Research Progress on the Correlation between miRNA and Tamoxifen Resistance in Breast Cancer

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Abstract: MicroRNA (miRNA) plays a crucial regulatory role in the mechanism of tamoxifen resistance in breast cancer. This article conducts a systematic review on the molecular mechanisms, clinical significance, and potential therapeutic strategies of miRNA regulating tamoxifen resistance in breast cancer. A variety of miRNAs exert promoting or inhibitory effects on the occurrence and development of tamoxifen resistance by targeting key molecules such as the estrogen receptor signaling pathway, apoptosis-related genes, and drug transporters. These miRNAs can not only serve as biomarkers for drug resistance but also become potential therapeutic targets for reversing drug resistance. A profound understanding of the miRNA-mediated drug resistance mechanism is of great significance for improving the prognosis of breast cancer patients.
***Keywords*:** miRNA, breast cancer, tamoxifen resistance, research progress

1. Introduction

As a class of key post-transcriptional regulators, microRNAs (miRNAs) have attracted increasing attention for their roles in tumorigenesis, tumor development, and drug resistance. By binding to the 3' untranslated region of target gene mRNAs, miRNAs regulate the level of gene expression and play a critical role in biological processes such as cell proliferation, apoptosis, and migration. A large number of experimental studies have confirmed[1] that the abnormal expression of specific miRNAs is closely associated with tamoxifen resistance in breast cancer, providing new insights into clarifying the resistance mechanism and developing novel therapeutic strategies.

2. Molecular mechanisms of miRNA regulating tamoxifen resistance in breast cancer

2.1 Regulatory effect of miRNA on the estrogen receptor signaling pathway

Estrogen receptor α (ERα) is the main target for tamoxifen to exert its effect, and its expression level and activity state directly determine drug sensitivity. Research data indicate [2] that specific miRNAs can directly target ERα mRNA or regulate its upstream signaling molecules to affect the expression and function of ERα. miR-221 and miR-222 were the first miRNAs verified to regulate ERα expression. By binding to the 3' untranslated region of ERα mRNA, they significantly reduce the level of ERα protein, thereby weakening the sensitivity to tamoxifen. The expression levels of these two miRNAs are significantly increased in tamoxifen-resistant breast cancer cell lines, while remaining low in drug-sensitive cell lines.

In addition to directly regulating ERα expression, some miRNAs can also indirectly regulate its expression by affecting ERα transcriptional regulators. miR-18a, a member of the miR-17-92 family, can target and inhibit the expression of the ERα transcriptional coactivator AIB1, thereby reducing the transcriptional activity of ERα. Studies have found [3] that in cell lines with acquired tamoxifen resistance, the expression of miR-18a is significantly increased, while the protein levels of AIB1 and ERα are decreased. This regulatory pattern provides a molecular basis for the occurrence of tamoxifen resistance.

MiR-342, as a key epigenetic regulator, can affect the estrogen receptor signaling pathway through multiple pathways. This miRNA can not only directly target ERα mRNA but also regulate the expression of histone deacetylase HDAC1, influencing the changes in the histone modification state in the ERα promoter region. In the analysis of clinical samples, poor therapeutic response to tamoxifen in breast cancer patients is significantly associated with low expression of miR-342, indicating its great significance in maintaining drug sensitivity.

2.2 Impact of miRNA on apoptosis and proliferation-related pathways

Apoptosis resistance is one of the important characteristics of tamoxifen resistance. A variety of miRNAs affect the sensitivity of tumor cells to drug-induced apoptosis by regulating the expression of apoptosis-related genes. MiR-21, a classic oncogenic miRNA, plays an important role in tamoxifen resistance of breast cancer. This miRNA can target and inhibit multiple tumor suppressor genes, such as programmed cell death 4 (PDCD4) and phosphatase and tensin homolog (PTEN), leading to the activation of the PI3K/Akt signaling pathway, promoting cell survival and inhibiting apoptosis [4].

In the context of drug-resistant cell lines, the high expression of miR-21 is closely associated with the upregulation of anti-apoptotic protein Bcl-2 family members.

The downregulation of certain tumor-suppressive miRNAs is also related to tamoxifen resistance. miR-34a can target and regulate multiple apoptosis-related genes downstream of p53, including Bcl-2, Survivin, and Cyclin D1. In tamoxifen-sensitive breast cancer cells, miR-34a is highly expressed, which can effectively induce cell cycle arrest and apoptosis; however, in drug-resistant cells, the expression of this miRNA decreases sharply, resulting in cell resistance to drug-induced apoptosis.

Abnormal cell cycle regulation is another key mechanism by which tumor cells acquire drug resistance. miR-125b can target and regulate the expression of cyclin-dependent kinase CDK6 and cyclin Cyclin D3, affecting the transition process from the G1 phase to the S phase. In breast cancer cells with acquired tamoxifen resistance, the expression level of miR-125b is significantly downregulated, followed by an increase in the protein levels of CDK6 and Cyclin D3, and the cell proliferation activity is enhanced [5].

2.3 Regulatory effect of miRNA on drug metabolism and transport systems

Abnormal expression of drug transporters is one of the important causes of tamoxifen resistance, among which the overexpression of ATP-binding cassette (ABC) transporter superfamily members such as ABCB1 (P-gp) and ABCG2 is the most common. By regulating the expression of these transporters, miRNAs affect the accumulation and distribution of drugs in cells. Evidence shows [6] that miR-27a can directly target the 3' untranslated region of ABCB1 mRNA, inhibit the synthesis of P-gp protein, increase the intracellular concentration of tamoxifen, and thereby enhance drug sensitivity. In preclinical research, overexpression of miR-27a can significantly reverse the resistance of multidrug-resistant breast cancer cells to tamoxifen.

MiR-326, another important drug transport regulator, can target both ABCB1 and ABCG2, two key drug efflux pumps. The expression level of this miRNA is relatively high in normal breast epithelial cells but significantly downregulated in drug-resistant cell lines. Restoring the expression of miR-326 can effectively reduce the level of drug transporters on the cell membrane, increase the intracellular accumulation of drugs, and restore the sensitivity of cells to chemotherapeutic drugs.

Changes in the activity of drug-metabolizing enzymes are also a key factor affecting the efficacy of tamoxifen. Tamoxifen in the body is mainly metabolized into the active metabolite endoxifen by the cytochrome P450 enzyme system, among which the activity of the CYP2D6 enzyme plays a crucial role. Experiments have found that miR-200c can regulate the expression level of CYP2D6 and interfere with the metabolic efficiency of tamoxifen. In patients with low CYP2D6 activity, the high expression of miR-200c may lead to more severe drug resistance. This finding provides a new theoretical basis for personalized medicine.

3. Clinical significance of miRNA in tamoxifen resistance of breast cancer

3.1 Application value of miRNA as a biomarker for drug resistance

The expression profile of specific miRNAs can accurately predict the response of breast cancer patients to tamoxifen treatment, providing important references for the selection of personalized treatment plans. The high expression of miR-21 is significantly associated with poor disease-free survival and overall survival, and it can independently predict the risk of treatment failure in multivariate analysis [7]. As a direct transcriptional target of p53, the expression level of miR-34a can reflect the DNA damage repair ability and apoptosis sensitivity of tumor cells.

Circulating miRNAs in the blood are also regarded as ideal liquid biopsy biomarkers. Changes in the serum level of miR-155 can dynamically reflect the changes in tumor burden during treatment. In patients receiving tamoxifen therapy, a rapid decrease in the serum level of miR-155 in the early stage of treatment (usually within the first 2-4 weeks) generally indicates a good therapeutic response, while the persistent high expression suggests a potential risk of drug resistance. This non-invasive detection method provides clinicians with an effective means to monitor the therapeutic effect in real time.

3.2 Relationship between miRNA expression profile and prognosis evaluation

Gene expression profile analysis shows that miRNAs play a core role in regulating the biological behavior of tumors. By integrating miRNA and mRNA expression data, researchers have constructed a molecular network map containing key regulatory nodes. In this network, the core miRNAs in the central region often have stronger prognostic predictive capabilities [8]. Members of the miR-200 family can not only regulate the epithelial-mesenchymal transition process but also affect a series of biological processes such as angiogenesis and immune escape. Changes in their expression levels have a comprehensive impact on patient prognosis.

The integrated analysis of multi-omics data creates new opportunities for accurate prognosis evaluation. The comprehensive prognostic scoring system constructed by combining multi-level information such as genomic mutations, copy number variations, DNA methylation, and miRNA expression can more accurately predict the survival probability of individual patients. This method not only takes into account the molecular heterogeneity of tumors but also can identify prognostic-related information that cannot be covered by traditional pathological parameters, providing more comprehensive support for clinical decision-making.

3.3 Role of miRNA in monitoring therapeutic response

Continuous monitoring of the dynamic changes in miRNA expression levels during the treatment process can provide real-time feedback for evaluating the therapeutic effect and adjusting the treatment strategy. In the neoadjuvant endocrine therapy stage, the early decrease in the expression levels of miR-21 and miR-155 in tumor tissues (usually within the first 2-4 weeks after the start of treatment) occurs earlier than the reduction in tumor volume observed by imaging examinations. This temporal precedence makes miRNAs ideal early efficacy prediction indicators.

The occurrence of treatment-related side effects is also related to the expression pattern of specific miRNAs. In patients receiving long-term tamoxifen treatment, the increase in the plasma level of miR-122 is significantly associated with the risk of abnormal liver function. By regularly monitoring this indicator, clinicians can take preventive intervention measures before the appearance of side effects, improving the safety and compliance of treatment. Similar associations may exist in other common side effects such as cardiovascular toxicity and decreased bone mineral density.

Early identification of drug resistance is crucial for timely adjustment of treatment plans. In the early stage of acquired drug resistance, a series of adaptive changes in miRNA expression occur in tumor cells. The upregulation of miR-181b and the downregulation of miR-126 are regarded as early events in the development of drug resistance, occurring months or even years before the manifestation of clinical symptoms. Through the detection of these early biomarkers, it is expected to achieve early warning of drug resistance and preventive intervention [9].

4. MiRNA-Based strategies for reversing tamoxifen resistance in breast cancer

4.1 Design and application of miRNA mimics and inhibitors

In response to the functional loss or overactivation of specific miRNAs, researchers have developed corresponding miRNA mimics and inhibitors (anti-miRs) to restore the regulatory balance. miRNA mimics are chemically synthesized double-stranded RNA molecules with sequences identical to those of target miRNAs, which can mimic the function of endogenous miRNAs. During in vitro experiments, transfecting miR-34a mimics into drug-resistant breast cancer cells can significantly enhance the sensitivity of cells to chemotherapeutic drugs and induce cell cycle arrest and apoptosis.

The anti-miR technology exerts its effect by specifically binding antisense oligonucleotides to overexpressed miRNAs and neutralizing their activity. In humanized tumor xenograft models, systemic administration can significantly reduce the activity of miR-21 in tumor cells, restore the expression levels of tumor suppressor genes such as PTEN and PDCD4, enhance the anti-tumor effect of chemotherapeutic drugs.

Optimizing the carrier system is one of the key factors for the success of miRNA therapy [10]. Different delivery systems such as cationic liposomes, polymer nanoparticles, and viral vectors have their own advantages and disadvantages. Due to their good biocompatibility and high transfection efficiency, lipid nanoparticles have enabled several miRNA drugs based on this technology to enter the clinical trial stage. These formulations can protect miRNAs from nuclease degradation and promote their effective uptake and release in target cells.

4.2 Combined application of miRNA and other therapeutic approaches

A single therapeutic approach is often difficult to overcome the complex drug resistance mechanism, so combined therapy has become a key direction to enhance the therapeutic effect. The combined application of miRNA therapy and traditional chemotherapeutic drugs shows a synergistic effect. In breast cancer cell lines with paclitaxel resistance, the combined administration of miR-200c mimics and paclitaxel can produce a significant synergistic effect. The mechanism is related to the inhibition of ZEB1/2 transcription factors by miR-200c, thereby restoring the expression of E-cadherin and enhancing drug-induced apoptosis.

The combined application of targeted therapeutic drugs and miRNAs also shows broad prospects. In HER2-positive breast cancer cells, the combined use of trastuzumab and miR-34a mimics can significantly enhance the anti-tumor effect. miR-34a can not only directly inhibit the proliferation of tumor cells but also reduce the expression level of PD-L1 and enhance the anti-tumor immune response of the body. This dual mechanism makes the effect of combined therapy much

better than that of single therapy [5].

The combination of immune checkpoint inhibitors and miRNA therapy highlights a new trend in tumor treatment. As an important immune regulatory factor, changes in the expression level of miR-155 can affect the function of immune cells in the tumor microenvironment. In the triple-negative breast cancer model, upregulating miR-155 can enhance the antigen-presenting ability of dendritic cells, trigger the T cell-mediated anti-tumor immune response, and synergistically exert the anti-tumor effect together with PD-1 antibodies.

4.3 Development trend of novel miRNA therapeutic strategies

MiRNA editing based on CRISPR/Cas9 technology provides a new tool for accurately regulating miRNA expression. By designing specific guide RNAs, researchers can permanently correct miRNA expression defects at the genomic level. In breast cancer cell lines, knocking out the gene locus of the oncogenic miR-21 using CRISPR technology can stably eliminate its oncogenic effect without off-target effects. This gene editing method provides a theoretical basis for the radical treatment of diseases.

Circular RNA (circRNA), as a natural miRNA sponge, can specifically bind to and sequester specific miRNAs, thereby eliminating their inhibitory effect on target genes. The exosome-mediated miRNA delivery system opens up a new way for targeted therapy. Exosomes derived from tumor cells have natural targeting and penetration capabilities and can successfully deliver the carried miRNAs into recipient cells. Modifying the surface proteins of exosomes using genetic engineering technology can further enhance their targeting specificity and therapeutic efficacy. Engineered exosomes loaded with tumor-suppressive miRNAs show great application potential in breast cancer treatment.

5. Conclusion

MiRNAs play a multi-level and multi-target regulatory role in the mechanism of tamoxifen resistance in breast cancer. Their abnormal expression not only affects the basic biological characteristics of tumor cells but also is directly related to the response of patients to endocrine therapy. With the increasing understanding of the miRNA regulatory network, miRNA-based diagnostic biomarkers and therapeutic strategies are moving from the laboratory to clinical application. Although there are still technical challenges such as the safety of delivery systems and treatment specificity, the great potential of miRNA therapy has been widely recognized. Future research should focus on the development of more accurate personalized treatment plans, select the most suitable miRNA intervention strategy based on the unique molecular characteristics of patients, and multi-disciplinary collaboration will further promote the transformation of miRNA basic research results to clinical practice, ultimately achieving the goal of precise treatment of breast cancer and bringing better therapeutic effects and quality of life to patients.

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References

[1] Zhu B, Qin X H. Research Progress of miR-27a in Breast Cancer Drug Resistance [J]. Medical Recapitulate, 2020, 26(7): 1309-1313. (In Chinese)

[2] Yang Y, He X, Gong P J, et al. Construction of a Prognostic Risk Model for Estrogen Receptor-Positive Breast Cancer Patients Based on TCGA Database [J]. Journal of Wuhan University (Medical Edition), 2022, 43(2): 243-249. (In Chinese)

[3] Lei Z X, Yang H Y, Xie H, et al. Research Progress of miRNA in Breast Cancer [J]. Journal of Huazhong Agricultural University, 2024, 43(5): 149-156. (In Chinese)

[4] Sun L, Jiao W Y, Cui Q F, et al. tRF-Leu Reverses Breast Cancer Cells Chemoresistance by Regulation of BIRC5 [J]. Discover Oncology, 2024, 15(1): 449-449.

[5] Ding Y Z, Xia Z W, Yan Z, et al. Expression of Phosphatase and Tensin Homolog Deleted on Chromosome Ten on the Development of Cisplatin Resistance in Breast Cancer by TGF-beta(1) Signal Pathway [J]. Journal of Biomaterials and Tissue Engineering, 2021, 11(10): 1900-1907.

[6] Saliha M, Junaid D B, Khalid I, et al. Biofabricated Platinum Nanoparticles: Therapeutic Evaluation as a Potential Nanodrug against Breast Cancer Cells and Drug-Resistant Bacteria [J]. RSC Advances, 2021, 11(40): 24900-24916.

[7] Xiaochuan L, Jun Y, Xudong Z, et al. ATF3 Modulates the Resistance of Breast Cancer Cells to Tamoxifen through an

N6-Methyladenosine-Based Epitranscriptomic Mechanism [J]. Chemical Research in Toxicology, 2021, 34(7): 1814-1821.
[8] Zhou L L, Shen M, Zhang Q Y. Effect of B7 Homolog 4 Molecule on miRNA Expression Profile of Breast Cancer Cells [J]. Journal of Fujian Medical University, 2024, 58(2): 82-92. (In Chinese)
[9] Zhou K, Tian B X, Yin X X, et al. Effect of miRNA-381 Regulating CCNA2 Expression on Proliferation, Migration and Prognosis of Breast Cancer [J]. Chinese Journal of Clinical Laboratory Science, 2022, 40(9): 667-672. (In Chinese)
[10] Rui X, K. H P, Jiong Z, et al. Lead Based Development and Evaluation of Selective Estrogen Mimics in Tamoxifen Resistant Breast Cancer [J]. Abstracts of Papers of the American Chemical Society, 2014, 248.