Relationship between microRNA-9 and breast cancer

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Review

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Abstract

Breast cancer is the most frequent malignancy in women and has devastating effects on both their physical and emotional wellbeing. More cases of it are expected to surface in the future. Mounting data shows that microRNAs (miRNAs) play critical roles in carcinogenesis and development. This study highlights the contrasting roles of miR-9 in breast cancer, which is important since miR-9 plays a crucial role in both the development and the progression of the disease. The major focus of this article is a brief summary of miR-9's functions in the development of breast cancer.

Keyword: Tumorigenesis and development of breast cancer, miR-9, oncogene, tumor suppressor

1. Introduction

Among women, breast cancer has the highest incidence rate and is the second greatest cause of cancer-related mortality [1]. Breast cancer has a complicated and multifaceted etiology. More and more evidence suggests that miRNAs (microRNAs) have a role in controlling breast cancer development and progression [2,3]. Small noncoding RNAs (ncRNAs) called microRNAs (miRNAs) are found in all eukaryotic cells and are responsible for posttranscriptional regulation of gene expression by interacting with the 3′ untranslated regions (3′UTRs) of target transcripts. More than 2500 mature miRNAs were found in human to far, which are involved in individual development, cell proliferation, differentiation and apoptosis [4]. Due to their central roles in carcinogenesis, cancer invasion, metastasis, relapse, and medication resistance [5, 6], miRNAs have received considerable interest in cancer research over the last several decades. Researchers found that miR-9 expression is distorted in breast cancer. The roles of miR-9 in controlling breast cancer, however, have been shown to be counterintuitive. In this article, we will examine the methods by which miR-9 influences the onset and progression of breast cancer.

2. Where microRNAs came from

While RNA polymerase II is the primary mediator of miRNA transcription, several other enzymes and proteins are involved in the maturation process [4]. The exact mechanism is as follows: Firstly, the first transcripts of miRNAs with

stem-ring structure are produced, designated as primary miRNAs(pri-miRNAs)which contain the thousands of nt in length. Secondly, the nucleic acid endonuclease Drosha cleaves the stem-ring structure, producing the pre-miRNAs with a hairpin length of around 70 nt. These pre-miRNAs are then exported to the cytoplasm by exportin 5, where they are further cleaved by another endonuclease, Dicer, into approximately 22 nt double-stranded RNAs. A number of cofactor proteins are involved in the cleavage of Drosha and Dicer; for example, DGCR8 is required for Drosha-mediated cleavage of pri-miRNA [6], while TRBP is required for Dicer-mediated cleavage of pre-miRNA [7]. In the end, these dsRNAs are loaded into Ago protein, establishing the RNA-induced silencing complex (RISC) [8], where one chain is kept in RISC to carry out its activities and the other is eliminated. Target 3′UTRs are targeted by miRNA, which directs RISC to block, cleave, or destroy the corresponding mRNA. Cleavage of target transcripts by RISC necessitates full complementary pairing of the miRNAs with target transcripts; however, the matching degree of miRNAs with target transcripts is not great in animals, leading to the unusual cleavage in animals. Given that a single miRNA may control several downstream targets, miRNAs have broad effects in both healthy and diseased states. Professor RA Weinberg of MIT is a renowned oncologist who has written two evaluations on the subject of cancer, "Hallmarks of Cancer" in 2000 and "Hallmarks of Cancer: the next generation" in 2011. He summed up cancer's defining features, discussed every angle of the disease, and is often referenced for his work. According to these two studies, miRNAs control every aspect of malignancies [9,10]. This article summarizes the current understanding of miR-9's functions and associated pathways in breast cancer.

In the research carried out by Mojdeh Mahmoudian and her colleagues, it was shown that the expression of particular microRNAs was higher in BC tumors than it was in the tissues that were next to the tumors. To be more specific, hsa-miR-25-3p, -29a-5p, -105-3p, and -181b1-5p were all found to have an increased expression level, whilst hsa-miR-335-5p and -339-5p were found to have a decreased expression level. With the exception of hsa-miR-339-5p, it was discovered that the TNM phases were related with the upregulation or downregulation of these putative microRNAs. In addition, all of the potential microRNAs linked with the status of HER-2, with the exception of hsa-miR-105-3p. In addition, the results of the analysis of ROC curves demonstrated that the combination of these six microRNAs has the potential to act as a biomarker that differentiates between breast tissue samples that include tumors and those that do not have tumors.

3. miR-9 enhances breast cancer's propensity for metastasis and the development of CSCs (cancer stem cells).

Recent research has overwhelmingly shown that miR-9 has a tumor-promoting function in breast cancer growth, mostly by boosting the disease's metastatic potential (Table 1). According to global miRNA expression profiling done by Grarguard et al. [11] on 47 matched primary and metastatic breast tumor samples from 14 patients with or without lymph node and distant metastases, miR-9 is considerably elevated in the metastatic tumors. Because of their specific expression profiles in cancer cells and tissues, their ability to enter the body's fluid circulation, and their relatively high chemical stability, miRNAs have been identified as a promising and non-invasive tumor marker. For example, Naorem LD et al. [12] used meta-analysis to pool data from ten miRNA profiling studies of triple-negative breast cancer (TNBC) and found that miR-9 is highly expressed; this finding has important implications for TNBC diagnostics.

CSCs have been proven to be the origin of cancer development and therapy resistance in recent investigations [13]. Cancer stem cells (CSCs) are a subset of tumor cells that may self-renew, undergo cell-to-cell differentiation, and react to phenotypic changes in the tumor microenvironment [14]. When polarized, non-migrating epithelial cells undergo epithelial-to-mesenchymal transition (EMT), they acquire the properties of migrating and invading mesenchymal cells as well as the capacity for self-renewal and stem cell-like properties, thereby increasing the generation of CSCs [15]. According to a systematic search of PubMed and Medline databases conducted by Piasecka D et al. [16], four microRNAs (miR-9, miR-221/222, miR-373, and miR-10b) were found to be significantly upregulated and strongly associated with invasion and EMT/CSC properties. Strong evidence was shown by Cheng CW et al. [17] showing overexpression of miR-9 and miR-221 signals a bad result and may promote CSC formation leading to an invasive

phenotype. According to Gwak JM et al. [18], cancers with a CD44+/CD24- phenotype, vimentin expression, and E-cadherin loss are more likely to express miR-9 than luminal tumors, those with a high tumor stage, and those with a high histologic grade. In sum, miR-9 is a perfect predictor of breast cancer start, metastasis, and chemoresistance since CSCs are thought to be at the root of carcinogenesis, development, and drug resistance.

4. MiR-9 is significantly associated with breast cancer outcome and recurrence.

Furthermore, miR-9 is an independent risk factor for shorter times without illness. There is a strong correlation between miR-9 and recurrence and survival in breast cancer (Table 1). MiR-9 is emerging as a biomarker for diagnosis and prognosis, and miR-9-based medication is a potential therapeutic for breast cancer, as revealed by a study of miRNAs implicated in the onset and course of the disease by Bertoli et al. [19]. Furthermore, miR-9 was included in a summary of miRNAs identified as possible diagnostic miRNAs in breast cancer by Bertoli et al. [20]. Low miR-9 expression appears to have a protective effect and is associated with improved overall survival (OS), smaller tumors, and ER (estrogen receptor, ER)-positive (ER+) cancers, as determined by an analysis of 985 breast cancers from The Cancer Genome Atlas (TCGA) by Sporn JC et al. [21]. High miR-9 levels may be a prognostic marker in TNBC, as demonstrated by Jang MH et al. [22]. This is because they are substantially correlated with poor disease-free survival and distant metastasis-free survival. In ER+ breast cancer cases, Zhou X et al. [23] showed that miR-9 level predicts LR, and that patients with a lower miR-9 level had a better 10-year LR-free survival.

Taken together, miR-9 might boost breast cancer metastasis and CSCs-like features notably in highly aggressive breast cancer such as TNBC. Furthermore, miR-9 might be a potential biomarker for breast cancer detection and prognosis, since it is strongly linked to breast cancer recurrence and a poor prognosis. So, how does miR-9 function?

5. The mode of action of miR-9

5.1. The post-transcriptional regulation of gene expression by miR-9 occurs by direct binding to target genes.

By binding to the 3′-untranslated regions of target genes, miRNAs suppress their expression after transcription has already taken place. This mechanism (Fig. 1) is another way in which miR-9 promotes the onset and progression of breast cancer. Breast cancer cells' migration and invasion may be encouraged by miR-9 because it targets forkhead box O1 (FOXO1). This was validated by Liu DZ et al. Ma L et al. [25,26] revealed that the production of miR-9 is triggered by MYC and MYCN, and its overexpression leads to enhanced cell motility and invasiveness by directly binding to the critical metastasis-suppressing protein E-cadherin. Cancer cells become more metastatic when E-cadherin is downregulated, which accomplishes two things: (a) it prepares the cells for epithelial-mesenchymal transition (EMT) and invasion; and (b) it activates -catenin signaling, which increases VEGF expression and thus tumor angiogenesis. Ma L et al. [27] further examined E-cadherin-independent effects of miR-9 and found leukemia inhibitory factor receptor (LIFR) as a miR-9 target in E-cadherin-negative tumor cells and a novel metastasis suppressor, which inhibits metastasis by activating the Hippo-YAP pathway. As a result, LIFR depletion is associated with a dismal prognosis in breast cancer. Previous research from our lab showed that miR-9 promotes EMT and metastasis in breast cancer by focusing on STARD13 [28]. Our findings are supported by those of D'Ippolito E et al. [29], who found that ligand-dependent activation of PDGFR signaling induced endogenous miR-9 expression, which in turn repressed STARD13 and promoted the creation of vascular-like structures in TNBC cells.

5.2. MiR-9 mediates interactions between competing endogenous RNAs (ceRNAs) that control the development of breast cancer.

RNAs with the same miRNA binding sites might cross-talk by competing for miRNAs; this phenomenon was termed ceRNA and added to post-transcriptional suppression of targets by miRNAs. One of the hottest topics in recent years is the ceRNA mechanism, which explains how coding and non-coding genes may mutually control expression by

binding competitively to the same miRNAs [30]. The CeRNA mechanism introduces a novel paradigm for regulating gene expression and a fresh approach to studying the transcriptome, allowing for a more in-depth and thorough explanation of a variety of biological events. As can be shown in Fig. 1, miR-9 may play a mediating role in ceRNA interactions that drive breast cancer growth. 2. Inhibiting the metastasis of breast cancer cells by inducing E-cadherin expression through the miR-9-mediated ceRNA mechanism [31] is one such example. Our previous study confirmed that miR-9 could bind to both the FOXO1- and E-cadherin-3′UTR, and that there was competition of miR-9 between FOXO1- and E-cadherin-3′UTR. Additionally, our earlier findings revealed that CYP4Z1 3′UTR limits the migration and EMT of breast cancer cells by functioning as a ceRNA for E-cadherin, since CYP4Z1 is a possible target of miR-9 too [32]. We further confirmed that the 3′UTRs of CDH5, HOXD1, and HOXD10 suppress breast cancer metastasis by acting as STARD13 ceRNAs, which prevents the miR-9, miR-10b, and miR-125b from doing their jobs [28]. These findings point to a crucial function for miR-9-mediated ceRNA regulatory networks in the development of breast cancer.

5.3. Exosomal miR-9 promotes breast cancer development.

Importantly, miRNA may be transported via exosomes to exercise its effects. Exosomes, which have dimensions between 50 and 150 nm, are a kind of membrane-bound extracellular vesicle. Some molecules, such microRNAs (miRNAs), are packaged within exosomes. More and more data suggests that tumor cells secrete and transmit exosomal miRNAs to interact with both other tumor cells and cells present in the tumor microenvironment. More critically, exosomal miRNAs are shown to act as signaling molecules to control tumor development, angiogenesis, metastasis, susceptibility to chemotherapy, and immune evasion [33]. Tumor-secreted miR-9 may be transported by exosomes to recipient normal fibroblasts (NFs), as shown by S Baroni et al. [34], and this absorption contributes to the conversion of NFs into CAFs, which in turn increases cell motility in breast cancer. Treatment of MCF-7 cells with exosomes from MDA-MB-231 cells leads to the downregulation of target gene PTEN of MCF-7 cells, hence making MCF-7 cells more metastatic, as previously reported by Kia V et al. [35]. Inducing CSC traits and chemotherapy resistance, Shen M et al. [36] found that breast cancer cells secrete multiple microRNAs (miRNAs) into extracellular vesicles (EVs), including miR-9, miR-195, and miR-203a-3p. These miRNAs all target the transcription factor One Cut Homeobox 2 (ONECUT2).

6. The potential of miR-9-based pharmaceuticals

Due to its intricate regulation mechanism, miRNA has the potential to be used as a therapeutic target in a wide range of pathological diseases. A single miRNA may control many target genes, and a single target gene can be targeted by numerous miRNAs. Meanwhile, advancements in RNA molecular delivery technologies have raised the feasibility of treating illness using miRNAs. Just over 20 years after its discovery, miRNA research has moved out of the lab and into the clinic. Phase I clinical studies have been completed successfully, and phase II trials are now under way. The mi34 (MRX34) miRNA analogue is one of the most rapidly expanding areas of cancer therapy. It has shown promising therapeutic results in phase I clinical trials for the treatment of patients with primary liver cancer, small cell lung cancer, lymphoma, melanoma, multiple myeloma, and renal cell carcinoma. In addition, there have been phase I clinical trials of miR-16 analogues in patients with malignant pleural mesothelioma or non-small cell lung cancer, where EGFR antibody-coated EDV nanoparticles are used to deliver miR-16 to cancer tissues and five patients recruited in the first batch achieve some extent of therapeutic effects [37]. Based on the observation that miR-9 is overexpressed in breast cancer, Yu Y et al. developed a cascade miRNA recognition system to selectively kill cancer cells by inducing the expression of a reporter gene (fluorescent protein) or the anticancer gene p53. Nude mice have tumors that are 58% smaller in volume and weight than control mice, indicating that miRNAs may be employed as biomarkers and have

significant promise as a cancer treatment [38]. Given that miR-9 has been shown to sensitize acute myeloid leukemia (AML) to Daunorubicin [39] and that chemotherapy induces breast cancer cells to secrete miR-9-based EV resulting in chemoresistance [36], this raises the intriguing possibility that miR-9 could be combined with other drugs to improve the efficacy of treatment and attenuate drug resistance, or be a predictor of response to chemotherapy in breast cancer.

7. Proliferation of breast cancer cells is inhibited by miR-9.

It is intriguing that miR-9 may have a tumor-suppressing function in breast cancer proliferation regulation. The tumor suppressor-like action of miR-9 in breast cancer cells was shown by Selcuklu SD et al. [40], who found that miR-9 may decrease cell proliferation and increase cell death by directly targeting MTHFD2. Supporting Selcuklu SD's position, Zhao X et al. [41] discovered that the lncRNA taurine-upregulated gene 1 (TUG1) promotes cell proliferation by inhibiting miR-9 and that TUG1 positively regulates the expression of MTHFD2 in MCF-7 cells. Baldassari F et al. [42] also demonstrated that the combination of specific miRNAs, including miR-181a, miR-326, miR-9, and miR To better understand the differences between tumoral and peritumoral tissues in breast cancer patients, G Sun et al. [43] found a profile of miRNAs (miR-9, miR-148a, miR-31, miR-375, miR-21, miR-135b, miR-196a, and miR-196b). By directly targeting Her-2, ectopic expression of miR-9 suppressed colony formation and tumor engraftment in breast cancer cells and enhanced their sensitivity to docetaxel (DOC) and cyclophosphamide.

8. Prospectives

Breast cancer is a deadly illness that poses a major risk to human health due to its widespread prevalence among women across the globe. microRNAs are very important in breast cancer progression and survival. MicroRNAs (miRNAs) have the properties of multi-target and efficient regulation since a single miRNA may affect numerous target genes. Using miRNAs as a therapeutic target has the potential to open up new avenues in cancer therapy. An increasing body of research confirms that miR-9 is abnormally expressed in breast cancer. Studies to date have suggested that miR-9 acts as an anti-oncogene in breast cancer proliferation, preventing the disease in its earliest stages, but as an oncogene in the dissemination of more malignant breast cancers. Therefore, the stage of breast cancer determines the miR-9 level and its function in breast cancer.

Cancer biomarker research has increasingly focused on circulating miRNAs due to their small size, stability, and non-invasive access, making them ideal candidates for usage as inexpensive, readily available, and therapeutically applicable molecular biomarkers for diagnosis and prognosis. With the advancement of sequencing technology, miR-9 may be used as a non-invasive tumor marker of breast cancer by measuring miR-9 level in human blood, urine, or bile due to its specificity in expression in breast cancer and its ability to enter the humoral circulation and stability. Further investigation into exosomes may one day allow for their application in the delivery of miRNA-9 inhibitors to breast cancer tissues. Finally, miR-9-knockout mice combined with the spontaneous breast cancer model (MMTV-PyMT) mice can be better used for evaluating the function of miR-9 in breast cancer, and other genetically-modified mice models with miR-9 knockout should be used for this analysis as well.

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