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Review Article

A review of research on relationships between breast cancer and microRNAs

Xiping Zhang[1], Binbin Tang[2], Bin Xu[3], Shuai Zhao[1]

[1]Department of Breast Surgery, Zhejiang Cancer Hospital, Hangzhou 310022, Zhejiang Province, China; [2]Second Outpatient Department of Traditional Chinese Internal Medicine, Tongde Hospital of Zhejiang Province, Hangzhou 310012, Zhejiang Province, China; [3]Institute of Occupational Diseases, Zhejiang Academy of Medical Sciences, Hangzhou 310013, Zhejiang Province, China

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Abstract: As the leading cause of death for women, breast cancer is highly metastatic and quite likely to mutate. As a type of small-molecule non-coding RNAs. MicroRNAs (miRNAs) have been discovered to be useful for regulating breast cancer. They affect cycle, apoptosis, proliferation, migration, metastasis and drug resistance of breast cancer cells, breast cancer stem cells and epithelial-mesenchymal transition, so they play certain roles in incidence, progression, metastasis and drug resistance of breast cancer. Research has suggested that some miRNAs may promote incidence and progression of breast cancer, while some others may inhibit them. In this paper, current research about roles of miRNAs in promoting and inhibiting incidence and progression of breast cancer, including phenotypes, mechanisms and some signaling pathways concerned, is summarized comprehensively. This paper proposes that breast cancer would be treated by intervening with miRNAs to inhibit breast cancer, and puts forward possible challenges to above ideas about breast cancer treatment.

Keywords: Breast cancer, miRNAs, signaling pathways

Introduction

As a category of short non-coding RNAs, MicroRNAs (miRNAs) are made up of about 22 nucleotides. They are negative gene regulators that may upregulate expressions of target genes. Although miRNAs target at numerous genes, they are very few. Generally, a miRNA may interact with multiple target genes, so several miRNAs may even have interactions with hundreds of mRNAs, Hence, they are considered to be one of the most important regulators for gene regulation, and play their roles in a way as follows: miRNAs are fused into untranslated regions (UTRs) at 3' or 5' ends of target mRNAs and thereby lead to degradation of the mRNAs or inhibited translation [1, 2].

Distributed in different positions of genes, some miRNAs are located in antisense regions of introns, whereas some of them lie in exons. They are produced through a similar process as follows no matter where they are distributed. First of all, pri-miRNAs with nearly 1,000 nucleotides are generated after the transcription of RNA polymerase II before the formation of pre-miRNAs closer to the mature ones with the regulation of Drosha which belongs to a RNase III family [2, 3]. Subsequently, a double-stranded miRNA is produced when a type of RNase III known as Dicer is cut. At last, one strand interacts with RNA-induced silencing complex (RISC) to produce a mature miRNA, while the other strand is degraded [4, 5].

Breast cancer is one of the most common tumors for women all over the world and a cause of 20% women's deaths annually [6]. It was reported that in 2015, patients who were diagnosed with breast cancer increased by over 230,000 in the United States. According to statistics, the incidence of breast cancer is similar in developed and underdeveloped countries. Breast cancer is highly metastatic and exposed to polygene mutation, so it is clinically hard to cure [7].

In 2005, it was the first time that human beings revealed miRNA profiles related to breast cancer and detected differentially expressed miRNAs of breast cancer tissues, including miR-125b, miR-145, miR-21 and miR-155 [8]. Subsequently, lots of research has been conducted to study miRNA related to breast cancer, in hope of obtaining some research findings useful for treating this disease. At present, certain research has suggested that some miRNAs may promote incidence and progression of breast cancer, whereas some others may inhibit them.

miRNAs that promote incidence and progression of breast cancer

The expression of some miRNAs that may promote incidence of breast cancer is detected to be upregulated in most cases of breast cancer. These abnormally expressed miRNAs regulate complicated cellular physiological processes and promote the progression of breast cancer. miRNAs promote the progression of breast cancer with distinct mechanisms in different cases. To be exact, they mainly (1) strengthen metastatic potential of breast cancer cells, (2) promote abnormal growth of breast cancer cells, (3) stimulate drug resistance and (4) improve characteristics of breast cancer stem cells, to promote the progression of breast cancer [9].

miRNAs that increase metastatic potential of breast cancer cells

miRNAs play important roles in increasing metastatic potential of breast cancer cells. In 2009, Hurst and some other scholars firstly defined miRNAs that regulated tumor metastasis and called them metastamiRs [10]. Thereafter, different dysregulated miRNAs of breast cancer were carefully classified and investigated [11]. For instance, miR-182 is discovered to be dysregulated in metastatic breast cancer cells. It will promote invasion and migration of breast cancer once its expression is ectopic, thereby resulting in its distant metastasis. Research about pertinent mechanisms suggests that in breast cancer cells, miR-182 is effective for targeted inhibition of missing genes in metastasis (MIM), activation of RhoA genes and formation of stress fibers [12]. Downregulating expression of E-cadherin and upregulate expression of Snail, miR-217 strengthens invasion of breast cancer cells and promote tumor progression by downregulating the expression of PTEN and activating AKT [13].

miRNAs that promote abnormal growth of breast cancer cells

Furthermore, research suggests that miRNAs may promote abnormal growth of breast cancer cells by stimulating cell-cycle progression, downregulating tumor suppressors or reducing apoptosis rate [14]. miR-196a, miR-375 and miR-423 may promote the incidence of breast cancer by facilitating cell-cycle progression. mi-196a is highly expressed in breast cancer, which may be inhibited from development and progression by inhibiting the expression of this gene. Thus, it is considered as a factor that may promote incidence of breast cancer. According to certain research, the expression of UBE2C (i.e. a gene that promotes carcinogenesis) may be upregulated by activating miR-196a, in order to promote growth and expansion of breast cancer cells [15]. Highly expressed in ER-α positive breast cancer cell lines, miR-375 may stimulate ER-α activation and cell proliferation. Further research has suggested that RASD1 is the direct target of miR-375 [16]. Detected to be highly expressed in several types of tumors and positively correlated to breast cancer, miR-423 is carcinogenic owing to its special 3p strand [17]. miR-24-3p, miR-93 and miR-300 may induce abnormal growth of breast cancer by downregulating tumor suppressors. miR-24-3p was also detected to be highly expressed in breast cancer cells and tissues. According to analyses of bioinformatics and proteomics, miR-24-3p directly regulates p27Kip1 (cyclin-dependent kinase inhibitor 1B, a tumor suppressor gene), and the proliferation of breast cancer cells may be promoted by downregulating the expressions of p27Kip1 [18]. With high expressions in triple-negative breast cancer (TNBC, a type of breast cancer hard to cure) [19], miR-93 is discovered in research about its functional properties to be effective for promoting clone formation, microsphere formation, migration and DNA damages of tumor cells when it is overexpressed in MCF-10A of breast cancer cell lines, while all of these are caused by direct impacts of miR-93 upon NRF2 (i.e. a tumor suppressor gene) [20]. Likewise, the expression of miR-300 is upregulated in human breast cancer, so this gene may promote prolif-

eration of breast cancer cells and progression of cancer, which shall be attributable to direct targeting of miR-300 at p53 (i.e. an important tumor suppressor gene) [21]. miR-150, miR-221 and miR-191 are discovered to promote abnormal growth of breast cancer by reducing apoptosis. miR-150 is overexpressed in breast cancer that it may stimulate growth and clone formation of breast cancer cells while reducing apoptosis. Additionally, miR-150 may directly regulate P2X7 (i.e. a receptor for glycation distributed on cell membrane and act in collaboration with G-protein), which may stimulate several signaling pathways (including TNF-α, TRAIL, p38, JNK/SAPK and NF-κB cascades) by binding with ATP, and has close connections with cancer progression [22]. Discovered to have higher expressions in breast cancer cells and tissues, miR-221 is negatively correlated to ARH1 (a tumor suppressor), and overexpressed ARH1 may inhibit cell proliferation by inducing apoptosis [23]. miR-191 will promote the progression of breast cancer when it is induced by estrogen, and regulate estrogen-mediated cell proliferation. Research suggests that miR-191 directly acts upon STAB1 to downregulate expressions of tumor suppressors such as ANXA1 and SOCS2 [24].

miRNAs that enhance drug resistance of breast cancer cells

Research findings suggest that intrinsic or acquired drug resistance is a significant variable of clinical treatment. Certain research reveals that miRNAs may directly impact drug resistance of breast cancer by regulating related genes [25]. miR-10b, miR27a, miR-95, miR-452 and miR-520h are found to be correlated to the drug resistance of breast cancer. Among these genes, miR-10b is detected to be highly expressed in ERα-positive (ERα+) breast cancer and directly target at HDAC4. Mechanism-related research shows that the resistance of ERα+ breast cancer to Tamoxifen (i.e. an estrogen antagonist for treating breast cancer or female infertility) may be enhanced by down-regulating HDAC4 with miR-10b [26]. As a carcinogenic gene, miR-27a is discovered to have higher expressions in breast cancer and decrease drug susceptibility of breast cancer to multiple chemotherapy drugs [27]. Highly expressed in docetaxel-resistant human breast cancer cells, miR-452 may directly target at APC4 to reduce susceptibility of breast cancer cells to docetaxel [28]. The high expression of miR-520h is positively correlated to drug resistance of breast cancer cells. It is also discovered that death-associated protein kinase 2 (DAPK2) is the direct target of miR-520h, and the drug resistance may be strengthened by suppressing expression of DAPK2 [29].

miRNAs that promote characteristics of breast cancer stem cells (CSCs)

In promoting characteristics of breast cancer stem cells (CSCs), miRNAs may regulate self-renewal of stem cells and transform signal transduction [30, 31]. The expression of miR-125a is found to be positively correlated to stem cell populations of breast cancer cells and directly target at the leukemia inhibitory factor receptor (LIFR) to impact downstream molecules of LIFR on the Hippo signaling pathway, so as to regulate breast cancer stem cells (CSCs) [32]. COX-2 may induce high expression of miR-526b in breast cancer cells to contribute to breast cancer progression. Mechanism related research suggests that miR-526b may induce stem cell-like phenotypes and regulate EP4-regulated signaling pathways [33]. Highly expressed in breast cancer stem cells as a carcinogenic gene, miR-205-5p may strengthen resistance of breast cancer to targeted therapies by suppressing ERBB2 and EGFR directly and indirectly [34].

It is thus clear that miRNAs may contribute to breast cancer progression from multiple perspectives. Although miRNAs have been introduced above from several different aspects, they have distinct impacts in practices. For instance, the apoptosis is usually inhibited while the cell-cycle progression is promoted. Thus, these mechanisms can't be viewed superficially, but shall be comprehensively considered.

miRNAs that suppress occurrence and progression of breast cancer

Research about roles of miRNAs in promoting incidence and progression of breast cancer has been summarized comprehensively. Furthermore, substantial research progress has been made in suppressing incidence and progression of breast cancer with miRNAs. Therefore, more evidences have been available for treat-

ing breast cancer. Research findings suggest that miRNAs suppressing tumors are often significantly downregulated or fully inhibited together with metastasis and abnormal proliferation of tumors. The re-expression of miRNAs does not only suppress breast cancer metastasis and growth of breast cancer cells, but also decreases drug resistance of these cells, thereby suppressing progression of breast cancer [35].

miRNAs that inhibit growth of breast cancer cells

The miRNA inhibits growth of breast cancer cells mainly by inducing apoptosis of breast cancer cells and promoting cell cycle progression. miR-16, miR-146a and miR-200c induce apoptosis of breast cancer cells. Once they are overexpressed, expressions of Cyclin D1 and BCL2 (i.e. two types of carcinogenic genes) will be downregulated at the level of transcription and translation to inhibit growth of breast cancer cells and induce their apoptosis [36]. miR-146a inhibits proliferation, migration, invasion and anti-apoptosis competence of breast cancer cells by downregulating CXCR4 [37]. Some research report also suggests that BRCA1 suppresses EGFR (a gene that contributes to breast cancer) by activating miR-146a in breast cancer as well [38]. The expression of miR-200c is much lower in patients with TNBC than normal tissues of mammary glands, which indicates that this gene is possibly a negative regulator of tumors. It has been discovered in further research that miR-200c induces apoptosis and inhibits cell proliferation by suppressing expression and activity of XIAP [39]. Besides, miR-29b, miR-34c, miR-122 and miR-125b may prevent cell cycle progression. To be exact, there is a smaller amount of miR-29b in breast cancer, where the overexpressed miR-29b inhibits switching of G1/S (i.e. a cell cycle) to suppress cell proliferation and oncogenesis. According to the forecast of bioinformatics, STAT3 is the target of miR-29b [40]. With a low expression in breast cancer, miR-34c is related to poor prognosis, hindering the switch of the cell cycle between G2 and M by regulating CDC23 (namely a gene related to cell cycle) when it is highly expressed [41]. Generally with low expression in breast cancer, miR-122 is found to directly target at insulin-like growth factor 1 receptor (IGF1R) (a receptor that promotes cell proliferation) and regulate Akt/mTOR/p70S6K signaling pathway to induce breast cancer cells to arrest in the G1 phase to inhibit cell proliferation and clone formation [42]. Overexpressed miR-125b inhibits proliferation of breast cancer cells. This gene is discovered to inhibit cell proliferation by directly targeting at ETS1 (a gene related to physical immunity) and the cell cycle is thus arrested in the G1 phase [43].

miRNAs that suppress breast cancer metastasis

The miR-1, miR-31 and miR-200a are discovered to play certain roles in suppressing breast cancer metastasis. TNBC (triple-negative breast cancer) is the most malignant among multiple types of breast cancer. For TNBC, miR-1 is significantly downregulated. It negatively regulates metastasis and migration of breast cancer cells by directly fusing into 3' UTR (3' untranslated region) of mRNA from Slug. Interestingly, MALAT1, as a long carcinogenic non-coding RNA, lowers the expression of miR-1 to promote tumor progression [44]. miR-31 is negatively correlated to GNA13, which has positive correlations with metastasis of breast cancer cells. miR-31 may significantly decrease the activity of GNA13 and thereby make MDA-MB-231 cells which belong to a category of TNBC cell lines less invasive [45]. Discovered by earlier research to have lower expression in breast cancer, miR-200a is a negative regulator of breast cancer progression. Further research has shown that EPHA2 is possibly a direct target of miR-200a as an important carcinogenic gene that affects metastasis of human TNBC [46].

miRNAs that decrease drug resistance of breast cancer cells

As tumor suppressors, miRNAs may also make breast cancer cells less drug-resistant by regulating several types of signaling pathways [47]. For instance, miR-34a, miR-101 and miR-133a may decrease drug resistance of breast cancer and increase drug susceptibility. Research has discovered that the expression of miR-34a is deficient for contributing to incidence of TNBC, so it is possible to inhibit proliferation, migration or invasion of breast cancer cells, accelerate cellular aging and make breast cancer more susceptible to dasatinib, which is an anticancer

drug [48]. With much lower expression in TNBC, miR-101 may suppress tumor growth and enhance susceptibility of breast cancer to paclitaxel which is an anticancer drug by binding with and downregulating the carcinogenic gene MCL-1 [49]. To increase susceptibility of breast cancer cells to doxorubicin (an anticancer drug), miR-133a may downregulate the expression of UCP-2, which is a protein located in mitochondria [50].

Thus, it is clear that miRNAs inhibit breast cancer progression. Even if they have been described above from different perspectives, these aspects shall be comprehensively taken into account in practices, on the grounds that they are often interconnected. For example, apoptosis is usually upregulated when the cell-cycle progression is inhibited. Therefore, related problems shall be comprehensively considered, but not separated from each other.

Relationships between miRNAs and EMT

EMT (Epithelial-to-Mesenchymal Transition) is a process for epithelial cells to develop into mesenchymal cells (MSCs) after a loss of intercellular junctions. Migration and invasion are two major characteristics of MSCs generated in this process [51]. EMT plays important roles in incidence and metastasis of breast cancer. The EMT of breast cancer is impacted by multiple factors, and plenty of miRNAs are involved in EMT. The miRNAs that promote incidence and progression of tumors strengthen invasion and locomotion of tumor cells by activating signaling pathways (e.g. TGF-β, FGF and Notch) and suppressing gene families, including Snail, Twist and ZEB. With higher expression on breast cancer with overexpressed HER-2, miR-21 has positive correlations with the resistance to neo-adjuvant trastuzumab and chemotherapies. Further research has suggested that PTEN and PDCD4 are direct targets of miR-21. Besides, miR-21 may affect the EMT by regulating PI3K signaling pathway [52]. Positively correlated to EMT in clinical breast cancer samples, miR-373 downregulates the expression of TXNIP (thioredoxin-interacting protein) to activate the HIF-1α-TWIST signaling axis, thereby enhancing EMT, migration, invasion and metastasis of breast cancer cells [53, 54]. In addition, pathways of EMT may be inhibited by suppressing miRNAs which function as tumor suppressors. As a suppressor of breast cancer, miR-7 will upregulate the expression of E-cadherin and downregulate the expression of Vimentin when it is overexpressed, in order to inhibit the EMT by direct inhibition of FAK (focal adhesion kinase) [55]. With low expression in breast cancer cell lines, miR-34a is associated with clinical pathological grading. Further research has suggested that miR-34a may inhibit EMT, breast cancer metastasis and invasion by directly targeting at TPD52 (a carcinogenic gene) [56].

Although more and more miRNAs have been discovered to be involved in EMT of breast cancer, it is still difficult to fully inhibit this transition process by regulating miRNAs, because: (1) it is still unclear if miRNA strengthens migration and invasion of breast cancer cells as the first class promoter or not, (2) perhaps several types of miRNAs are involved in strengthening EMT, so the effects would be insignificant if only one or two types of miRNAs are involved in that process, (3) miRNAs differ in expressions and importance, so it is uneasy to determine appropriate targets for intervention, (4) clinical data about regulation of miRNAs are mainly collected from a few countries that further research remains to be conducted to demonstrate whether the research findings about dysregulation of these miRNAs mentioned above are convincing on a global level or not.

Relationships between miRNAs and neoadjuvant therapies

According to current research, the expressions of miRNAs change before and after patients with breast cancer or breast cancer cells are treated by neoadjuvant therapies. The expressions of some miRNAs are upregulated, whereas some others are downregulated. In addition, the expressions of certain miRNAs are special before and after the intervention.

Concerning neoadjuvant chemotherapy, Al-Khanbashi M and some others have discovered that the serum levels of miR-451 and miR-3200 decline significantly in the process when patients with breast cancer receive neoadjuvant chemotherapies. Besides, higher serum levels of miR-451 and miR-3200 are connected with improved clinical and pathological responses, longer disease-free survival, small-

er residual cancer burden and lower recurrence [57], which indicates that patients' levels of miR-451 and miR-3200 may be used as indexes for predicting patients' responses to neoadjuvant chemotherapies and their survival. Having experimentally demonstrated that miRNAs from epithelium may be transferred to tumor cells through exosomes and their subtypes are thereby changed, Bovy N and some others have discovered that the content of miR-503 in exosomes released by epithelial cells decreased in case of any tumor and increased in serum of patients with breast cancer after neoadjuvant chemotherapies. Furthermore, they have identified two targets of miR-503, namely CCND2 and CCND3. It was the first report that revealed chemotherapies could regulate tumor progression by affecting recurrent miR-503 secreted by the epithelium [58]. Frères P and some others have reported that the expressions of miR-34a and miR-122 are upregulated in rather malignant breast cancer, so is the expression of miR-34a in residual tumor after neoadjuvant chemotherapy. According to their report, the specificity of miR-34a and miR-122 increases after the anthracycline-based chemotherapy. Neoadjuvant chemotherapies are discovered to specifically induce the expressions of certain miRNAs in serum and tumor tissues [59].

For neoadjuvant targeted therapies, De Mattos-Arruda L and some other researchers have reported that the expression of miR-21, which is significantly correlated to residual disease, will be upregulated in breast cancer tissues when patients are treated by trastuzumab combined with chemotherapy. They have also discovered that miR-21 impact patients' responses to trastuzumab combined with chemotherapy by activating IL-6/STAT3/NF-κB signaling loop and PI3K pathway [52], which indicates that the expression of miR-21 is possibly helpful for choosing suitable ways of treatment for some patients with breast cancer. Müller V and some others measured the content of miR-21, miR-210 and miR-373 in serum before and after HER-2 positive patients with breast cancer were treated by chemotherapy combined with trastuzumab or lapatinib. The results suggest that compared with healthy women, the content of miR-21 is much higher in serum of patients with breast cancer after chemotherapies, the content of three types of miRNAs in serum further increases after chemotherapies and higher content of miR-373 is significantly correlated to the breast cancer with higher pathological grading. Moreover, it has been found that miR-21 is related to overall survival of patients whichever anti-HER-2 therapies are performed. The research does not only show the impacts of neoadjuvant targeted therapies upon specificity of miR-21, miR-210 and miR-373 in patients with breast cancer, but also reveals that miR-21 would be used as an indicator for prognosis of breast cancer [60].

Above all, the changes to content of certain miRNAs in serum and/or tumor tissues of patients with breast cancer after neoadjuvant chemotherapies or neoadjuvant targeted chemotherapies may reflect the therapeutic effects of these therapies, so these genes deserve further research and development.

Relationships between miRNAs and gene splicing

miRNAs are discovered to play roles in gene splicing related to differentiation processes of certain tumors or muscles. For instance, Boguslawska J and some others have reported that miRNAs regulate gene splicing and expression of osteopontin by targeting at SRSF7 which is a splicing factor [61]. microRNA-1 that suppresses tumors has been reported by Yoshino H and some others to directly inhibit the splicing factor SRSF9/SRp30c in bladder cancer and thus regulate the new apoptosis pathway [62]. Cardinali B and some other researchers have reported that MicroRNA-222 regulates alternative splicing of related genes via Rbm24 during the differentiation of skeletal muscle cells [63]. It has been reported by Zhang BW and some others that miR-30-5p regulates alternative splicing of genes related to muscle differentiation and muscles by targeting at MBNL [64]. Even if aberrant splicing has been reported earlier to be associated with incidence and development of breast cancer, there are still no exact evidences that may prove regulatory roles of miRNAs in these aspects, which are possibly parts of our future research interests.

Conclusions

To sum up, miRNAs influence processes of breast cancer cells such as cell cycle, apopto-

sis, cell proliferation, migration, metastasis, drug resistance, breast cancer stem cells and EMT as important regulators of breast cancer. Some miRNAs promote the progression of breast cancer, while some others inhibit breast cancer. So far, lots of research has focused on developing miRNAs as indicators for diagnosing breast cancer, judging prognosis and predicting progression. Researchers have realized that each tumor has its special miRNA fingerprint to distinguish itself from normal tissues and other types of cancer. Apart from investigating specific miRNAs, certain research has noticed the significance of the expression profiles of multiple miRNAs for diagnosing breast cancer, judging prognosis and predicting progression. In addition, it is possibly novel and challenging to treat breast cancer by intervening with miRNAs. On one hand, miRNAs that promote breast cancer may be suppressed with shRNA technology. On the other hand, the expression of miRNAs that inhibit breast cancer may be upregulated with miRNA mimics. Nevertheless, many factors are concerned in incidence and progression of breast cancer. For instance, breast cancer is so mutant that it is still necessary to further demonstrate whether mutant breast cancer cells are sensitive to interventions or not. Therefore, some ideas mentioned above need to be further verified in fundamental and clinical research.

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Disclosure of conflict of interest

None.

Authors' contribution

Zhang Xiping and Tang Binbin wrote the main manuscript text, Xu Bin and Zhao Shuai participated in the translation and revision of this paper. All authors contributed to the intellectual context and approved the final version.

Address correspondence to: Xiping Zhang, Department of Breast Surgery, Zhejiang Cancer Hospital, Banshanqiao, No. 38 Guangji Road, Hangzhou 310022, Zhejiang Province, China. Tel: +8605718-8122012; E-mail: zxp99688@vip.163.com

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