treat, high throughput drug screening can be performed by organoids, and four compounds, papirinestat, patinib, TAK-901 and JIB-04, can play effective activities on TNBC organoids. In summary, BC organoids are good tumor drug screening models with advantages such as high fitting degree and high throughput drug screening, and have broad application prospects in disease modeling, tumorigenesis mechanism and drug efficacy evaluation. The efficiency and success rate of drug development are greatly improved, and the clinical trial rate of drugs is also guaranteed. In the future, further research can be carried out in 3D printing technology and personalized medicine, which will bring hope for the early defeat of BC.

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