REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

MicroRNAs in Breast Cancer: Insights into Diagnosis, Mechanisms, and Targeted Therapy

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Abstract

Breast cancer (BC) is the most prevalent cancer amongst women and a major contributor to cancer-related death globally. It accounts for a significant portion of new cancer cases annually, reflecting its widespread prevalence and public health impact. Advances in molecular classification have identified subtypes such as luminal A, luminal B, HER2-positive, and triple-negative breast cancer (TNBC), which have revolutionized personalized treatment approaches. Early detection methods, including advanced diagnostic imaging and molecular biomarker profiling, have further contributed to improved survival rates. However, challenges such as metastasis to distant organs and recurrence of the disease after initial treatment remain significant obstacles to achieving long-term remission. Numerous studies have spotlighted the critical role of microRNAs (miRNAs) in BC pathogenesis. Through regulating gene expression, miRNAs influence various processes such as tumor growth, metastasis, and therapy resistance. Their biogenesis and mechanisms of action, particularly their roles in suppressing translation and promoting mRNA degradation, highlight their potential as diagnostic biomarkers and therapeutic targets. This growing understanding of miRNAs is paving the way for innovative and precise approaches to BC management.

Keywords: Breast cancer; Diagnosis; miRNAs; miRNA biogenesis; Treatment.

1. Introduction

Breast cancer (BC) remains a pressing global health challenge, representing the most common malignancy among women and a significant cause of cancer-related deaths. Its high prevalence and mortality underscore the urgency of advancing our understanding of its complex nature and refining approaches to diagnosis and treatment **(Trapani et al., 2022)**. BC is a heterogeneous disease, exhibiting diverse molecular and genetic profiles, which have prompted the development of precise classification systems and personalized therapeutic strategies **(Olopade et al., 2008)**.

The exploration of noncoding RNAs (ncRNAs), particularly microRNAs (miRNAs), has unveiled their pivotal role in gene regulation and their implications in cancer biology. MiRNAs, small RNA molecules involved in post-transcriptional

gene silencing, are increasingly recognized for their contributions to BC pathogenesis **(Liu et al., 2017)**. Insights into miRNA biogenesis and their mechanisms of action have expanded the potential for miRNA-based diagnostic and therapeutic applications. Acting as either oncogenes or tumor suppressors, miRNAs influence critical processes in BC, including proliferation, metastasis, and treatment resistance **(Bertoli et al., 2015)**.

This review aims to provide a comprehensive overview of BC, with a focus on its classification, diagnostic strategies, and treatment approaches. Furthermore, it will explore miRNA biogenesis and mechanisms of action, emphasizing their pivotal role in advancing BC diagnosis and treatment, and highlighting their potential to shape future clinical practices.

2. Breast cancer

Globally, BC is the most common malignancy in women with high mortality and incidence rates **(Yun et al., 2023)**. Women today have a one in eight lifetime risk of acquiring BC (**Arnold et al., 2022)**. Screening, early diagnosis and proper effective and targeted treatment are deemed as the cornerstones for improved BC survival rates. However, the ability of BC to metastasize to distant organs such as brain, bone, lung and liver as well as BC recurrence after treatment and eradication of the primary tumor make it almost difficult to cure **(Sadoh et al., 2021)**. BC is a complicated and heterogeneous disease with numerous genetic and molecular abnormalities **(Zubair et al., 2021)**.

2.1. Epidemiology of breast cancer

Breast cancer is a significant global and national public health issue, being one of the leading causes of cancer incidence and mortality. BC is the second most common cancer for both genders both globally and in Egypt, contributing to 11.5% and 17.8% of new cancer cases in 2022, respectively. Among females, BC is the most prevalent cancer worldwide (23.8%) and in Egypt (34.9%) **(Bray et al., 2024)**.

Regarding mortality, BC ranks fourth globally and second in Egypt for both genders, responsible for 6.8% and 10.1% of cancer-related deaths, respectively. It is the leading cause of cancer deaths among women globally, making up 15.4% of female cancer deaths, and in Egypt, it accounts for 22% of female cancer deaths, second only to liver cancer **(Bray et al., 2024)**.

2.2. Molecular subtypes of breast cancer

Breast cancer exhibits considerable genetic and clinical heterogeneity, manifesting in distinct subtypes. The most widely recognized classification relies on immunohistochemical profiling, which assesses the expression of key hormone receptors: estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). This classification framework delineates BC into four primary subtypes: luminal A, luminal B, HER2-positive, and triple-negative breast cancer (TNBC) **(Al-thoubaity, 2020; Johnson et al., 2021)**.

2.3. Diagnosis of breast cancer

Breast cancer diagnosis relies on a combination of imaging techniques and molecular biomarker testing to ensure early detection and precise treatment planning. Imaging methods like mammography (the gold standard), ultrasonography, magnetic resonance imaging (MRI), and positron emission tomography (PET) provide detailed information on tumor morphology, size, and location **(Chung et al., 2024)**. Molecular biomarker tests, including hormone receptor (ER and PR) status, HER2 overexpression, and genetic markers like BRCA1/2 mutations, play a pivotal role in classifying the cancer subtype and predicting treatment response **(Duffy et al., 2017; Sadeghi et al., 2020)**. Serum markers like CA15.3 and CEA further aid in monitoring disease progression and treatment efficacy **(Duffy et al., 2010; Banin Hirata et al., 2014)**.

2.4. Treatment of breast cancer

Breast cancer treatment integrates surgery, radiation, chemotherapy, and targeted therapies to manage the disease effectively. Surgery, often the first-line approach, includes lumpectomy or mastectomy with advances like skin-sparing techniques improving outcomes **(Magnoni et al., 2021; Veronesi et al., 2023)**. Radiation therapy follows surgery to eradicate residual cancer cells, while chemotherapy is used pre- or post-surgery and for metastatic disease (**Mir, 2023; Mir and Mir, 2023)**. Targeted therapies, such as hormonal treatments for hormone receptor-positive cancers, HER2-targeted drugs like Trastuzumab, and newer options like Poly ADP-ribose polymerase (PARP) inhibitors for BRCA-mutated cancers, offer

personalized and precise treatment **(Abraham and Staffurth, 2020; Singh et al., 2021; Yoon and Oh, 2024)**. Emerging therapies targeting specific molecular pathways, including PI3K inhibitors and CDK4/6 inhibitors, further enhance treatment efficacy and patient survival **(Wekking et al., 2024; Zhang et al., 2024)**.

3. Noncoding RNA

Noncoding RNAs constitute the majority of the human transcribed genome surpassing protein-coding RNA, which comprises only < 3% of the genome. This class of RNA plays diverse roles in a multitude of cellular processes and has been implicated in many pathological conditions, especially cancer **(Zhang et al., 2019)**. ncRNA can be categorized based on the length into two groups small and long ncRNAs. Small RNAs, less than 200 nucleotides, include various types such as miRNA, small interfering RNA (siRNA), small nucleolar RNA (snoRNA), small nuclear RNA (snRNA) and PIWI-interacting RNAs (piRNA). While long ncRNA molecules, more than 200 nucleotides, include long non-coding RNAs (lncRNAs), pseudogene, circular RNA (circRNA) **(Figure 1) (Parasramka et al., 2016; Yan and Bu, 2021)**.

4. Overview of miRNA discovery and historical context

MicroRNAs are 18-25 nucleotides single-stranded small non-coding RNA that have a vital role in genes posttranscriptional regulation **(Xiao et al., 2019)**. miRNAs are one of the most extensively researched classes of ncRNAs; they were initially identified in 1993 in the nematode Caenorhabditis elegans **(Lee et al., 1993)**. It was shown that in order for *C. elegans* larvae to advance from the first (L1) stage to the second (L2) stage, the protein LIN-14 needed to be downregulated. The lin-4 gene played a role in the downregulation of LIN-14; nevertheless, it was found that the lin-4 transcript does not code for a protein. Instead, it generates two short RNAs, one 21 nucleotides long and the other 61 nucleotides long. It was discovered that the longer RNA was a precursor to the shorter RNA. Studies showed that the 3' untranslated region (UTR) of lin-14 mRNA was sequence complementary to the short RNA generated from the lin-4 transcript **(Lee et al., 1993; Wightman et al., 1993)**. Then, it was discovered that LIN-14 is downregulated at the protein level as a result of short lin-4 RNA binding to lin-14 mRNA, and that this is crucial for the developmental progression **(Diermeier and Leask, 2023)**. At first, it was thought that *C. elegans* was the only species that exhibited this type of gene control by a short noncoding RNA. However, in 2000, let-7, another short RNA, was found to play a role in the developmental processes of *C. elegans* larvae **(Reinhart et al., 2000)**. Over the following years, and after the discovery of let-7 in several organisms, including humans, it became clear that these short RNA molecules (miRNA) constitute a large class of ncRNA and are involved in the regulation of multiple genes across numerous eukaryotes **(Pasquinelli et al., 2000)**.

5. miRNA biogenesis

Cells can use various mechanisms to produce functional miRNAs. While the canonical pathway is the standard route, some miRNAs are formed through alternative, non-canonical pathways that bypass one or more canonical steps **(Abdelfattah et al., 2014)**.

5.1. Canonical pathway of miRNA biogenesis

This is the primary pathway for miRNA biogenesis, and it occurs in three main steps. Initially, miRNA is transcribed within the nucleus. This is followed by nuclear processing and subsequent export to the cytoplasm. Finally, cytoplasmic processing takes place, producing the mature miRNA ready for its regulatory functions **(Achkar et al., 2016)**.

5.1.1. miRNA transcription

In the nucleus, RNA polymerase II (Pol II) is responsible for transcription of miRNA genes into a long primary transcript, primary miRNA (pri-miRNA), with a hairpin structure containing miRNA sequence. Pri-miRNA is made up of single-stranded RNA segments at both the 5′ and 3′ sides, a terminal loop, and a 33–35 bp stem **(Komatsu et al., 2023)**.

5.1.2. Nuclear Processing and Export

The microprocessor complex, which includes the double-stranded RNA-binding protein DiGeorge syndrome critical region 8 (DGCR8) and Drosha

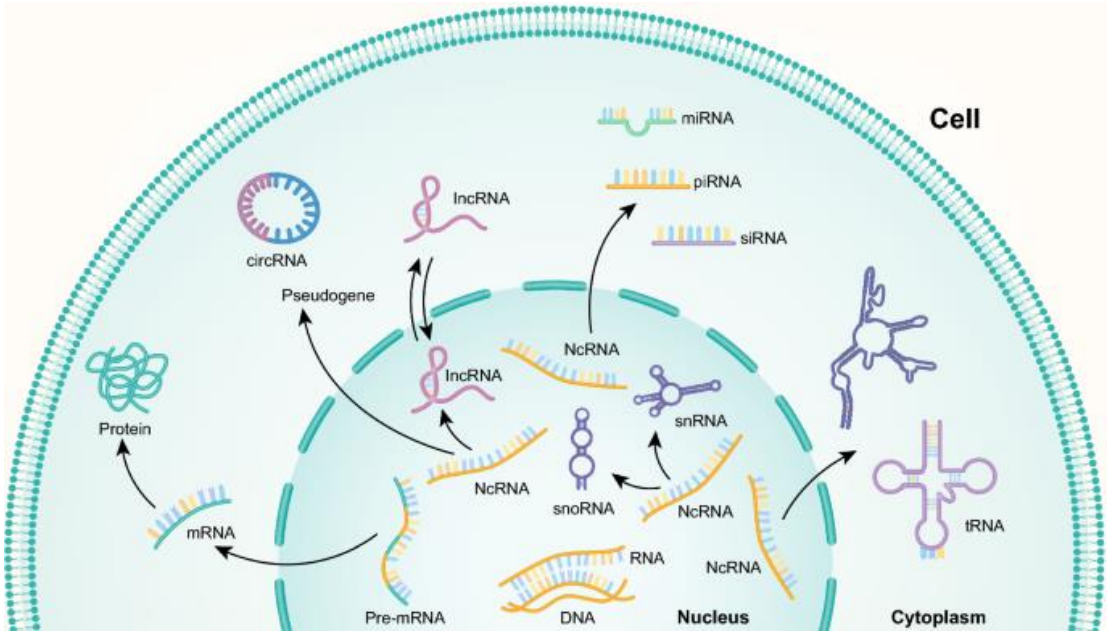

Figure 1. Different classes of ncRNA molecules **(Xu et al., 2020)**

RNase III endonuclease, cleaves pri-miRNA in the nucleus. The two RNase III domains of DROSHA cleaves the pri-miRNAs to liberate ~60–70-nucleotide hairpin-shaped precursor miRNAs (pre-miRNAs). Then, exportin-5 and Ran-GTP interact to export pre-miRNA to the cytoplasm **(Lin and Gregory, 2015; Li et al., 2023)**.

5.1.3. Cytoplasmic Processing

Subsequently, per-miRNA is cleaved by RNase III endonuclease Dicer-TAR RNA-binding protein (TRBP)- PACT complex producing a 20–24 nt miRNA duplex (miRNA:miRNA*, where miRNA is the guide strand and miRNA* is the passenger strand). Then, miRNA duplex becomes associated with argonaute (Ago) proteins inducing the formation of miRNA-induced silencing complex (miRISC) and the miRNA* strand is discarded **(Kimbrough et al., 2020)**. The RISC/miRNA complex and members of the GW182 proteins family, binds to complementary target mRNAs and represses their translation or promotes their degradation **(Figure 2) (Bofill-De Ros and Vang Ørom, 2024)**.

5.2. Noncanonical miRNA Biogenesis Pathways

Using deep sequencing analyses, various RNA classes have been identified that share similar functions and structures with miRNAs but do not follow the usual biogenesis pathway; these are referred to as non-canonical miRNAs. Non-canonical miRNA biogenesis pathways are categorized into two types: Drosha/DGCR8-independent pathways and Dicer-independent pathways **(Abdelfattah et al., 2014)**.

One of the first discovered non-canonical pathways was the mirtron pathway. Mirtrons, which are short pre-miRNAs, are processed by Dicer in the cytoplasm without the need for the nuclear Drosha/DGCR8 complex for pre-miRNA formation. Instead, miRNA hairpins are produced in the nucleus by the action of spliceosomes, which are then exported by Exportin-5 to the cytoplasm and cleaved by Dicer **(Samoilă et al., 2023)**.

6. Mechanism of action of miRNA

6.1. Formation of the miRNA-induced silencing complex (miRISC)

The regulatory effects of miRNAs arise from the formation of the miRISC, which enables the miRNA seed region, comprising nucleotides 2-8 from the 5′ end, to recognize and bind to complementary sites in the 3′ untranslated regions (3′UTR) of mRNA, known as miRNA response elements (MRE). This binding subsequently suppresses translation and induces mRNA degradation **(Dasgupta and Chatterjee,**

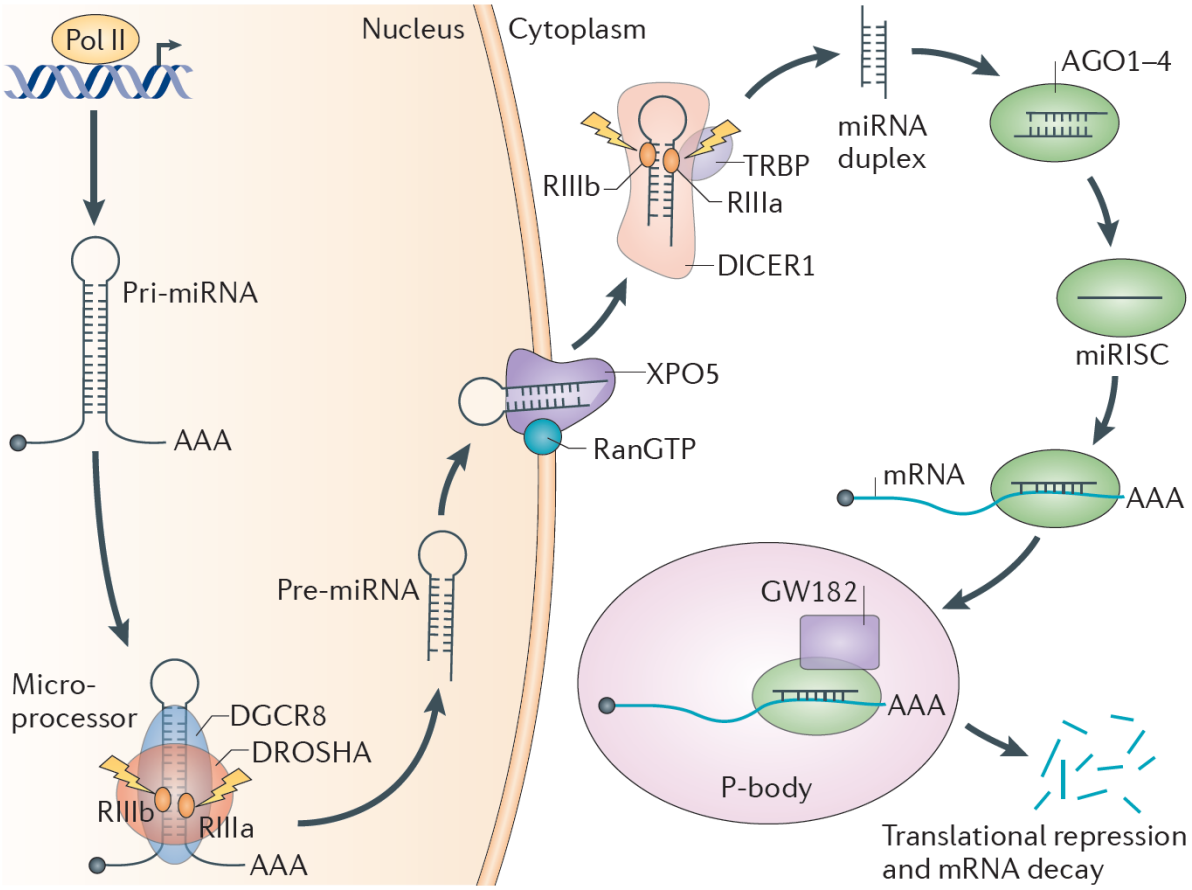

Figure 2. Overview of canonical miRNA biogenesis and mechanism of action **(Lin and Gregory, 2015)**.

2021; Hill and Tran, 2021). Since target recognition depends on short seed sequences, one miRNA can affect the expression of numerous genes, and the expression of a single gene could be regulated by several miRNAs **(Komatsu et al., 2023)**.

6.2. miRNA-mRNA interaction

Seed-matched sites types include one 6mer, two 7mers, and one 8mer **(Grimson et al., 2007)**. The 6mer site perfectly matches the 6-nucleotide miRNA seed. The 7mer-m8 site extends the seed match by incorporating a Watson-Crick pairing with the miRNA's 8th nucleotide. The 7mer-A1 site complements the seed match by pairing with an adenine nucleotide opposite the miRNA's 1st nucleotide. Finally, the 8mer site combines both the m8 and A1 features alongside the seed match **(Figure 3) (Friedman et al., 2009)**.

6.3. Mode of action

The regulation mechanism of miRNA is influenced by the degree of complementarity between specific AGO protein, miRNA, and the target mRNA **(Bartel, 2009)**. Only a small number of miRNAs display nearly complete complementarity with their mRNA targets, allowing for immediate cleavage and degradation of the target mRNA. However, most miRNAs are only partially complementary to their target mRNAs, resulting in mRNA translation repression rather than degradation **(Filipowicz et al., 2008)**.

7. miRNA in Breast Cancer

miRNAs play critical roles in the regulation of gene expression and are increasingly recognized as important players in BC development and progression **(Yan and Bu, 2021)**. miRNAs have been implicated in various hallmarks of cancer, such as proliferation, metastasis, and resistance to therapy **(Abolghasemi et al., 2020)**.

miRNAs can function as oncogenes or tumor suppressors, depending on the genes they regulate **(Annese et al., 2020)**. For instance, miR-21 is one of the most studied oncogenic miRNAs and

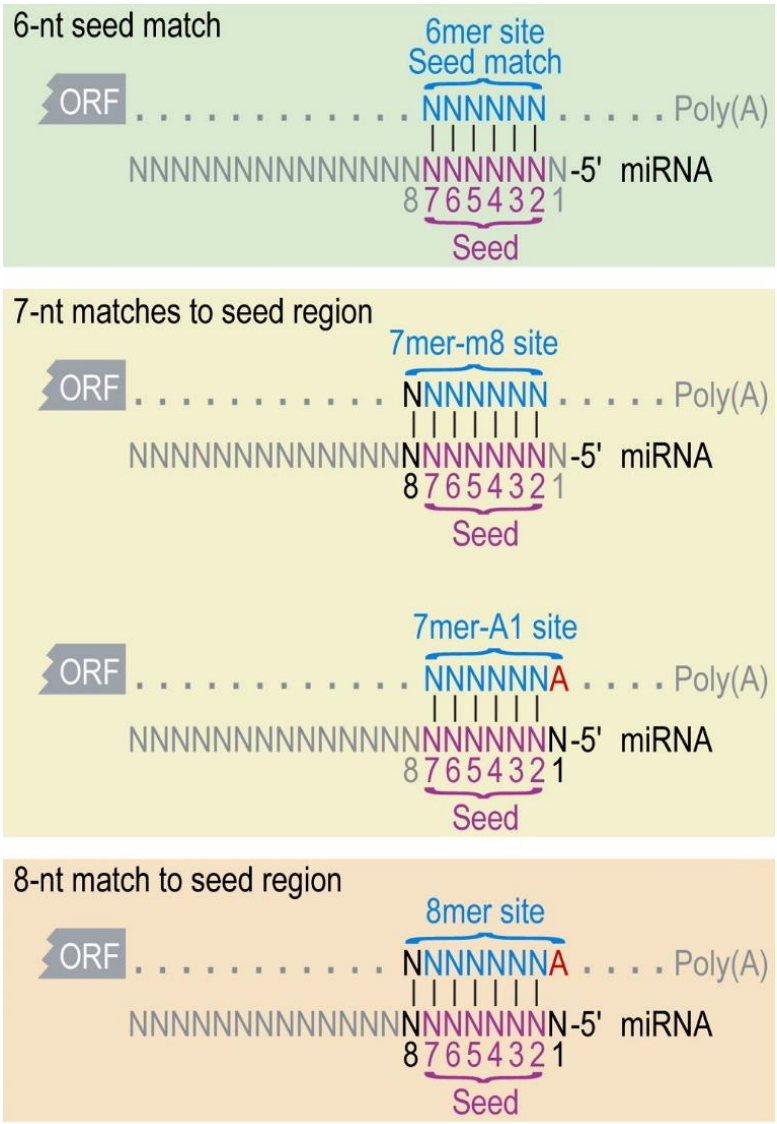

Figure 3. Different types of miRNA seed-matched sites **(Grimson et al., 2007)**

promotes tumor growth by inhibiting tumor suppressor genes like PTEN and PDCD4, enhancing cell proliferation and reducing apoptosis **(Wang et al., 2017)**. Conversely, let-7 family members act as tumor suppressors by targeting oncogenes like RAS and HMGA2, thus inhibiting tumor cell growth **(Lee and Dutta, 2007)**.

The expression profiles of specific miRNAs can serve as diagnostic and prognostic biomarkers in cancer **(Corsini et al., 2012)**. For instance, elevated levels of miR-155 are frequently observed in BC and are associated with greater tumor aggressiveness and lower survival rates. High miR-155 expression is linked to advanced tumor stages, making it a promising marker for poor prognosis in BC **(Grimaldi et al., 2020)**. Similarly, in ovarian cancer, overexpression of miR-200 family members correlates with advanced disease stages, underscoring their role as potential indicators of cancer progression (**Zhang and Lu, 2020)**.

MicroRNAs have been extensively studied in BC. Strategies targeting miRNAs involve either inhibiting oncogenic miRNAs (using miRNA inhibitors or antagomirs) or restoring tumor-suppressive miRNAs (using miRNA mimics). Clinical trials are ongoing to explore miRNA-based therapies in BC **(Hashemi and Gorji-bahri, 2020)**.

miR-21 acts as an oncogenic miRNA in BC. Therapeutic strategies using antagomiR-21 showed promising results by suppressing tumor growth and angiogenesis. It targets tumor suppressor genes like PTEN and VEGF signaling. Combining miR-21 inhibition with chemotherapy-enhanced anticancer effects **(Grimaldi et al., 2021)**.

miR-205 has emerged as a promising target in cancer therapy, particularly due to its tumor-suppressive role in various cancers, including BC. It plays a crucial role in inhibiting EMT, a process essential for cancer metastasis. By restoring miR-205 levels through miRNA mimics or nanotechnology-based delivery systems, researchers have observed reduced tumor proliferation, migration, and invasion. Additionally, miR-205 has shown potential in overcoming drug resistance and enhancing chemosensitivity, making it a valuable tool in personalized cancer treatment approaches **(Chauhan et al., 2020)**.

8. Conclusion

Breast cancer remains a global health challenge due to its high prevalence, mortality, and molecular complexity. Advances in classification, diagnostic imaging, and biomarker profiling have improved early detection and guided personalized treatment strategies, including surgery, radiation, chemotherapy, and targeted therapies. Emerging research on miRNAs has highlighted their critical roles in BC pathogenesis, acting as oncogenes or tumor suppressors, and influencing proliferation, metastasis, and treatment resistance. Insights into miRNA biogenesis and mechanisms of action reveal their potential as biomarkers and therapeutic targets, offering new avenues for precision medicine. Integrating these innovations holds promise for transforming BC diagnosis and treatment, improving patient outcomes.

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