The Role of MicroRNAs in the Progression, Prognostication, and Treatment of Breast Cancer

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NACS | Novel Approaches in Cancer Study
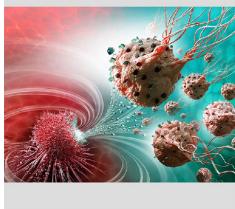
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Abstract

MicroRNAs (miRNAs) are conserved, small, non-coding RNA molecules, which recently have attracted enormous attention in numerous physiological and pathological conditions. Several studies have shed light on their biogenesis, regulatory mechanisms, and role as effective therapies in diseased conditions. Of interest, miRNA deregulation in numerous cancer types has been researched as potential diagnostic and prognostic tool. Breast cancer (BCa) is the most predominant tumor in women and the main cause of death. Despite advances in diagnosis and new treatments, the death toll from this disease is still higher than many other types of cancer in men and women. A major global health issue plaguing the health and clinical research industry is resistance to BCa treatments. A lot of attention is increasingly directed towards miRNAs as a potential predictor's response to treatments and as an alternative therapy to BCa treatment. Increasing evidence reveals a fundamental role miRNA plays in cancer development, progression, and treatment. Repeated findings have reinforced evidence of miRNA modulations in breast cancer cells by their effects in cell migration and invasion. Recently, miRNAs have been described as a diagnostic and prognostic tool, which offers promises as biomarkers for advancement of non-invasive and precise methods for screening tumor growth and progression. This review summarizes an overview of miRNA in breast cancer growth and progression, recent applications as biomarkers in a clinical setting in this type of cancers.

Introduction

MicroRNAs (miRNAs)are small single-stranded RNA molecules found in several organisms including plants, animals and some viruses. They are a member of a family of functional RNA molecules referred to as small non-coding RNAs (ncRNAs), which has about 22 nucleotides and functions in RNA silencing and post-transcriptional regulation of gene expression by repressing target gene expression at the translation level [1,2] miRNAs and their roles as regulatory ncRNAs are the most extensively studied member of this class. miRNAs are evolutionarily conserved in both plants and animals and, hence, believed to be fundamental participants in gene regulation right from early life [3-6]. They originate from regions of RNA transcripts that form short hairpins by folding back on themselves. This is one major distinction between these Small interfering RNA (siRNA), which have their origin from longer regions of double-stranded RNA [7].

Non-coding RNAs can be categorized into two groups based on their function. Those involved in infrastructure and those that participate in regulatory functions. The regulatory ncRNAs can be further divided in two groups based on their length and origin, and still further as those larger than 200 nucleotides, and those up to 200 or smaller than 200 nucleotides [8-10] (Figure 1). Ambros and his group discovered lin-4 in *C. elegans* as the first miRNA member in 1993 [1]. and they were observed to repress mRNAs during the translation process that encode proteins of the heterochronic developmental timing pathway in these organism [7] let-7 RNA, a second small RNA was shortly thereafter characterized seven years later as a repressor of lin-41 and also discovered to be conserved in many species. These and several other studies later led researchers to conclude that they might play a related role in regulating the timing of development in humans and other animals [11,12]. Since their description, about 29,000 miRNAs have been discovered different large and microorganisms

[13]. Although a little more than 2000 have been discovered in humans, much is still not completely understood regarding their specific cellular function and role in disease progression [14,15]. However, their ability to regulate genes have revealed that they are vital in numerous physiological functions [16] and pathological conditions [17,18], such as early development, cell proliferation, differentiation, apoptosis, disease pathology, tumorigenesis, development and clinical therapy [19,20].
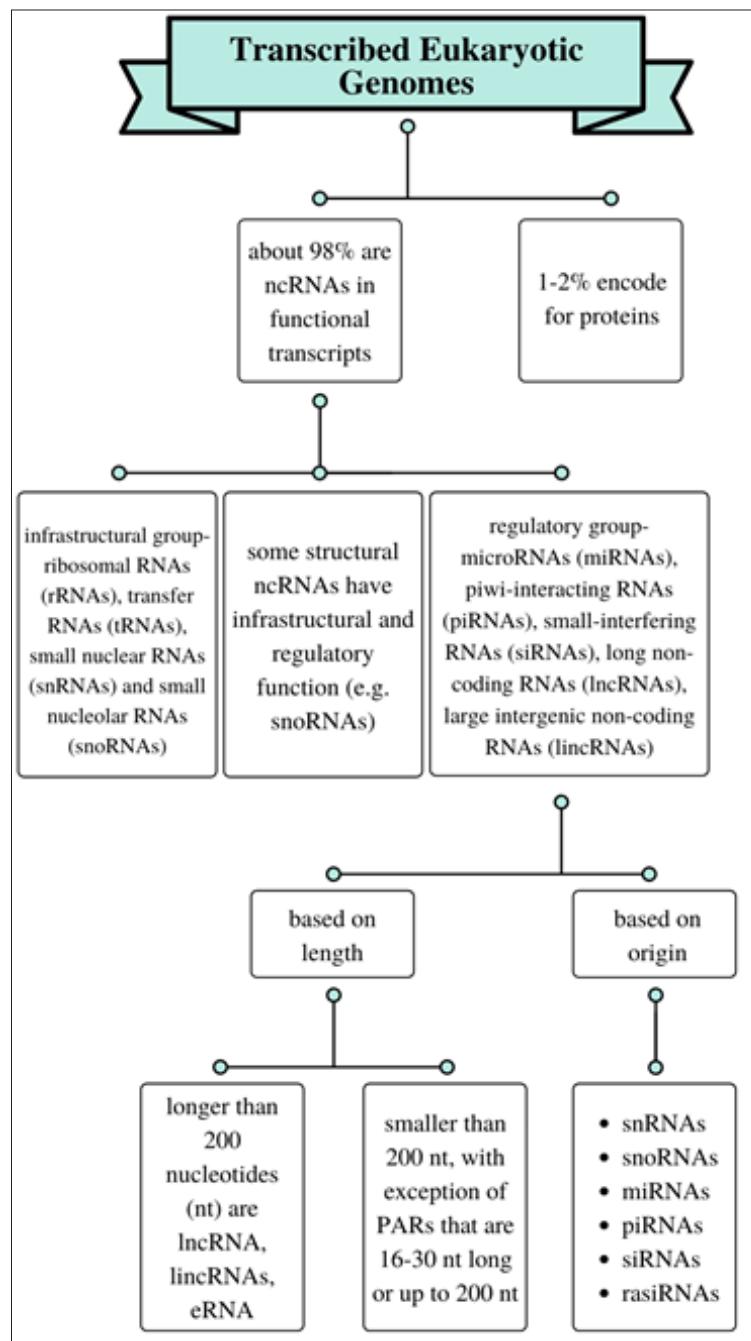

Figure 1: Overview of categorizing RNAs in eukaryotic genome.

miRNAs in humans are largely located in the introns of genes or the ncRNA transcript regions [2] with different groups expressed in different cell types and tissues [21,22]. These small group of gene regulators function by binding to complementary sequences located in the 3' untranslated region (UTR) of target mRNA, inducing negative regulation [23]. They will induce the degradation of that target when they bind completely to sequences of the complementary mRNAs (an observation commonly noticed in plants). Conversely, a partial binding between a miRNA and its target will lead to translational repression [24]. A specific miRNA

molecule can regulate several mRNAs, various miRNAs can work in tandem to regulate a specific mRNA target, and as many as 30% of genes involved in protein coding in humans are mediated by miRNAs [25]. These processes function through an interplay between the miRNA and several signaling molecules, such as cytokines, growth factors, transcription factors, pro-apoptotic and anti-apoptotic genes [26].

The expression of miRNAs is determined by innate cellular factors and different environmental cues [27]. About half of miRNAs can be found in locations prone to tumor formation [28], and abnormally expressed miRNAs have been implicated in most tumors (designated as oncogenic miRNAs-oncomiRs) by acting directly or indirectly on oncogenes and tumor suppressor genes to regulate their expression [19,29,30]. Current research reveals miRNAs as possible tumor biomarkers and are increasingly being studied as novel therapeutic targets. Although most miRNAs are found within the cell, some have also been discovered in extracellular environment such as several biological fluids [31]. This class of miRNAs, generally referred to as circulating miRNAs or extracellular miRNAs, have been identified at high levels in the circulation, and have observed in cell signaling activities with great potential use as non-invasive biomarkers [32-34].

This paper aims to provide a brief overview of the biogenesis and regulation miRNA and describe the mechanisms by which its expression is dysregulated in human diseases in general and specifically in breast cancer- as oncogenes or tumor suppressors.

Furthermore, we highlight miRNAs as potential biomarkers in cancer diagnosis, prognosis and treatment and, finally, we discuss some of the research challenges in identifying novel miRNAs and their biological functions and describing their applications in the treatment of diseases.

MicroRNA Biosynthesis

miRNAs synthesis consists of several significant stages. First, RNA polymerase II (and sometimes RNA polymerase III), typically generated from hundreds to several kilobases of pri-miRNA transcripts in the nucleus [35-37] structurally similar to matured transcripts but with a structural stem loop [36,38]. The pri-miRNAs then forms a microprocessor complex by interacting with the ribonuclease Drosha and double stranded RNA binding protein, DiGeorge syndrome critical region gene 8 (DGCR8), which cleaves it to generate a ~ 85-nucleotidestem–loop structure called precursor miRNA (pre-miRNA) hairpin [39,40].

Subsequent to this, the pre-miRNA is exported to the cytoplasm by Exportin 5 (the nucleocytoplasmic shuttle) where the ribonuclease Dicer complex and transactivation-responsive RNA-binding protein 2 (TARBP2) cleaves the loop, converting the pre-miRNA into a double-stranded miRNA duplex [41]. Following a strand separation, one of the strands of the miRNA duplex binds onto Argonaute (a protein family that binds different classes of small non-coding RNAs) to create the miRNA-Induced Silencing Complex (miRISC), while the other strand gets degraded [42-46] (Figure 2).
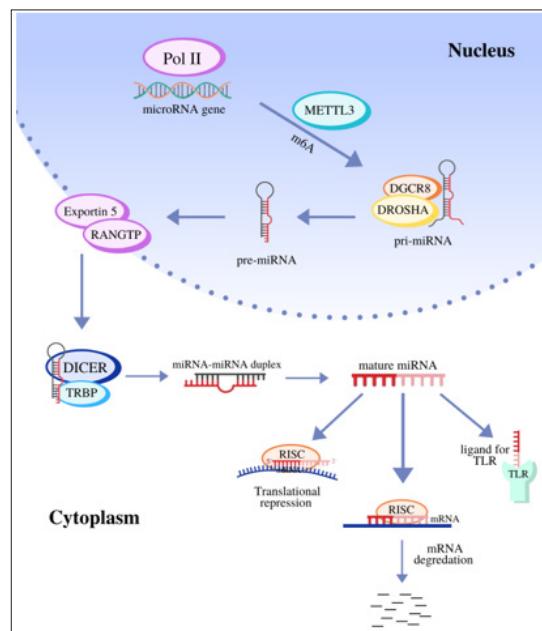
Figure 2: The biosynthesis pathway for miRNAs.

Note: RNA polymerase II is usually involved in transcribing miRNA genes, producing large primary transcripts called pri-miRNAs. The pri-miRNAs are cleaved by a microprocessor complex into a stem–loop structure called pre-miRNA. The pre-miRNAs are processed by another RNase III enzyme Dicer to a ~ 20–22-nucleotide miRNA/miRNA* duplex after they are transported from the nucleus to the cytoplasm by Ran/GTP/Exportin 5 complex. Following the separation of the duplex, the mature miRNA is combined with a protein complex termed RISC, which can then mediate gene silencing by cleavage and degradation, or repressing translation [47].

This newly formed complex is now set for down-regulating gene expression by either perfectly binding all along their length to target complementary mRNA transcripts-degrading the transcript, or more frequently, partially binding with complementary transcripts- inhibiting translation [1,47] (Figure 2).Although the primary mechanism of miRNA action in mammals is thought to be as described above, it has several functional roles [9]. Usually, in animals, it's key mechanism of action involves reducing mRNA translation, and individual miRNA can subsequently inhibit the translation of over 200 target genes [7,48-50]. Additionally, it is purported that some miRNAs have other activities other than post-transcriptional suppression, for instance some studies have revealed that some may epigenetically regulate transcription by targeting promoters. Astonishingly, they have also been observed under specific circumstances to increase translation and, consequently, up-regulate gene expression [9], miRNAs can also frequently initiate histone modification and DNA methylation of promoter regions, thereby affecting the expression of specific genes [51,52]. These diverse actions can create a state that miRNAs confer upon them ability to play integral roles in normal cellular functions [53-58] and, if dysregulated, disease [59].

The Role of MiRNAs in Cancers and Other Human Diseases

Calin et al. [60] were the first to reveal a link between miRNA s and human disease when they reported in 2002 that deregulation of certain miRNA (miR-15 and miR-16) results in B-cell chronic lymphocytic leukemia (CLL). Eventually, many other miRNAs came to be linked to cancer incidence [61] because of altered expression of miRNA through such actions like DNA amplification, deletion and mutations on specific miRNA loci, epigenetic silencing or inhibition of certain miRNA processing [62]. Subsequently, it has been reported that other diseases could arise from the mechanisms just listed, dysfunction of miRNA biogenesis and dysregulation of miRNAs and their targets [63]. Currently, several other instances where miRNA genes are either deleted or amplified in tumors have been compiled from numerous studies [64] and concluded that miRNAs can be implicated in numerous human diseases, including myocardial infarction and cardiovascular diseases [65-68] and cancer [58] (Table 1).

Although almost 100 miRNA-linked diseases have been described [63,64], scientists are still trying to better understand the mechanisms of miRNAs in diseases and the patterns of involvement. Lu M, et al. [63] in their analysis of associations between human microRNA and disease, observed a negative correlation between microRNA tissue specificity and the number of diseases associated with it. They also reported a link between microRNA conservation and disease. This conservation is also linked with the susceptibility to a human disease, further unraveling the roles of miRNA in diseases.

Further, the researchers stated that the fundamental mechanisms underlying respective diseases might be different, although this different group of diseases may be linked to the same miRNA. A phenomenon they suspect might be due to a correlation between miRNA tissue specificity and a disease [63]. A dysfunction in members of the miRNA family would show a similar phenotype because they may possess analogous functions and participate in the same biological processes [69,70]. Finally, usual factors, under identical circumstance and function, can regulate miRNAs in surrounding cells, and an abnormality in these functions could cause same disease [63].

There is adequate evidence to show that miRNAs are key players in the initiation and progression of human cancer [71]. The deregulation of miRNA in various cancer sub types has been widely researched since Calin et al. [60] first showed the biological role of miRNAs in cancer development. miRNAs have been identified to be linked to numerous and different cancers including lung, breast, and prostate, ovarian, colorectal, acute leukemia, pancreatic, squamous cell carcinoma hepatocellular carcinoma, and several others [69,72-74] Table 1.

Table 1: Somatic diseases and concomitant OMD.

Disease	
Cancer	B-cell lymphoma
	Breast cancer
	Lung cancer
	Gastric cancer
	Liver cancer
	Prostate cancer
	Ovarian cancer
	Colorectal cancer
	Acute Leukemia
	Pancreatic cancer
	Bladder
	Thyroid tumors
	Esophagus
Viral diseases	Squamous cell carcinoma
	Hepatocellular carcinoma
	Influenza virus
Immune-related diseases	Multiple sclerosis
	Systemic lupus erythematosus
	Type II diabetes
	Nonalcoholic fatty liver disease
	Non-alcoholic steatohepatitis
	Systemic lupus erythematosus
	Psoriasis
	Type II diabetes
Neurodegenerative diseases	Parkinson's disease
	Alzheimer's disease
	Down syndrome
	Rheumatic arthritis
Other	Cardiac hypertrophy

These discoveries, subsequently, has led to increase attention and studies in the downregulation of miRNAs in cancer tissues compared with normal tissues. Also, there are some evidence that miRNAs in stress conditions, such as hypoxia, stimulate some targets [75-76]. For instance, miR-210 may be involved as a vital player in HIF-1a-induced macrophage necroptosis [77]. Intriguingly, several of these studies have revealed that all cancers display unique microRNAs [78,79]. The abnormal expression of miRNA in tumors has led scientists to conclude that the dysregulated miRNAs could influence one or numerous hallmarks of cancer initiation and progression. MiRNAs dysregulation in human cancers (which can be at the transcriptional or translational level) acts as either oncogenes or tumor suppressors, depending upon their target transcripts. Table 2 shows the hallmarks of breast cancer associated with the deregulation of several respective miRNAs [80]. For instance, miR-155, has been shown to be upregulated in several hematopoietic malignancies and tumors of the breast, lung and pancreas [81,82] and miR-29 functions as a tumor suppressor through its pro-myogenic function [83].

Table 2: miRNAs as key regulators of Breast cancer hallmarks. Expression of miRNAs (up-regulated and down-regulated) grouped according to their function in the hallmarks of breast cancer.

Up regulated	Hallmarks of Breast Cancer	Down regulated
miR-25,128a	Resisting Apoptosis	miR-195;125a
miR-103	Genome instability and mutation	miR-103
miR-210	Sustained angiogenesis	miR-126
miR-10b	Activating invasion and metastasis	miR-126
	Tumor-promoting inflammation	
	Enabling replicative immortality	miR-127
miR-155	Avoiding immune destruction	
	Evading growth suppressors	miR-451
miR-202	Sustaining proliferative signaling	miR-126
miR-210	Deregulation of energy metabolism	

The major distinction between the mechanism of action of oncogenic miRNAs (OncomiRs) and tumor suppressor miRNAs is that while the former represses the expression of tumor suppressor genes and are often upregulated in cancer, the latter targets oncogenes and are often downregulated in cancer [84-88]. For example, one of the most overexpressed miRNAs in human epithelial malignancies, miRNA-21 (miR-21), downregulates numerous tumor suppressors [89], and some studies have suggested the involvement of the tumor suppressor gene, p53, in the regulation of miRNAs [90], and miR-506 has been shown to induce apoptosis in cervical cancer cells, through its direct target hedgehog pathway transcription factor. [91] Although, many studies have revealed several miRNAs that function in both ways- oncogenic or tumor suppressive abilities, depending on tumor type and cellular context [92]. Furthermore, miRNAs have been observed to be involved in

tumor metastasis [93] and because miRNAs exhibit impressive tissue specificity (and patterns of gene activity), it is often possible to establish the tissue of origin of a metastasis in patients with unidentified primary tumors [78,94].

Role of miRNAs in Breast Cancer Progression and Treatment

Breast cancer is the second most commonly diagnosed cancer among American women after skin cancer, and fifth most common cause of cancer mortality worldwide. In the United States, there were about 266,120 new cases of invasive breast diagnosed in the women and 2,550 cases diagnosed in men 2018. In that year, an estimated 41,400 breast cancer deaths were estimated, 480 men and more than 3.5 million survivors [95]. The treatment of this disease has proven to be very challenging due to its multifaceted and heterogeneous nature, comprising of numerous molecular subtypes, each with diverse respective cellular origin, treatment response, and clinical outcome [96,97].

Various genetic and epigenetic changes in these cells activate the various features of cancer (sustaining proliferative signaling, evading growth suppressors, resistance to cell death, immortality, angiogenesis, stimulating invasion and metastasis, reprogramming energy metabolism, and escaping immune destruction), which all leads to malignant breast tumor progression [98]. Recent studies have implicated noncoding RNAs (ncRNAs), like MiRNAs, as sources of epigenetic alteration, genetic variations, modifications in miRNA biogenesis, and transcriptional repression [8,99]. An example of an oncogenic miRNA associated with breast cancer is MiR-21, which is one of the most highly expressed miRNAs in breast cancer. It has been shown to inhibit several tumor-suppressor genes and consequently promotes cell growth and invasion, and tumor metastasis, and its upregulation is associated with poor prognosis [89]. MiR-155, another oncogenic miRNA, is known to target, a human breast cancer susceptibility gene (BRCA1) involved in DNA repair and cell cycle progression and thereby regulate several signaling pathways linked to the cell's growth and survival [100-102] miR-335, an example of a tumor-suppressor, influences vital cellular functions such as proliferation and apoptosis in breast cancer cells [103] miRNAs are involved also in breast cancer metastasis, one of the key factors associated with mortality [95].

To become metastatic, tumor cells must acquire epithelial-mesenchymal transition (EMT) and angiogenesis [104] and several miRNAs target mechanisms that promote these processes in breast tumors [105], for instance by inducing phenotypic changes related to the development of metastasis [106]. One of such is miR-205, which target genes' expression vascular endothelial growth factor's A(VEGF-A) that has been linked to breast cancer progression migration and metastasis), have proven to promote breast carcinoma survival [107]. In addition to promoting metastasis, certain miRNAs have also been linked to different factors that affect breast cancer prognosis. For instance, studies have reported that the expression levels of miR-210 were correlated with tumor aggressiveness and poor prognosis, and therefore can be associated

with breast cancer development [108,109]. Other examples include miR-9 [110,111] which may be useful as biomarkers for predicting metastasis and the possibility of the tumor recurring- a negative prognosis of patients with breast cancer.

miRNA expression is deregulated in cancer and the physical appearance of these cells are often altered by targeting the expression. These discoveries have thereby established the basis for the use of miRNAs in anticancer therapy [112]. The two-prong approach employed in using miRNA in anticancer therapy is either by inhibiting the function of miRNAs as oncogenes or upregulating the expression of their tumor-suppressive functions [113]. One main approach employed in blocking the expression is by a direct strategy, which involves either blocking the expression of oncogenic miRNAs or substituting for the loss of expression of a tumor suppressor miRNA through the use of oligonucleotides or virus-based constructs. Another strategy, an indirect approach, targets their transcription and processing by altering the expression of the miRNA with the use of drugs [114].

Certain miRNAs have been used to successfully perform a wide- ranging silencing of cancer pathways due to their ability to target those genes from identical pathways and those from cross linking pathways. miR-205 was one of the miRNAs discovered to be a potential compound in breast cancer therapeutics [115]. Early studies revealed that miR-181a possesses an anti-breast cancer function by inhibiting tumor invasion and metastasis, has the ability to induce cancer cell death, and improve drug sensitivity. However, it was observed in studies that downregulation is more aggressive or late stage breast cancer, thereby functioning as a tumor suppressor gene [116-118]. A benefit of using miRNAs as the anti-cancer therapy includes the fact that they are produced in human cells unlike other synthetic compounds like chemotherapies. Another advantage is that microRNAs target multiple genes from the same pathway [119].

The first miRNA drug developed was by the company Santaris Pharma A/S. It was an LNA-modified oligonucleotide, SPC3649 used to repress the expression of miR-122, in treating chronic hepatitic C virus (HCV) infection [120]. An understanding of miRNAs as oncogenes and/or tumor suppressors in cancers, has paved the way for researchers to study their potential use as therapeutic targets for clinical application and as biomarkers for cancer detection and development. miRNAs have been considered a vital candidate for biomarkers because they have some advantages over candidates such as proteins and metabolites, for instance, they are stable enough to resist several enzymes in body [121].

MicroRNAs as Potential Biomarkers in Cancer Diagnostic

Detecting and diagnosing breast cancer early in patients offers more favorable outcomes in treating the disease [122] and clinicians and researchers are increasingly relying on the use of biomarkers to detect early stages of breast cancer. Biomarkers have prognostic value; used in predicting patient's outcome, disease advancement and relapse, despite ongoing treatment. It is therefore

not surprising that several studies, both past and ongoing, involve a search for viable prognostic biomarkers. miRNAs have been linked with clinical and pathological features, making them ideal for prognostic purposes in several tumor categories and subcategories of breast cancer patients [106,123,].

The discovery that miRNAs can target various genes and modify numerous pathways and hence target gene expression, made them attractive candidates as diagnostic, prognostic, or predictive breast cancer biomarkers in recent years [124]. For instance, several studies have reported that the expression of miR-181a is correlated with of clinic pathological features of breast tumors [105,125-128] and in prostate cancer patients, miR-141 is upregulated [129].

Additionally, miRNA biomarkers have a greater potential to reveal early diagnosis and are easier to analyze using biotechnology methods because of their locations upstream in regulation cascades. miRNAs are released into circulation from the primary tumor and other cell types. They are then secreted into the extracellular space, from there they move into the circulating body fluid, and can eventually be detected in almost all fluids in the body including the whole blood, serum, plasma, saliva, urine, and several others. [130]. Although biomarkers can be measured in tissues, body fluids, or both, researchers prefer, when evaluating healthy individuals, to analyze body fluid. Thus, circulating serum miRNAs have been speculated as a potential, non-invasive diagnostic and prognostic biomarkers for cancer and other diseases such as, diabetes mellitus and neurological disorders [131-133].

However, the total amount of distinct miRNAs is considerably different among the numerous fluids, with the highest detected in saliva, breast milk, and seminal fluid the highest; the lowest in human urine [129,130,134-136]. Non-invasive miRNA biomarkers are more attractive because they present fewer complications linked to the collection of specimens. Due to certain intrinsic characteristic they possess, these circulating miRNAs are ideal candidates for non-invasive biomarkers. circulating miRNAs have been detected in various disease conditions, and, when detected in the peripheral blood circulation and other body fluids could indicate disease progression [137-139]. Some circulating miRNAs can also function as prognostic biomarkers in breast cancer patients, and numerous research studies have reported their possible use in diagnosing metastasis [140].

The use of circulating miRNAs as breast Cancer biomarkers has been plagued with some challenges. One major challenge is their low abundance, which made their detection difficult using microarrays or other basic miRNA profiling techniques [141]. However, scientists have come up with several methods to overcome these obstacles. Another main challenge in the analysis of miRNAs in body fluids is the need for an internal normalization. Certain genes, often used as internal normalization during miRNA analysis in cells and tissues, are not feasible in serum analysis since these controls are easily degraded and not detected in serum [142]. Further research is still required to ascertain the specificity of the microRNA biomarkers for the respective type of cancer in addition to methods to standardize collection and analyze samples. Also, a

broad profiling data of circulating miRNA during chemotherapy treatment will be very essential to identify novel circulating markers of response to treatment.

Conclusion

The survival and clinical outcome of breast cancer patients following treatment has been linked to the heterogeneity of the disease. Numerous past research studies in this field has focused on understanding the mechanism involved in initiating and developmental of phenotypic alterations that occur on the epithelial tissue of the breast gland, and although many culprits have been identified as active participants in this process, recent studies coming out have revealed the strong involvement that miRNAs plays in the regulation of breast cancer- either as suppressors or initiators of tumor development. Also, miRNAs have been shown to be potential reliable prognostic biomarkers for breast cancer progression and overall survival, which could be useful in monitoring patient's progress and the identification of effective treatments.

Research has taken a long stride in the area of improving breast cancer prognostication and numerous mRNA-based tests are presently available towards that goal; however, its clinical use still presents some limitations. This calls for new biomarkers that will provide more accurate monitoring and revelation of treatment protocols and therapeutics, as well as follow-up plans on a personalized basis. Current research in this area seem to be mainly preclinical and, therefore, inconclusive from patient cohorts. Although the results thus far are encouraging, a lot of study still persists in identifying miRNAs as true predictors of success or failure in individual patient's treatment.

Despite the huge potential of miRNA research in vitro, and its promise to advance precision medicine in breast cancer, more elaborate in vivo models will greatly help to better establish the roles of individual miRNAs and their families. Furthermore, a broad comprehension of their mechanism of action and the pathways they regulate can be acquired through enhanced experimental approaches that will identify specific and critical miRNA targets involved in cancer and determine their respective contribution to tumor transformation.

Although hundreds of different microRNAs have been currently described that can identify and act on specific genes in multiple ways, extensive studies are still needed to safely conclude and state the general function of microRNAs in breast cancer development. Therefore, it may be too premature to predict the total implication of the role of miRNAs in cancer, in general, and breast cancer in particular.

Conflicts of Interest

None to declare.

Acknowledgment

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