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Progress in Utilizing Circ RNAs for Initial Breast Cancer Diagnosis and Prediction

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ABSTRACT
Early detection of breast cancer, a prevalent cancer in women, is vital. Circular RNAs (circRNAs), unique non-coding RNAs characterized by closed circles and prevalent in numerous biological fluids, hold promise for research as biomarkers. Studies have shown that circRNAs are involved in the occurrence and development of breast cancer through a variety of mechanisms, including functioning as microRNA sponges, RNA-binding protein conjugations, regulating gene expression and translation templates, and have significant research value. This examination explores the molecular function of circRNAs in the advancement of breast cancer, the progression of clinical trials aimed at early detection and prognosis, and the exploration of their detection techniques and prospective development opportunities.

KEYWORDS
Breast cancer; CircRNAs; Biomarkers; Diagnosis; Prognosis

1 Introduction

Breast Cancer, a common malignant tumor in women, results from mutations in the epithelial cells of the ducts or terminal lobular units of the breast. The tumor is characterized by rapid proliferation, invasive growth and metastasis. Early diagnosis is crucial for improving the prognosis of patients, and genetic diagnosis has received extensive attention due to its high timeliness and accuracy. Among all kinds of test samples, body fluid specimens such as blood and tissue are ideal test carriers because they are easily accessible and rich in biological information. Circular RNAs (circRNAs) are widely distributed in these body fluids and are closely related to the occurrence and development of breast cancer, and their abnormal expression patterns provide new molecular targets for early diagnosis and prognosis assessment.

1.1 Clinical challenges of breast cancer

Breast cancer rose to become the world's second most prevalent cancer in 2022, leading the charts among women, accounting for 23.8% [1] of all cancer cases in women. The initial stages of breast cancer (stage I-II) constitute 73.1% of all breast cancer cases, making the early identification of patients essential [2]. Diagnostic tests can effectively screen for early-stage or precancerous lesions of the tumor [3]. However, the current diagnosis and treatment of breast cancer face two major risks: the invasive risk of pathological biopsy and the lagging effect of imaging, which are not conducive to real-time assessment [4] of the tumor. Genetic testing technology can improve the accuracy of breast cancer diagnosis at the molecular level, provide new ideas for building a dynamic monitoring system, help optimize treatment plans, and play a key role [5] in prognosis assessment and genetic risk analysis.

1.2 Biological characteristics of circRNA

Circular RNAs (circRNAs) consist of non-coding Rnas that are covalently sealed and can withstand degradation by exonucidase. These entities exhibit enhanced stability and a higher abundance compared to linear mRNAs, maintaining their sequence integrity [6]. circRNAs are widely involved in human disease progression [7], and these molecules are involved in breast cancer progression through mechanisms such as acting as miRNA sponges, as RBP conjukers, as translation templates, and as transcriptional regulators [8] (Figure 1). An in-depth investigation into how circRNAs are produced in breast cancer could elucidate their biological roles and enhance their practical clinical use. In addition, circRNA is widely expressed in body fluids such as blood and tissues and has the potential to become a biomarker for breast cancer. Circular RNAs were initially discovered through RNA sequencing, and then specific circRNAs were mainly verified by qRT-PCR and digital PCR (ddPCR). With the rapid progression in sequencing techniques and bioinformatics, databases like circBase [9] and CIRCpedia v2 [10] are continuously evolving, offering crucial backing for additional studies.

1.3 Study significance

circRNA is highly stable, conserved and specific, and is widely present in blood and tissues and readily accessible.

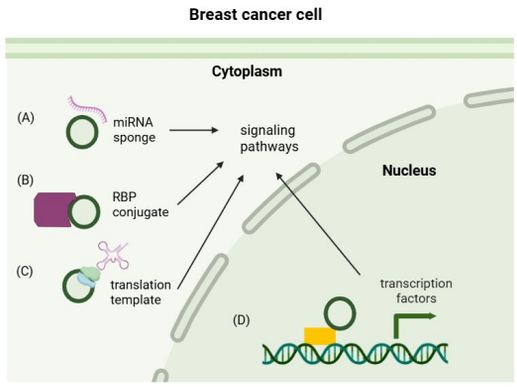

Figure 1 Regulatory mechanisms of circRNAs. (A) circRNAs can spongy miRNAs and control the expression of related genes; (B) circRNAs can be coupled with BRP; (C) circRNAs can serve as translation templates; (D) circRNA can act as a transcriptional regulator.

circRNAs are closely involved in the occurrence and development of breast cancer and can serve as promising diagnostic and prognostic biomarkers [11]. Ongoing advancements in genetic testing techniques aid in accurately diagnosing and treating breast cancer, while the use of multi-gene testing (MGA) in initial-stage patients facilitates immediate monitoring and prognostic assessment [5]. Consequently, a thorough evaluation of circRNA's clinical effectiveness in early breast cancer diagnosis and prognosis prediction can yield crucial molecular proof for the practice of precision medicine.

2 Application of circRNA in the early diagnosis of breast cancer

2.1 Screening and identification of specific circRNAs

Globally, breast cancer ranks among the top malignant cancers in women, with its significant mortality rate underscoring the need for prompt diagnosis and treatment. In recent years, circular RNAs (circRNAs), as a new type of non-coding RNA, have become ideal biomarkers for the early diagnosis of breast cancer owing to their steadiness in bodily fluids and crucial function in the formation and growth of tumors . (Table 1.) The evaluation of the clinical efficacy of biomarkers depends not only on the validation of routine test specimens (such as plasma, urine), but also on diagnostic efficacy analysis (such as ROC curve) to assess their disease-suggesting role. The ROC curve is a statistical tool used to measure the overall performance of diagnostic tests. AUC values can be used to compare the diagnostic performance of different markers and assist in determining the best diagnostic approach, including combined diagnostic strategies [12].

Using microarray methods, scientists detected varying levels of circRNA expression for individuals suffering from breast cancer. Initially, hsa_circ_0008673 was recognized for its notably elevated expression levels in breast cancer tissues. Then, with large sample validation, its diagnostic efficacy (AUC=0.833) was superior to that of CA153 (AUC=0.697) and CEA (AUC=0.520) [13]. The expression of hsa_circ_0104824 decreased in BC tissues and peripheral blood, and the expression was specific and closely related [14] to the tumor stage, grade and metastasis of breast cancer.

Likewise, the process of screening biomarkers may rely on circRNA databases or findings from studies on functional mechanisms. CircPRMT5 exhibits an AUC of 0.932 [15] ,while circ_0047303 shows notable tissue expression, registering an AUC of 0.7 [16]. With an AUC value of 0.799, has_circ_0000615 surpasses conventional biomarkers in early breast cancer diagnosis [17].

The joint identification of several circular RNAs proved to be more diagnosable than a solitary circRNA. Although circFBXW7, circABCB10, and circ0103552 all exhibited AUC values close to 0.700, their combined usage resulted in an AUC reaching up to 90.8%, signifying an elevated [18] diagnostic significance. The combined detection of hsa_circ_0000091, hsa_circ_0067772 and hsa_circ_0000512 significantly increased [19] the positive rate of BC. The joint diagnostic effectiveness of Circ-ELP3 and Circ-FAF1 is [20] superior.

2.2 Challenges and optimizations

Although diagnostic performance evaluation methods have been relatively standardized, there are still differences among different studies. In the application of early diagnosis of breast cancer, circRNA sample acquisition and processing are crucial steps. Different laboratories mainly collect blood and tissue samples, and factors such as the criteria included in the collection, the testing and processing procedures, and the testing platform (reagents/instruments) may still affect diagnostic efficacy.

New biomarker sources are worth exploring and discovering, such as circRNAs in extracellular vesicles (EVs) in plasma,

which is applicable in the initial detection [21]of breast cancer. Currently, real-time quantitative PCR and microarray analysis techniques are mainly used, while new sequencing techniques, such as Indro-RT-mediated circRNA sequencing (IMCR-seq), can enhance detection efficiency and comprehend [22] siveness.. At the same time, it is important to establish a unified inclusion standard for breast cancer patients. As research progresses, the optimization of bioinformatics tools is an important part of improving the efficiency of screening and identification, such as the use of machine learning algorithms for optimization [23].

Table 1 Circular RNA markers with diagnostic potential in breast cancer

circRNA	Sample	Expression changes	Clinical association	Detection methods	AUC	References
hsa_circ_0008673	Plasma	↑	Degree of malignancy of tumor	qRT-PCR	0.833	[13]
hsa_circ_0104824	Tissue Plasma	↓	Breast cancer tumor staging, grading, and metastasis	qRT-PCR	0.823 0.849	[14]
circPRMT5	Serum	↑	Tumor size, TNM stage, lymph node metastasis, distant metastasis	RT-qPCR	0.932	[15]
circ_0047303	Organization	↑	Tumor size, tumor stage, and lymph node metastasis	qRT-PCR	0.7	[16]
hsa_circ_0005046 hsa_circ_0001791	Tissue	↑ ↑	no	qRT-PCR	0.77 1.0	[24]
Has_circ_0000615	Plasma	↑	no	qRT-PCR	0.799	[17]
circFBXW7 circABCB10 circ0103552	Serum	circFBXW7 ↓ circ0103552 ↓ circABCB10 ↑	no	qRT-PCR	0.908	[18]
hsa_circ_0000091 hsa_circ_0067772 hsa_circ_0000512	Plasma	hsa_circ_0000091 ↓ hsa_circ_0067772 ↑ hsa_circ_0000512 ↑	no	qRT-PCR	0.974	[19]
Circ-ELP3 Circ-FAF1	Serum	Circ-ELP3 ↑ Circ-FAF1 ↓	no	qRT-PCR	0.891	[20]

indicates high expression, ↓ indicates low expression. Both RT-qPCR and qRT-PCR represent real-time quantitative PCR

3 Investigating circRNA's function in predicting breast cancer outcomes

3.1 Prognostic circRNAs

The screening of prognostic circRNAs is based on the detection of patient specimens to determine their differential expression patterns (such as high/low expression). Its association with breast cancer prognosis was evaluated by Kaplan-Meier survival analysis, and its biological role in breast cancer progression was analyzed using in vivo and in vitro models. Kaplan-Meier(KM) survival analysis is a method of constructing survival curves as functions of time, which can be intuitively used to analyze the incidence [25] of a given event. In prognostic studies of biomarkers, after potential biomarkers were initially identified through mechanism research, further validation of their clinical predictive efficacy was still needed, and KM analysis became one of the important assessment methods. Integrating KM analysis with Log-rank test or Cox proportional hazards model enhances the evaluation of statistical variances. Time-dependent area under the ROC curve (AUC) can be used to quantify the ability [26] of markers to predict future clinical outcomes.

The presence of several circular RNAs (circRNAs) is intimately linked to the prognosis and clinical traits of breast cancer. (Table 2) In triple-negative breast cancer (TNBC), circCD44 [27] , circFGFR4 (lower overall survival (OS) [28]and higher recurrence rate for patients exhibiting elevated expression levels) and circEPSTI1 (reduced disease-free survival and overall survival in patients with high expression)[29] . Each of these factors is intimately linked to the dimensions of tumors, their spread, and survival rates in breast cancer patients, with elevated expression indicating a grim outlook.

3.2 CircRNA regulatory mechanism and its function in breast cancer

In triple-negative breast cancer (TNBC), multiple circular RNAs (circRNAs) promote tumor progression through different mechanisms:

circCD44 influences the advancement of TNBC [27] via the miR-502-5p/KRAS and IGF2BP2/Myc pathways. circACTN4 collaborates with FUBP1 in controlling MYC transcription and fostering the development of BC [30]. circHMCU sponges the let-7 family and increases the expression [31] of MYC, HMGA2, and CCND1. circATP2C1 in BC cells stimulates miR-432 and

miR-335 to increase CCND1 levels [32]. circFGFR4 regulates the miR-185-5p/CXCR4 axis in TNBC and participates in immune evasion [28]. Circepsti1-mir-4753/6809-bcl11a axis affects proliferation and apoptosis of TNBC, and circEPSTI1 is expected to become an independent prognostic marker [29] for survival in TNBC patients.

Table 2 Functional mechanisms and clinical implications of prognostic circRNAs

circRNA	Molecular subtypes	Expression levels	Functional mechanisms	Prognostic indicators	References
circCD44	TNBC	↑	miRNA sponge		[27]
circACTN4	no	↑	Regulating gene transcription		[30]
circHMCU	no	↑	miRNA sponge	OS	[31]
circATP2C1	no	↑	miRNA sponge	OS	[32]
circFGFR4	TNBC	↑	miRNA sponge	OS	[28]
circEPSTI1	TNBC	↑	miRNA sponge	OS, DFS	[29]

TNBC= triple-negative breast cancer, ↑ indicates high expression, ↓ indicates low expression, PFS (progression-free survival), OS (overall survival), DFS (disease-free survival)

4 Current challenges and future directions

4.1 Research limitations

Research on circular RNAs (circRNAs) in the prognosis assessment of breast cancer is progressing rapidly at present, but there are still many limitations that affect the effectiveness and reliability of their clinical application. Insufficient sample size is a significant problem. Most of the existing studies are based on small samples and lack large-scale, multi-center clinical validation. As an illustration, research involving microarray analysis on merely three sets of breast cancer and nearby normal tissues pinpointed 2,021 distinct circRNA contenders, but the universal applicability of the results still needs to be verified through repeated experiments with larger sample sizes.

Secondly, the functional mechanisms of circRNAs still need to be analyzed in depth. Research indicates that circRNAs play a role in breast cancer's emergence and progression [33] through their function as miRNA sponges and interactions with proteins, yet the comprehension of their distinct biological roles and action mechanisms is still restricted. Furthermore, it's crucial to focus more on the operational mechanisms of circRNAs in various breast cancer subtypes, and a thorough comprehension of their function in breast cancer aids in accurate diagnosis and the development of specific therapeutic drugs, enhancing patient outlook.

Finally, with the progress of circRNA research, its biological characteristics and functional mechanisms are constantly being updated, closely related to disease progression, and the clinical needs are increasing, which requires the development of more specialized circRNA tools to meet these needs [34]. Therefore, there are currently limitations in the application of circRNA in the early diagnosis and prognosis assessment of breast cancer in terms of sample size, functional mechanisms, and biological tools.

4.2 Emerging fields

With the advancement of technology, researchers should pay attention to the application of circRNA in liquid biopsy. The rise of liquid biopsy technology has made it possible to diagnose cancer early by analyzing circRNAs in the blood. As an illustration, the extraction of circRNAs from plasma exosomal for non-invasive liquid biopsies facilitates the identification and treatment of breast cancer [35]. With the deepening of research on the functional mechanisms of circRNAs, targeted therapy based on circRNAs has also emerged as a new research direction.

Interdisciplinary collaboration is also an important direction for future research on the clinical application of circRNAs. Research on circRNA involves multiple disciplines such as molecular biology, clinical medicine, and data science. The clinical application of circRNA can be accelerated by integrating knowledge and technology from different disciplines. For example, by utilizing emerging sequencing technologies and data analysis techniques such as machine learning, it is possible to identify circRNAs related to breast cancer within vast genomic data, and to construct effective predictive models to assess patient prognosis [36].

5 Conclusions

Circular RNAs (circRNAs), a rising biomolecule, have recently demonstrated significant promise in early breast cancer diagnosis and prognosis evaluation, thanks to their distinctive structure and stability. Research indicates a strong correlation between certain circRNAs and both the emergence and progression of breast cancer, as well as a substantial link to clinicopathological traits and predictions of patient survival. These findings offer a fresh perspective on the

biological characteristics and clinical manifestations of breast cancer.

Our examination of various studies revealed that circRNA's role in breast cancer is multifaceted and varied. Its regulatory network can influence key biological processes such as proliferation, migration and invasion of tumor cells, thereby promoting the occurrence and development of tumors. This discovery not only broadens our understanding of breast cancer biology, but also provides new biomarkers for clinical practice, offering possible evidence for early diagnosis and prognosis assessment.

Furthermore, using exosomal circRNA as a biomarker in liquid biopsies shows significant promise for non-intrusive detection and ongoing tracking of breast cancer. By analyzing circRNA in body fluids, it is possible to monitor tumor changes in real time and provide support for personalized treatment. This non-invasive testing approach not only enhances patient comfort but also has the potential to increase the chances of early detection of breast cancer, thereby improving patient survival rates.

However, despite the many advantages that circRNA has shown in breast cancer research, there are still some challenges in its clinical translation. Currently, the detection techniques of circRNAs is not regulated and the mechanism of circRNA analysis is not well studied. Simultaneously, the limited large-scale clinical validation hinders the widespread application of circRNA as a biomarker. Thus, future investigations will require increased investment in these domains to progress the clinical use of circRNA.

Future advancements in breast cancer diagnosis and treatment may be propelled by the integration of multi-omics data and AI technology, enhancing the application of circRNA. A comprehensive analysis of multilayered data including genomes, transcriptome, and epigenome provides insights into the biological function of circRNAs and their role in tumorigenesis and development. At the same time, the introduction of artificial intelligence technology will accelerate the analysis of circRNA-related data and improve its accuracy and efficiency in clinical decision-making.

Taken together, circRNAs exhibit considerable promise in breast cancer research, offering avenues for biomarker development and targeted therapy. Future studies should focus on establishing standardized circRNA detection methods, elucidating underlying mechanisms, and advancing clinical validation to enable precise diagnostic and therapeutic applications in breast oncology. Through multidisciplinary collaboration and innovation, it is hoped that more effective diagnosis and treatment options will be made available to breast cancer patients to improve their quality of life and survival prognosis.

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