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MicroRNAs as Therapeutic Targets in Human Breast Cancer

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1. Introduction

Cancer, which has unrestricted cell growth with the potential to invade or metastasize to other parts of the body is a complex group of diseases with many possible causes. The American Cancer Society reported that the most common type of cancer and the leading cause of cancer-related mortality among females in the world is breast cancer (BC), with about 235,000 new cases expected in the United States in 2014. One in eight women has a chance of developing BC in her lifetime.

Technological improvements in the last decade have helped researchers to understand this complex disease more thoroughly. In spite of the presence of promising tools for breast cancer therapy, the mortality rate of metastatic breast cancer cases is still high. Thus it is necessary to identify significant therapeutic targets by investigating the molecular basis of the disease. In recent years, studies aimed at determining the possible molecular mechanisms of breast cancer have increased in number. Many treatment strategies have been developed. Nevertheless, these methods induce a range of therapeutic responses and therapeutic resistance can develop in breast cancer patients, therefore new methods must be developed.

MicroRNAs (miRNAs) have been reported as playing important roles in cancer development. miRNAs are potential alternative therapeutic targets for cancer. They are also candidate diagnostic and prognostic indicators of breast cancer. miRNAs are small non-coding RNAs that bind to the 3' untranslated region of target mRNAs and down-regulate their translation to protein or degrade the mRNAs. miRNAs play critical roles in many different cellular processes including metabolism, apoptosis, differentiation, and development. They are also linked to human diseases, including cancer. Since their initial discovery in 1993, during a study

of the gene *lin-4* in *Caenorhabditis elegans*, more than 2000 molecules have been identified in humans, regulating the expression of almost 30% of genes.

miRNAs role as mainly in a tumor suppressive or oncogenic manner. Significantly increased miRNA expression can cause differences in cancer initiation, progression, migration, invasion and metastasis. If circulating extracellular miRNAs are detectable in plasma of BC patients, they can supply novel, non-invasive biomarkers for BC diagnosis and prognosis. Furthermore, new discoveries about miRNAs indicate that they may be involved in the response to chemotherapy or radiotherapy. For instance, MiR-21 is a significant BC-related intracellular and extra-cellular biomarker and a therapeutic target with upregulated expression detected in human BC tissues and cell lines, and plays a key role in all phases of BC pathogenesis. Today, investigation of the association of miRNAs with breast cancer has advanced. miRNAs are being utilized as diagnostic and prognostic biomarkers for patient stratification and also as therapeutic targets and agents in clinical laboratories.

Consequently, the aim of this chapter is to present the current knowledge and concepts concerning the involvement of microRNAs in breast cancer. The oncogenic role of miRNAs in BC etiopathogenesis and as treatment response predictors and therapeutic targets in BC management will be described.

2. The regulation of MicroRNAs

MicroRNAs (miRNAs) are a class of endogenous small RNAs displaying a role in gene regulation at the post transcriptional level in the cell. They have roles in the central dogma and exist extensively in the genome of high level eukaryotic cells in which miRNA genes constitute 1–2% of introns or genes [1]. miRNAs control gene expression via transcription and translation of genes, including mRNA deterioration and translation suppression. The removal of an adenylate group is followed by loss of poly(A)-binding protein initiation 5' decapping, hence promoting exonucleolytic digestion from the 5' end [2]. miRNA interferes with gene expression through inhibition of translation. miRNAs can thereby independently stop translation, beginning by a cap-dependent mechanism. For translationally active polysomes of lower mass initiation is impaired [3]. Furthermore, recent studies indicate that miRNAs cause an m⁷G cap-dependent impediment to the recruitment of 80S ribosomes to mRNA [4]. As a result, the basis of the cap binding affinity of the miRNA-binding protein Ago was identified, in which the cap is inaccessible and thus unable to be bound to the initiation factor eIF4E [5]. Although, several proteins interfere with mRNA degradation and translational repression, some of them are necessary components of the RNA induced silencing complex (RISC) that transports those small RNAs to complementary sites within mRNA [6]. miRNAs assert their silencing role generally by interactions with the 3'-untranslated related RISC complex and can affect miRNA targeting specificity. The result of these miRNA interactions is that they regulate a huge number of protein coding genes. These targets include several signalling pathways, and their effects trigger amplification of certain genes. miRNAs have characteristic roles in changing cellular and signalling pathways which can induce cancer development and progression [7] (Figure 1).

miRNAs are transcribed by RNA polymerase II by using large RNA precursors known as pri-miRNAs [8]. The variation of transcription factors just as of protein-coding genes regulate transcription of miRNA genes [9]. The regulatory network of miRNAs and their targets is complicated. A single miRNA can regulate various mRNAs, and conversely a single mRNA can be targeted by a number of distinct miRNAs. Based on computational estimations, it has been determined that miRNAs regulate one third of all human protein-coding genes [10].

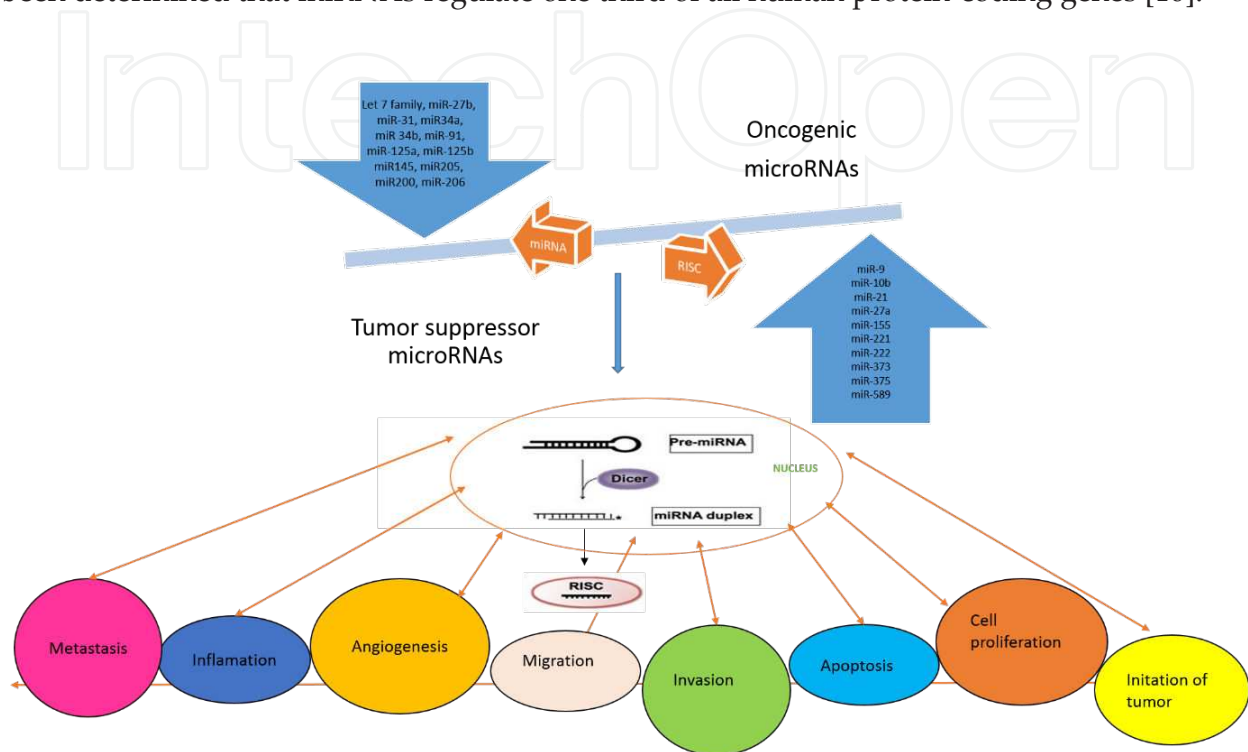


Figure 1. The changes induced by miRNAs in breast cancer pathogenesis. The decreased of suppressive miRNA control inhibition on oncogenes in breast cancer. The upregulation of miRNA inhibits tumor suppressors. Both mechanisms control gene expression and play specific roles in BC predisposition, initiation, cell proliferation, resistance to apoptosis, invasion, angiogenesis, inflammation and metastasis in BC cells. (RISC: RNA-induced silencing complex)

3. Types of microRNAs

miRNAs are 20-21 nucleotides in length and regulate the expression of almost 30% of genes. Approximately 706 miRNAs have been identified in humans. In the miRBase database there are more than 5000 miRNAs that have been identified in various organisms, each with a different genomic organization and different biogenetic mechanisms [11]. Since their initial discovery in 1993, in a study of the gene *lin-4* in *Caenorhabditis elegans*, more than 2000 molecules have been identified in humans so far, and these are involved in regulating the expression of almost 30% of genes identified. The first microRNA gene to be discovered was *lin-4* in *C. Elegans*, a gene associated with development [12]. miRNAs have different roles in gene regulation, and thereby control complex networks in eukaryotic organisms, including hematopoietic cell differentiation, cell proliferation, apoptosis and organ development [13].

While clustering miRNA genes, they were stratified as hosted and non-hosted. miRNA clusters generally contain between two to three miRNA genes, however there are also larger clusters. For example, the human hsa-miR-17 cluster has six members [14].

Lately, the expression of an enormous cluster of 40 miRNA genes located in the ~1 Mb human imprinted 14q32 domain was identified [15]. miRNA genes are clustered according sequence similarities. However, some of them can differ [16].

These miRNAs have different roles in oncogenesis, tumor-suppression, cancer initiation, progression and metastasis. Recent studies have shown that the miR-17-92 family contain miRNAs which play a role in carcinogenesis. These miRNAs are miR-17, miR-18a, miR-19a, miR-20a, miR-19b, and miR-92a. The same polycistronic cluster are all transcribed from chromosome 13. In mammals, the miR-106b-25 cluster on chromosome 7, and the miR-106a-363 cluster on the X chromosome are also two paralogs, miRNAs which have the same seed sequence and can share the same targets. According to the homology of the seed sequences, miRNAs in these paralogous clusters can be grouped into four different families, miR-17, miR-18, miR-19 and miR-92 [1].

4. MicroRNA biogenesis and function

By using RNA polymerase II, miRNA joins transcription of pri-miRNA precursor generally. In the nucleus, an endonuclease enzyme plays a role in the processing of the pri-miRNA and conversion into precursor miRNA (pre-miRNA). The pri-miRNAs are processed to mature miRNAs by the RNaseIII family enzymes, Drosha and Dicer. Drosha and Dicer, the RNaseIII family enzymes, process the pri-miRNAs to mature miRNAs. The Drosha and pasha cleaves pri-miRNA to pre-miRNA in the nucleus and subsequently Dicer processes it to a miRNA/miRNA* duplex of ~20 bp in the cytoplasm. This constitutes the miRNA-induced silencing complex, miRISC. miRNA (pre-miRNA) contain a stem loop secondary structure and have 80-100nt long sequences. Transportation of pre-miRNA from the nucleus to cytoplasm happens thanks to Exportin-5. Translation of a complement messenger RNA is controlled by the RNA induced silencing complex. Mature miRNA can detect and attach the 3' untranslated regions of an mRNA from the core region, that is generally position 2-7 in the miRNA. High complementarity is not required for regulation and a single miRNA can target multiple genes. miRNAs have a variety of roles including the development of heart and skeletal muscle, cell cycle control, different cell signalling pathways, neurogenesis, insulin secretion, cholesterol metabolism, aging, immune responses and viral replication [17]. Furthermore, miRNAs regulate histone modification and DNA methylation of promoter sites for expression of target genes [18].

Some miRNAs, such as the miR-17/20 cluster, the miR-221/222 cluster, and the let-7 and miR-34 families, play important roles in cell cycle control by targeting cell cycle regulators. These regulators include myc, E2Fs, and cyclin D1 which regulate miR-17/20 during transcription which triggers regulation of translation levels of E2F, pRb, and cyclin D1. miR-15/16 inhibits

cyclin D1, cyclin E, CDK4/6 and the miR-34 family suppresses E2F, cyclin D1, and cyclin E expression and they, in turn, control cell cycle [11] (Figure 2).

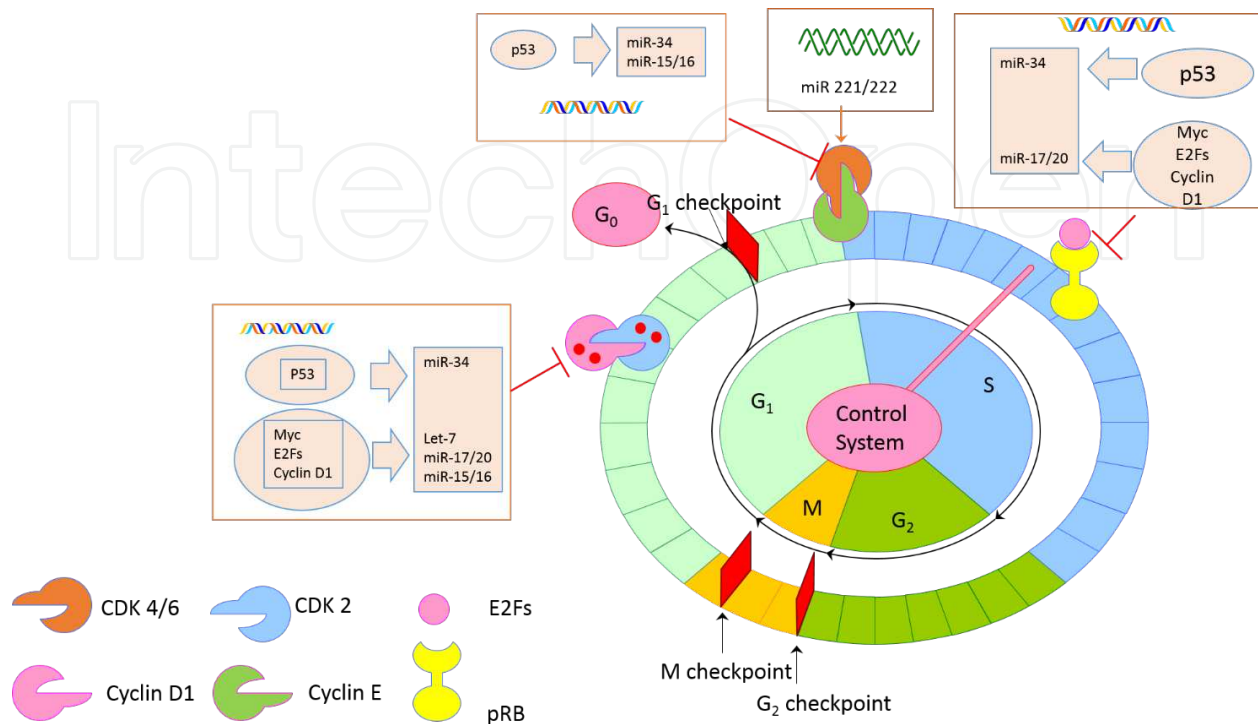


Figure 2. miRNAs in cell cycle regulation

miRNAs detect the specificity and sensitivity of post-transcriptional gene silencing. In order to find out mechanisms of miRNA, provide a chance to get knowledge about biological processes of organisms and covered reasons of diseases [19].

5. MicroRNAs and diseases

In eukaryotic organisms, altered expression of miRNAs can trigger disease development [20]. The association between human disease and miRNA dysregulation can be seen in miR2Dis-ease, a publicly available database [21]. miRNAs play various roles in cell proliferation, metabolism, apoptosis, development, neuronal gene expression, brain morphogenesis [22] cell differentiation, muscle differentiation [23], cell growth and stem cell division [24, 25].

In addition, miRNAs have significant roles in cancer development. miRNAs make decisions as to the fate of the cell [26]. miRNAs are regulated differently in each human cancer, with some of them upregulated and others down-regulated [27].

miRNAs have been determined to play a role in most biological processes and different human diseases including: cardiovascular disease [28], acute and chronic disease [29], neurodevelop-

mental diseases [30], autoimmune disease [31], liver disease [32], skeletal muscle disease [33] and skin disease [34].

Scientists foresee that miRNA present an immense prospect in diagnosis as well as therapy of diseases in the future. Recently, miRNA, antisense blocking and miRNA alteration techniques have been considered as alternative treatments for different cancers [35].

6. MicroRNAs and cancer

Thanks to advancing technology, the genetic study of disease at the molecular level has increased precipitously. The majority of these molecular studies are concerned with understanding cancer. At the molecular level, the etiology of cancer lies in various signalling pathways. Cancer is a multifactorial disease with many different varieties which differ significantly from one another. Due to its complexity and variety, common occurrence and high death rate, scientists have focused heavily on cancer research. In Singh and Mo's research, they indicated that miRNAs can be used to predict response to therapy as well as in prognosis in clinical cases. To illustrate, a variety of anticancer agents, when combined with miRNA reagents, such as anti-miR-21, result in more effective therapeutic approaches [7].

7. MicroRNAs and breast cancer

7.1. The role of MicroRNAs in breast cancer

Recently, the importance of microRNAs (miRNA/miRs) in cellular regulation has been shown. Some miRNAs are oncogenic and are related to breast cancer. They cause metastasis and then deregulation in cancer [36] (Figure 3). Circulating miRNAs can potentially be used to detect and prognose cancer early [37]. While in this field there are no studies about treatment with circulating miRNA, they can be used as a marker of chemoresistance in BC [38]. In the blood plasma of patients with BC, let-7, miR-10b, miR-34, miR-155 and miR-200c are low, while miR-21, miR-195 and miR-221 are abundant. Plasma levels of these miRNAs were measured and used to characterize treatment response [39].

In each breast cancer subtype, the expression and regulation of miRNAs in disease initiation is different. In a comparison of 10 normal breast samples and 76 breast cancer samples, the most significantly dysregulated miRNAs were identified as miR-125b, miR-145, miR-21 and miR-155 [40]. These miRNAs play different roles in BC. In order to prove the miRNAs capability of regulation of transition from ductal carcinoma in situ to invasive ductal carcinoma, 94 biopsies were analysed. Then, a nine-miRNA signature was identified in invasion, and five miRNAs were identified in metastasis. The downregulation of let-7d, miR-210 and miR-221 in ductal carcinoma in situ, and upregulation of them in the invasive transition is indicated [41]. There are a number of studies about miRNA in BC. In one of these, the peripheral blood samples of 189 patients and 89 healthy individuals were collected to determine charac-

teristic miRNA genotyping and expression. miR-499, miR-146a and miR-196a-2 were detected in postmenopausal patients and miR-196a-2 was determined in premenopausal breast cancer patients. This differs from healthy individuals [42]. In another study that included 23 BC patients and 10 controls, next-generation sequencing was used for analysis. Specific miRNAs were found to be co-expressed in the serum and tissue of BC patients. miR-103, miR-23a, miR-29a, miR-222, miR-23b, miR-24 and miR-25 are all upregulated. miR-222 has an especially high level in the serum of BC patients and serves as a specific biomarker [43].

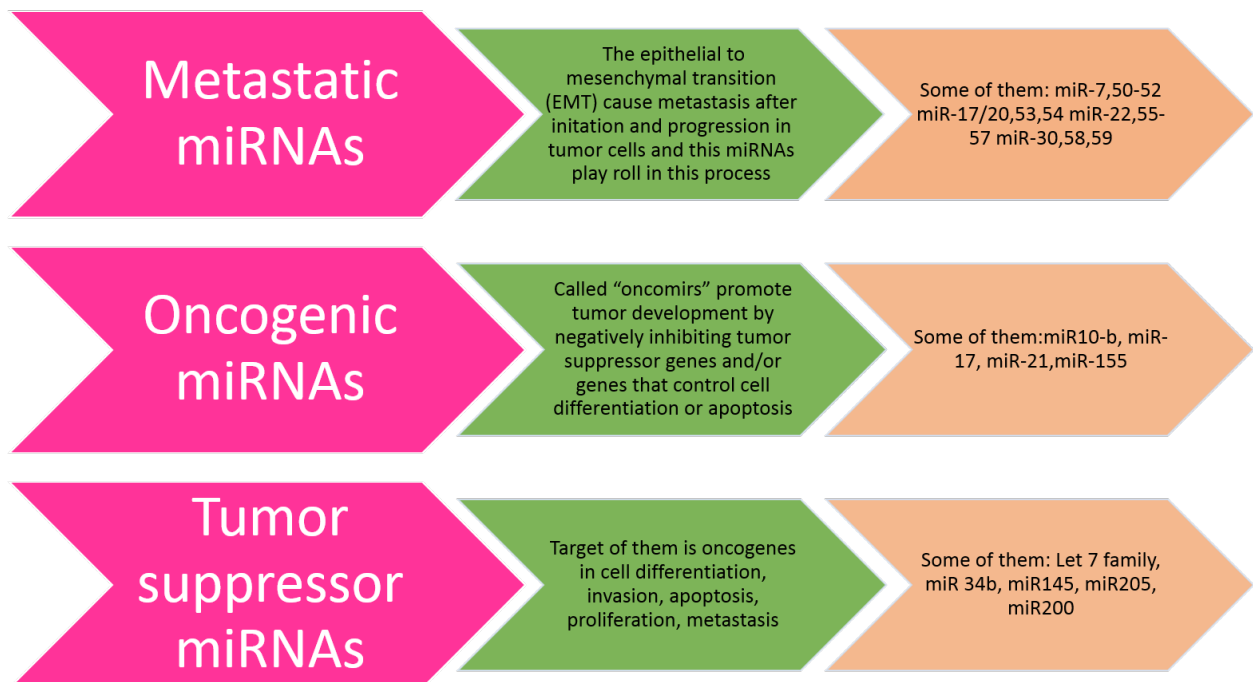


Figure 3. Classes of miRNAs in breast cancer

7.2. Tumor Suppressor MicroRNAs in Breast Cancer

7.2.1. *let-7* family

The Let-7 family is crucial for cell type determination during embryogenesis. This family was first discovered in *Caenorhabditis elegans* and was one of the first two microRNAs to be identified [44]. The subtypes of the let-7 family are: let-7a, let-7b, let-7c, let-7d, let-7e, let-7f, let-7g, let-7i, miR-98 and miR-202. They have functions in cell regulation, gene expression and development. Lin28 regulates biogenesis of let-7 at the post-transcriptional stage [45]. Downregulation of let-7 causes different cancers. The role of let-7 was determined in stem cells.

Let-7 was found to play role in self-renewal, differentiation and tumorigenicity in both breast tumor initiating cells (BT-IC) and non-BT-IC, all of which were isolated from primary breast cancer. Overexpression of let-7 family miRNAs decreases proliferation, leads to formation of mammospheres by BT-ICs *in vitro* and tumor formation and metastasis in NOD/SCID mice. Let-7 also targets H-RAS and HMGA2 and regulates BT-IC stem cell-like properties [46].

7.2.2. *miR-200 family*

The miR-200 family includes five subgroups: miR-200a, miR-200b, miR-200c, miR-141 and miR-429. The miR-200 family suppresses EMT which is mediated via the regulation of E-cadherin. The miR-200 family is not present in invasive breast cancer cell lines of mesenchymal phenotype; also, these cell lines did not express e-cadherin. [47]. There is a correlation between miR-200 family and E-cadherin, so it alters cell morphology. miR-200c controls breast cancer cell migration, invasion, elongation and stress fiber formation, and metastasis targets FHOD1 and PPM1F which are direct regulators of the actin cytoskeleton. In addition, downregulation of miR-200c is associated with drug resistance in human breast cancer. On the other hand, the role of miR-200c family is not clear in metastasis. miR-200c controls regulation of PLCG1, BMI1, TGF- β 2, FAP-1, ZEB and Suz12 [48]. Upregulation of the miR-200 family in metastatic 4TO7 cells regulates metastatic colonization [49].

7.2.3. *miR-205*

This miRNA is involved in the epithelial to mesenchymal transition (EMT) and tumor invasion by targeting the transcriptional repressors of E-cadherin, ZEB1 and ZEB2 in breast cancer [50]. miR-205 is expressed at low levels in breast tumor as compared to normal breast tissue [51]. The observed down-regulation in breast cancer cell lines such as MCF-7 and MDA-MB-231 is absent in the non-malignant cell line MCF-10A. It targets the HER3 receptor and vascular endothelial growth factor A (VEGF-A) via interaction with a binding site in the 3'-untranslated region (3'-UTR) of ErbB3 and VEGF-A. Also, activation of the downstream mediator Akt is inhibited by miR-205 which has a role in the proliferation pathway mediated by the HER receptor family [51, 52].

7.2.4. *miR-145*

When Iorio et al. compared normal breast tissue and breast cancer by microarray and northern blot analyses, they found that miR-145 is downregulated in breast cancer. miRNAs can be a novel biomarker for early cancer detection, because of its early appearance [53]. Spizzo et al. also reported the relation of TP53 activation and miR-145 as pro-apoptotic. The target of miR-145 may be estrogen receptor- α (ER- α) protein expression and cause apoptosis in both ER- α positive and wild type TP53-expressing breast cancer cells [54]. The oncogene c-Myc, which plays a role in cell proliferation and development *in vitro* and *in vivo*, is a target of miR-145 [7]. The transcription factor p53 is mutated in breast cancer. Several miRNAs such as miR-145 play a role in the transcriptional control of p53. There are different mechanisms in response to DNA damage, cell cycle arrest, apoptosis associated with p53 [55] (Figure 4).

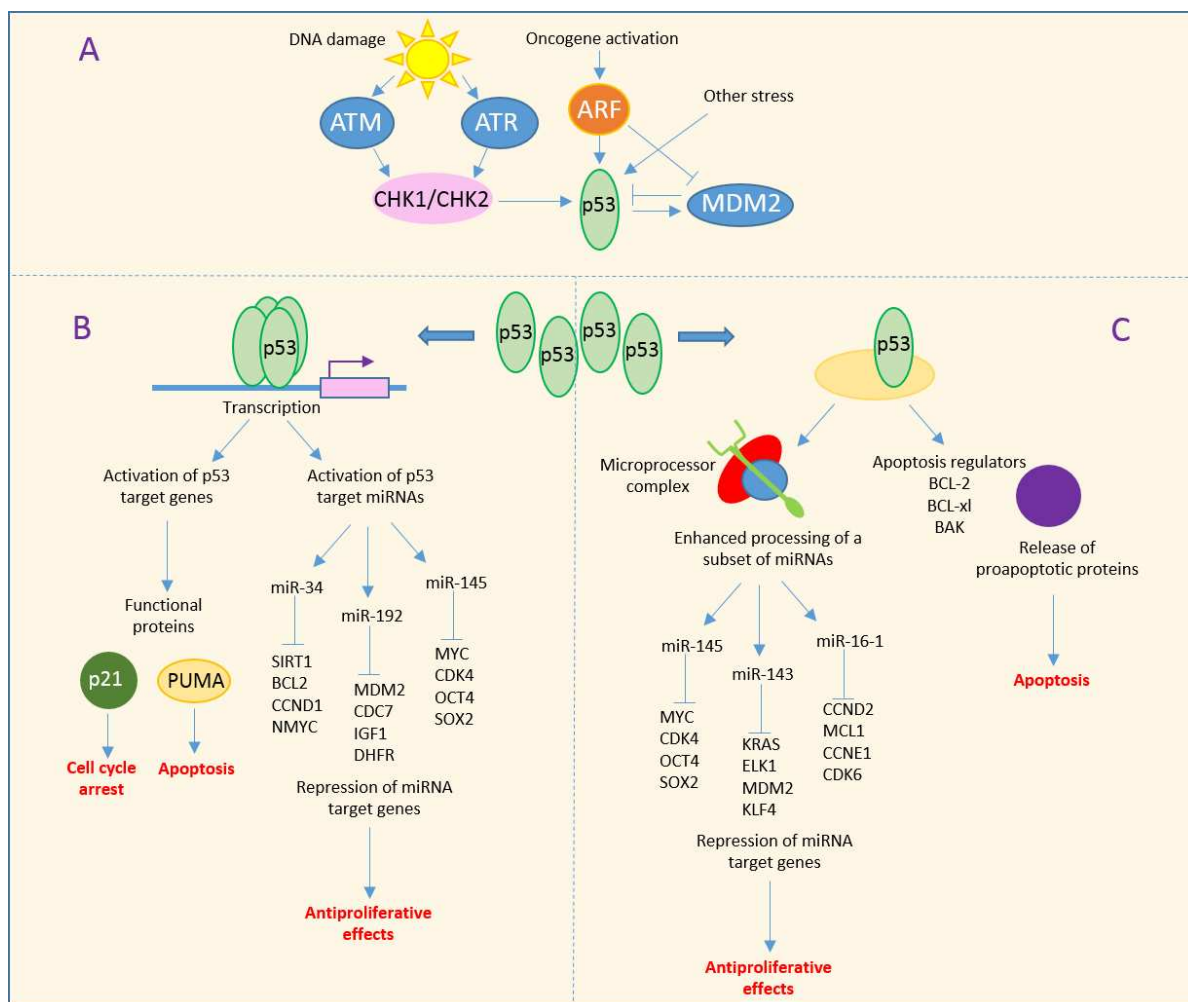


Figure 4. The effect of miRNAs in the p53 pathway. A. The main genes involved in the posttranscriptional control of p53. B. The mission of transcription factor p53 and activation of it by proteins and miRNAs. C. Post-transcription stage of p53. An association between miRNAs, p53, and apoptotic genes was demonstrated [55].

7.3. Oncogenic MicroRNAs in breast cancer

Some miRNAs, which suppress the expression of antioncogenes in apoptosis, metastasis, invasion and cell proliferation play roles as oncomirs and their expression is increased in breast cancer [56]. The oncogenic miRNAs and their families have been identified as miR-10, miR-15, miR-16, miR-17~92 cluster, miR-18, miR-19, miR-20, miR-21 family, miR-92 miR-155, miR-569.

7.3.1. miR-10

miR-10a and miR-10b are subtypes of the miR-10 family and play a role in metastasis and development [57]. The miR-10 family regulate Hox transcripts, and thus function in development [58]. The dysregulation of this miRNA family was identified not only in breast cancer, but also in colon cancer [59], melanoma [57], acute myeloid leukemia [60], glioblastoma [61], hepatocellular carcinoma [62] and pancreatic cancer [63].

The expression level of miR-10b is negatively correlated with E-cadherin, but it increases metastasis, tumor size, and clinical staging. It was observed in a murine xeno- graft model of breast cancer that when miR-10b is overexpressed, it increases invasion and migration [64].

7.3.2. *miR-17*

This miRNA was identified firstly as a member of the OncomiR-1. miR-17 plays a role in the cell cycle with transcription factor E2F1 and leads to cancerous growth [65]. The miR-17~92 cluster is amplified in lymphomas [66]. Although researchers detected that this miRNA cluster is downregulated in metastasis, miR-17-5p was different from them. It is expressed at very/ extremely high levels in invasive MDA-MB-231 breast cancer cells but not in non-invasive MCF-7 breast cancer cells. This group can cause migration in MCF-7 cells by targeting the HBP1/ β -catenin pathway and reduction of miR-17-5p suppresses the invasion of MDA-MB-231 cells in vitro [67]. In addition, this miRNAs has subtypes including miR-18b, miR-19b, miR-20a, miR-92, miR-93 and miR-106 which are found to be amplified in lymphomas [66, 68].

7.3.3. *miR-21*

Chan et al. first reported high levels of miR-21 in human glioblastoma tumor tissues [69]. It is a major miRNA for breast cancer, because of it roles in cell migration, invasion and tumor progression [70]. This is confirmed by studies from several groups. For instance, Singh et al., using real time RT-PCR array analysis, reported that overexpression of miR-21 in breast tumors as compared with normal breast tissues [71]. Iorio et al. used microarray and northern blot analyses, and found the aberrant expression of miR-21, miR-125b, miR-145 and miR-155 in human breast cancer [40].

Clinicopathologic features of miR-21 and the association of PTEN were determined in a study by Huang et al. using real-time RT-PCR and immunohistochemistry (IHC) analyses. They researched miR-21 expression in non-tumor and tumor tissues of 40 human invasive ductal carcinoma of the breast and reported that the association of PTEN (phosphatase and tensin homolog deleted on chromosome 10) and miR-21 expression inversely correlated in breast cancer and that miR-21 causes metastasis [72].

7.3.4. *miR-155*

This oncomir is highly expressed in human cancers. Suppressor of cytokine signaling 1 (SOCS1) is a target gene of miR-155 in human breast cancer. Research indicates that SOCS1 is negatively regulated by miR-155, and may be a potential target in breast cancer therapy [73].

7.4. Metastatic MicroRNAs in breast cancer

Metastasis is the primary cause of mortality in breast cancer. In metastasis, cancer migrates from a primary solid tumor to distant parts of the body [74]. Mesenchymal to epithelial transition (MET) and epithelial to mesenchymal transition (EMT) are causes of metastasis [75]. Recent research shows that some miRNAs levels decrease, but others accumulated during metastasis of breast cancer [76]. The miR-9,36 miR-10b,37,38 miR-21,39-45 miR-29a,46

miR-15547 and miR-373/520 families promote metastasis in BC [77]. For instance, miR-9 plays a role cell motility focusing on E-cadherin and raises the level of vascular endothelial growth factor (VEGF) [78]. Tristetraprolin, the target of miR-29a, regulates EMT and metastasis in BC [79]. miR-373/520 can increase invasion and migration by CD44. The connection of miR-373 and CD44 expression was displayed thanks to clinical metastasis samples [77]. Subgroups of miRNA that prevent metastasis in BC are: miR-7,50-52 miR-17/20, 53, 54 miR-22,55- 57 miR-30, 58, 59 miR-31,60-62 miR-126,63-68 miR-145,69-72 miR- 146, 73, 74 miR-193b,75 miR-205,76,77 miR-206,78-80 miR-335,32,81 miR-448,82 miR-66183,84 and let-7 [46].

Some miRNAs were selected to determine their roles in metastasis. Epidermal growth factor receptor (EGFR), a regulator of cellular processes and overexpressed in breast cancer, is associated with miR-7 and causes metastasis [80]. Several cancer types are inhibited by miR-7 include p21-activated kinase 1 expression which is a signaling kinase. If overexpression of miR-7 is present in BC cells, it causes migration to other tissues in BC [81].

miR-17 is known as an oncogenic miRNA in other cancers. When miR-17/20 is overexpressed in breast cancer cell lineage, it stops cell proliferation and causes G1 cell cycle arrest. This miRNA's target is cyclin D1 rolled in G1-S phase transition. In ~50% of human breast cancers cyclin D1 expression is increased. It has an inverse correlation with miR-17/20 [82].

When analyzed non-invasive breast cancer cell MCF-7 and invasive MDA-MB-231 cell line, miRNAs' role in inhibition of invasion was determined. While miRNA is inhibiting invasion, it connects IL-8 and cytokeratin 8 through cyclin D1 [83]. In vivo and in vitro investigation about breast cancer shows that overexpression of miRNA causes a reduction in cell motility through targetting CDK6, SIRT1 and Sp1. Furthermore, miR-22 targets estrogen receptor α (ER α) and suppresses cell proliferation on ER α -dependent breast cancer [84]. miR-145 and miR-146 are very important tumor suppressors miRNAs in breast cancer. miR-145 prevents metastasis by targeting IRS-1, mucin-1, c-myc, JAM-A and fascin [54]. In an MDA-MB-231 mouse model experiment, miR-146 induces EGFR, which plays a role in inhibition of metastasis [85]. It also downregulates interleukin receptor associated kinase and TNF associated factor 6 and controls NF κ B [86]. Mo's research displayed that the overexpression of miR-30 suppresses cell growth by targetting Ubc9, and plays a role in cell growth and cancer development. This pathway was also seen in breast cancer [87].

8. Conclusion

Recently, breast cancer has been thoroughly studied, because approximately 13 million women will be diagnosed with breast cancer globally and about 465,000 will die from the disease [10]. Researchers have conducted a variety of experiments concerning breast cancer and its pathways. Although there are many breast cancer therapies, alternative methods are being developed. In particular, research focused on molecular mechanisms are currently popular. miRNAs are an alternative methodology as a potential therapeutic target for breast cancer. The association of miRNAs and breast cancer is discussed, including miRNAs as candidate diagnostic and prognostic indicators in breast cancer. Combinations of different anticancer

agents with miRNA can be more effective as therapeutic approaches. Hence, some of miRNAs can be utilized as breast cancer biomarkers. Briefly, the main subtypes of miRNAs are discussed in this chapter, and several lines reseache focus on other types of miRNAs.

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