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Review Article

MicroRNAs in Breast Cancer: A Review

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ABSTRACT

MicroRNAs (miRNAs) are a class of small noncoding RNAs that control gene expression by targeting mRNAs and leading to either translation repression or RNA degradation. Their aberrant expression may be involved in human diseases, including cancer. Breast cancer is the most common cancer among females around the world that is the most prevalent cause of death among females suffering from cancer. Many studies have identified a large number of upregulated oncogenic miRNAs and down regulated tumor-suppressor miRNAs in this type of cancer. In this review, we provide an overview of the biogenesis and role of miRNAs in cancer and summarize the most recent studies focusing on distinctive expression of miRNAs and their potential to be useful as diagnostic and prognostic biomarkers in breast cancer.

Keywords: MicroRNA, Breast Cancer, Tumor-suppressor

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MicroRNAs (miRNAs) are small noncoding RNA molecules of 19–25 nt that work in the post-transcriptional regulation of gene expression and controls them in many cellular processes such as inflammation, cell-cycle regulation, stress response, differentiation, apoptosis, and migration (1). Pairing with messenger RNAs (mRNAs) of genes that code proteins, they lead to repression or degradation of mRNA translation (1-3). Thus, miRNAs have been implicated in the regulation of signaling in a cell, and their deregulation has been shown to play an essential role in the development and progression of various kind of diseases such as cancer (4). miRNAs can be found in blood, milk, urine and other body fluids and their levels have often been reported to be altered in patients. Circulating miRNAs became one of the most promising biomarkers in oncology for early diagnosis, prognosis and therapeutic response prediction (5). Now, microRNAs are intensely studied as candidates for diagnostic and prognostic biomarkers for cancers and predictors of drug response.

Breast cancer is the most common cancer among females around the world that is the most prevalent cause of death among females suffering from cancer. Breast cancer contains 25% of the total number of

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cancers by 1.7 million cancer cases reported in 2012 (6). Various miRNAs have been recognized, in which their expression were deregulated in the blood or tissue of patients with breast cancer.

Here we describe the origins and roles of miRNAs, and summarize the most recent studies focusing on their distinctive expression in breast cancer.

Biogenesis of miRNAs

miRNAs are small (~22 nucleotide long) non-coding RNAs that are part of a eukaryote system of genomic DNA within the nucleus which cary out gene regulation at the RNA level. MiRNAs work as post-transcriptional regulators of gene expression by base pairing with their target mRNAs. MiRNAs are first transcribed by RNA Pol II (7) as parts of longer RNA molecules (pri-miRNA)(8). pre-miRNA loops (~70 nts) are cleaved from the pri-miRNA by RNAse III enzyme and Drosha and transported into the cytoplasm by RAN-GTP and Exportin 5 (9). pri-miRNA will be processed further by Dicer in order to construct a ~22 nt long duplex(miRNA:miRNA*) (10).

The miRNA:miRNA* duplex is subsequently unwound and the mature miRNA is loaded into multi-protein RISC (RNA-induced silencing complex) (11) and miRNA* usually degrades. The miRNA biogenesis is illustrated in Figure 1. Depending on the degree of complementarity between the miRNA and its target mRNA sequence, mature miRNAs can cause translation inhibition or mRNA cleavage. Each miRNA may have multiple mRNA targets and each gene can be targeted by multiple miRNAs. It has been predicted miRNAs regulate more than one third of human genes (12).

miRNA function in cancer

Cancer development is the result of several complicated processes that involves multiple alterations in oncogenes and tumor suppressor genes over several years. A great deal of researches already determined an important role for miRNAs among the many regulatory factors involved in the pathogenesis of cancer. miRNAs are up or down regulated in tumors in comparison with the normal tissues, and they can be considered as oncogenes or tumor-suppressors, respectively. They contribute to cancer by regulating either oncogenes (tumor suppressor miRNA) or tumor suppressors (oncomiRs). Most of the time it has been seen that oncomiRs, such as miR-17-92 cluster (14) or miR-21(15), are upregulated and tumor suppressor

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miRNAs, such as let-7 family, are downregulated (16).

Dysregulation of the miRNAs expression leads to several disorders in critical biological processes such as proliferation, differentiation, apoptosis, EMT (epithelial mesenchymal transition) and migration which results in oncogenesis. As a known example of a deregulated miRNA, miR-21 is a miRNA which

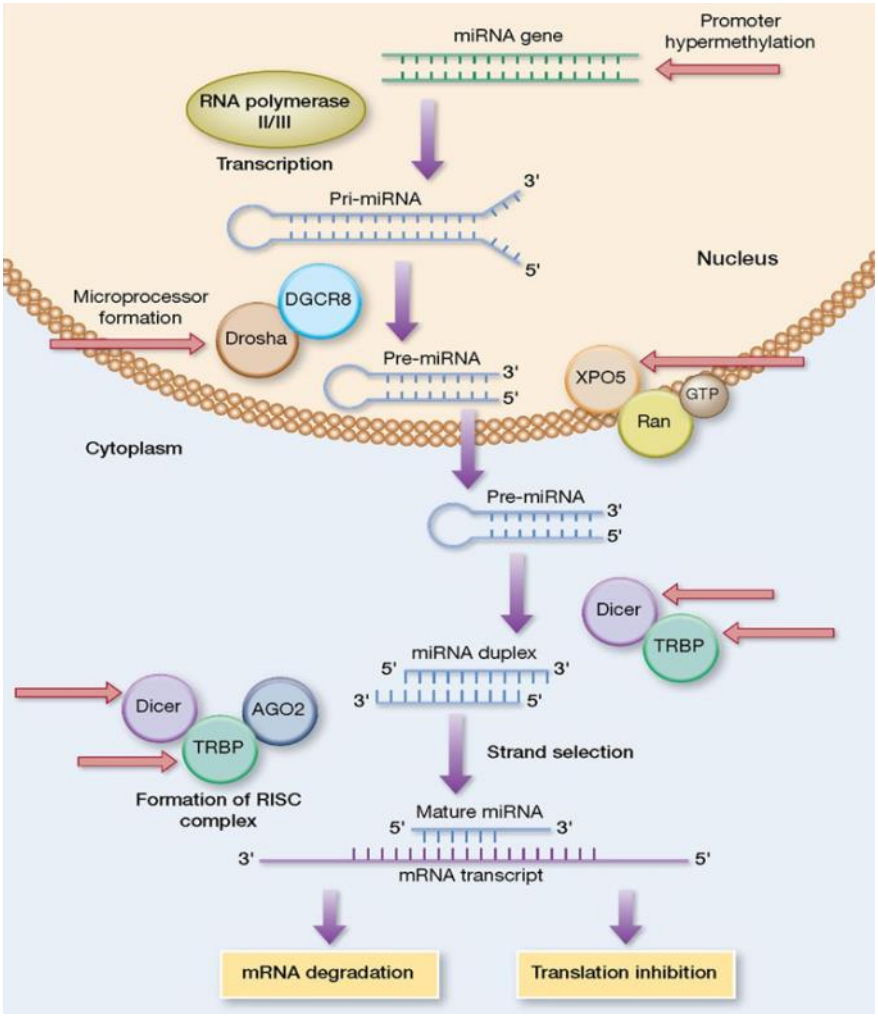

Figure 1: miRNA biogenesis process. A schematic representation of miRNA biogenesis. Each miRNA is transcribed by RNA polymerase II (pri-miRNA) from genomic DNA within the nucleus; pri-miRNA is processed by Drosha-DGCR8 and cleaved to pre-miRNA. Pre-miRNA is exported to the cytoplasm by exportin 5(XPO5), where it is processed and cleaved by DICER complex to a double strand miRNA (miRNA*-miRNA). The duplex is splitted, and only the mature miRNA is loaded into the RISC complex. The degree of complimentary of the miRNA to the 3′ UTR target sequence of the mRNA specifies the mRNA translational inhibition or degradation(13).

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is prevalently upregulated in any kinds of cancer (17). miR-21 affects all major pathways of carcinogenesis (proliferation, apoptosis, angiogenesis and invasion), through its multiple targets including PTEN (phosphatase and tensin homolog)(18), PDCD4 (tumor suppressor gene tropomyosin 4) (19)FasL (pro-apoptotic FAS ligand) (20), and TIMP3 (metalloproteinase inhibitor 3 precursor) (21).

Moreover an alteration of the expression or function of enzymes of the miRNA processing, such as Drosha, Dicer or DGCR8, was reported in cancer (22).

In addition, many studies indicate that the microRNA expression may be also affected by different epigenetic mechanisms leading to the silencing of the tumor suppressor microRNA including abnormal methylation of the promoter regions (23) or histone modifications (24).

Dysregulated miRNAs in breast cancer

breast cancer is the most common cancer in women worldwide. Several methods such as Mammography and ultrasound imaging have been employed for diagnosis of breast cancer and prolonged patient survival, but they are known to have some limitations for early detection, sensitivity and specificity. Several studies have focused on dysregulated miRNAs as potential biomarkers for early diagnosis of breast cancer which could be used along with other methods of detection. ubnormal expression of miRNAs can be found in tissue or body fluids of patients. Here we want to review some studies which have been done in this area of research. MiR-21 is one of the most commonly studied oncomiRNAs which has been reported to be up-regulated in serum of BC patients compared with healthy controls (25-26). Li and collagues performed a meta-analysis of six studies in order to assesse diagnostic capacity of miR-21 in breast cancer patients and showed that miR-21 could be a specific and sensitive biomarker for early diagnosis of breast cancer (27).

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Wu et al. (28) found the raised serum expression level of miR-21 and miR-29a in breast cancer patients using deep sequencing technique.

According to a large cohort study which designed to identify expression level of serum miRNA, a total of 1280 serum samples of breast cancer patients compared with healthy samples. As a result a combination of five miRNA (miR-1246, miR-1307-3p, miR-4634, miR-6861-5p and miR-6875-5p) was found to be able to detect breast cancer at early stage (29).

Moreover, Hagress et al quantified levels of 5 miRNAs in sera of breast cancer patients and control samples. They found that expression of miR-10b, miR155, and miR195 in breast cancer patients was significantly up-regulated than control group and could be used as potential novel biomarkers for breast cancer (30). Also miR-195 was up-regulated in 148 patients in Heneghan et al. study (31).

Another study which has been done by Iorio et al. identified 29 miRNAs that had significant differences in expression in breast cancer tissue compared to normal tissue. Among these miRNAs, miR-21 and miR-155 were up-regulated while miR 10b, miR-125b and mR-145 were downregulated in the breast cancer tissue (32). Also Wang and collagues examined the expression level of some microRNAs in tissues and sera from breast cancer patients. The expression level of miR-21, miR-106a, and miR-155 was up-regulated and miR-126, miR-199a, and miR-335 were down-regulated in tumor tissues in comparison with normal samples (33).

A research that was done with Enders et al. reported the up-regulation of miR-16, miR-21 and miR-451 in plasma of breast cancer patients. They also proposed that the signature of miR-451 and miR-145 could be potential biomarkers for screening breast cancer (34).

Aguilara and coworkers performed miRNA profiling on the serum of breast cancer patients and examined the sensitivity and specificity of miRNAs by construction of Receiver Operating Characteristic (ROC) curves. Seven miRNAs (miR-10b/21/125b/145/155/191/382) had different expression levels in the serum of cancer patients compared to normal controls. With ROC curve analysis three serum miRNAs (miR-145, miR-155 and miR-382) was suggested to be as novel noninvasive biomarkers for breast cancer detection (35).

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Conclusion

Breast cancer is the most common cancer among females around the world that is the most prevalent cause of death among breast cancer patients. Thus detection of disease at early stages is very important and vital. A large body of studies have been done to investigate expression level of miRNAs which their results indicate prognostic and predictive values of cancer-related circulating miRNAs or tissue specific miRNAs in breast cancer patients. Various miRNAs have been recognized, in which their expression were deregulated in the blood or tissue of patients with breast cancer. Since miRNAs are detectable in body fluids such as blood at very early stages of cancer, they can be employed as non-invasive biomarkers. However, because many parameter such as small sample size, sample type, experimental methods of profiling, treatment/tumor heterogeneity, stage, ethnic differences affect the results, additional studies in larger homogeneous populations are required to investigate the value of these biomarkers. Moreover, new technologies, such as microRNA microarray and next-generation sequencing, could help identify new potential miRNA biomarkers.