ROLE OF MICRORNAS IN BREAST CANCER: MOLECULAR INVESTIGATIONS

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1. Introduction

According to the International Agency for Research on Cancer (http://www.iarc.fr/), in 2020, breast cancer is the most common cause of death in women that include 4.4 million. It is a heterogeneous cancer type that have a particular gene expression profile (Aliya et al., 2022). To make an effective treatment of this cancer, it is important to understand the processes and mechanisms that are involved in the development of this cancer including malignancy (Kim & Cho, 2022). It is also required to find the actual findings of resistant coupled with cancer drugs and chemotherapies (Punekar et al., 2022).

It is known that miRNAs are important regulators of whole mRNA functions during normal and abnormal conditions, particularly in different cancers (Seneff et al., 2022). The irregularities of miRNAs in all cancers especially in breast cancer are associated with development, inhibition, metastasis and drug resistance (Najafi et al., 2022). So, these miRNAs can be targets for modulation of gene expressions for effective treatment of breast cancer. Recent literature is supporting this topic because they are secreting from exosomes and body fluids (Tenchov et al., 2022). It is also shown that the circulating miRNAs expression level is totally different in healthy people and cancer patients (Shi et al., 2022).

In this chapter, we summarize the major functions of miRNAs in breast cancer development from benign to metastasis and discuss the clinical applications of modulating miRNA associated to mRNA and finally find the available miRNAs relationship with breast cancer.

2. miRNAs Biosynthesis

MiRNAs are 20-25 base pair sequence (non-coding RNAs) which control post-transcriptional gene regulation (Xiong et al., 2022). RNA polymerase II is primarily responsible for miRNA transcription as lengthy primary transcripts known as pri-miRNAs, which are distinguished by hairpin topologies (Marquardt et al., 2022). Such pri-miRNAs are converted by the RNase III enzymes Drosha and its co-factor DGCR8 to 70-100 base prototype miRNAs (pre-miRNAs) in the nuclei (Nguyen et al., 2021). The mirtron process, in which introns are spliced and debranched by lariat debranching enzyme, as well generates a variety of pre-miRNAs (Campos-Melo et al., 2022). A component made up of both the RNase III enzyme Dicer and the transactivating response RNA-binding protein cleaves them into miRNA:miRNA duplexes after they have been exported to the cytoplasm by Exportin-5, a member of the Ran-dependent nuclear transport receptor family (TRBP) (Takahashi et al., 2015). In addition to forming a protein complex with Dicer in place of TRBP, the RNA editing enzyme adenosine deaminase working on RNA 1 can also enhance the processing of miRNAs (Ota et al., 2013).

3. Breast cancer and miRNAs

It is well documented that miRNAs are crucial for the growth of tumors. According to the molecular subtypes of tumors, they express differently, and the open spot of particular miRNAs categorize to tumor abnormalities (Oliveto et al., 2017). It is crucial that the amplification of specific genes results in the up- or down-regulation of miRNAs, which then silences or amplifies tumor suppressor genes (Meng et al., 2013). Therefore, deregulation of miRNA expression has an impact on cancer progression-related activities such metastasis, tissue invasion, and apoptosis escape.

Several miRNAs **(Table 1)** have been described as crucial regulators of tumor genesis, metastasis, and chemoresistance in breast cancer and have been identified as tumor suppressors or oncogenes. Conceptually, the four stages of tumor formation are: (i) tumor genesis, (ii) therapy resistance and tumor progression, (iii) malignant conversion, and (iv) tumor advancement.

Table 1. List of miRNAs that are targets particular genes to perform specific functions in breast cancer

Sr#	Functions	miRNAs	Targets	References
1	Enhance apoptosis	miR-155	TP53	Mikamori et al., 2017
2	Inhibition of cell cycle	miR-15a	CCNE1	Luo et al., 2013
3	Increase apoptosis	miR-155	TP53INP1	Mikamori et al., 2017
4	Influence cell cycle	miR-222-3p	SOCS3 / Jak2/Stat3/Bcl-2	Feng et al., 2017
5	Influence on cell cycle	miR-21	PTEN	Zheng et al., 2017
6	Downregulatıon of MDR1 in breast cancer	miR-200c	MDR1	Safaei et al., 2022
7	Inhibition of cell cycle	miR-20a-5p	SRCIN1	Guo et al., 2019
8	Inhibit growth/invasion	miR-590-5p	Skp2	Tong & Jin, 2022

9	Tumor supressor	miR-497	Septin 2	Cai et al., 2022
10	Regulation of immunity	miR-190	IL-1R1	Yu et al., 2018
11	Tumor supressor	miR-381	FYN, ERK, p38	Mi et al., 2018
12	Tumor supressor	miR -590-5p	PITX2	Gao et al., 2019
13	Regulation of expression	miR -150-5p	E-cadherin	Lu et al., 2019
14	Regulation of expression	miR-370-3p	NF- κB	Ren et al., 2021
15	Inhibition of cell cycle	Mir-7	*KLF4*	Okuda et al., 2013
16	Inhibition of cell cycle	miR-130-3p	*RAB5B*	Kong et al., 2018
17	Tumor supressor	*miR-4319*	*E2F2*	Chu et al., 2018
18	Tumor supressor	miR-155	CD44/ CD90/ ABCG2	Zuo et al., 2018
19	Inhibition of cell cycle	*miR-29a*	EGR1	Wu et al., 2019
20	Regulation of gene espression	*miR-9*	*Nanog/CD133* / *Oct4*	Cheng et al., 2018
21	Regulation of gene expression	*miR-221*	*Nanog/CD133* / *Oct4*	Cheng et al., 2018
22	Regulation of cell cycle	miR-195	FASN, HMGCR, ACACA, CYP27B1	McAnena et al., 2019
23	Tumor supressor	miR-206	NOTCH 3	Chaudhari et al., 2022

24	Regulation of cell cycle	miRNA-32	CPT1A	Zheng et al., 2022
25	Regulation of cell cycle	miR-8084	ING2, p53-BAX	Gao et al., 2018
26	Regulation of cell cycle	miR-484	PAX-5	Harquai et al., 2019
26	Regulation of cell cycle	miR-708-3p	ZEB1/ CDH2/ VIM	Lee et al., 2018
27	Regulation of cell cycle	miR-142-3p	Bach-1/CXCR4/MMP9/VEGFR	Mansoori et al., 2019
28	Regulation of cell cycle	miR-3178	Notch1	Kong et al., 2018
29	Regulation of cell cycle	miR-1266/miR-185/ miR-30c	BCL2L1	Ostadrahimi et al., 2018
30	Regulation of cell cycle	miR-655	COX2	Majumder et al., 2018
32	Regulation of cell cycle	miRNA-29b	AKT3 SPIN1	Li et al., 2017
33	Regulation of cell cycle	miRNA-100	VEGF	Pakravan et al., 2017
35	Regulation of cell cycle	miRNA-4530	VASH1	Zhang et al., 2017
36	Regulation of cell cycle	miR-1469	PI3K/ AKT	Zhang et al., 2019
37	Regulation of cell cycle	miR-425-5p	PTEN	Zhang et al., 2020
38	Regulation of cell cycle	miRNA-96-5p	FOXO3	Yin et al., 2020
39	Regulation of cell cycle	miR-206	DEPDC1	Zhang et al., 2019

40	Regulation of cell cycle	miR-205	TG2	Seo et al ., 2019
41	Regulation of cell cycle	miR-345	KISS1	Kaverina et al., 2017
42	Regulation of cell cycle	miR-503	L1CAM	Xing et al., 2018
43	Regulation of cell cycle	miR-532/502	SET8	Cantini et al., 2019
44	Regulation of cell cycle	miR-143/145	CIAPIN1	Deng et al., 2018
45	Regulation of cell cycle	miR-132/212	PTEN	Xie et al., 2018
47	Regulation of cell cycle	miR-137	SRC3	Guo et al., 2019
48	Regulation of cell cycle	miR-663b	TP73	Jiang et al., 2018
49	Regulation of cell cycle	miR-196a	HOX/FOX	Milevskiy et al., 2019
50	Regulation of cell cycle	miR-18a	MYBL2	Luengo-Gil et al., 2019
51	Regulation of cell cycle	miR-186-3p	EREG	He et al., 2019
52	Regulation of cell cycle	miR-26a	E2F7	Liu et al., 2018

3.1. Tumor Genesis

Cancer-initiating cells (CSCs) are in charge of the growth and spread of tumors (Ghanei et al., 2020). The cells have many physiological traits in common with typical somatic stem cells, such as their ability to divide asymmetrically as well as the potential to pump tiny compounds (Steinbichler et al., 2018). In a study, they revealed that breast samples' CD44+/CD24/low Lineage cells exhibit an exceptionally significant tumor-seeding potential (Abraham et al., 2005) while, in another study, some researchers said that Let-7 is a master regulator of CSC characteristics such self-renewal capacity and tumor-seeding capacity (Thammaiah & Jayaram, 2016). According to Acikgoz et al, breast malignant tissues' CD44+/CD24/low cell populations

exhibit strong tumorigenesis and epithelial to mesenchymal transition (EMT) characteristics (Acikgoz et al., 2022). The genetic factors and molecular processes driving that development of severity as well as the ensuing systemically dissemination by affected tissues are important to understand since EMT is frequently seen throughout metastasis and invasion (Nathanson et al., 2022). Therefore, the loss of epithelial markers like E-cadherin, up-regulation of mesenchymal markers like N-cadherin and vimentin, loss of cell-cell adhesion, cell polarity, and the development of cell invasive capacities are all characteristics of the EMT type (Hamidi et al., 2022). Cavallari et al. observed that miR-205, miR-200a, miR-200b, miR-200c, miR-141, and miR-429, are specifically associated with poor prognosis in different cells undergoing EMT (Cavallari et al., 2021). The miR-200 regulator was demethylated either by ten eleven translocation (TET) group, and miR-22 promotes the formation of CSC traits like EMT and just a metastasis nature by suppressing the miR-200 group (Karami Fath et al., 2022).

3.2. Therapy Resistance and Tumor Progression

Locally as well as remotely recurrent malignancies frequently demonstrate development of resistance to therapy, similar to how breast tumors or tumor-initiating cells may display inherent resistance to cancer treatments (Ji et al., 2021). The development of the cancer and the patient's outcome are intimately tied to therapy resistance (Mehraj et al., 2021). The significance of miRNAs in breast cancer therapeutic resistance is still poorly defined (Javdani et al., 2022). The activities of some miRNAs for controlling therapy resistance in vitro are described here, however their involvement in therapy resistance in breast cancer models in vivo has not yet been shown (Garrido-Cano et al., 2021). For example, in tamoxifen-resistant MCF-7 cells, ERa-negative breast cancer cells, and HER2- or ERa-positive primary breast cancer tissues, levels of miR-221/222 was shown to be up-regulated (Kalinina et al., 2021). Additionally, paclitaxel-resistant MDA-MB-435 breast cancer cells exhibited up-regulation of miR-221/222 and miR-125b (Shahrzad et al., 2021). It showed strong relationship between miRNAs and target genes in breast cancers (Zhang et al., 2022). When relative to the primary culture, doxorubicin-resistant MCF-7 cells (MCF-7/DOX) were shown to have a substantial percentage of down-regulated and up-regulated miRNAs (Yang et al., 2021). For illustration, down-regulated miR-127, miR-34a, miR-27b, and let-7 have been linked to higher levels of the anti-apoptotic targets, including BCL6, NOTCH1, CYP1B1, and K-RAS (Filkowski, 2010) whereas up-regulated miR-206, miR-106a, miR-21, and miR-214 have been linked to lower levels of the target proteins, including ERa, RB1, and PTEN etc (Llobat & Gourbault, 2021).

3.3. Malignant Conversion

The role of miRNAs in the regulation of metastatic processes is crucial in breast cancer. For instance, miR-10 showed a greater level of expression in metastatic disease than in non-metastatic breast cancer, therefore, it is known as a critical regulator of breast cancer metastasis (Harquail et al., 2012). Some miRNAs, such as miR-126, miR-206, and miR-335, shown their function as breast cancer metastasis suppressors (Tavazoie et al., 2008). While miR-206 and miR-335 prevent the invasion of metastatic cells, miR-126 contributes to the decrease of breast cancer tumors (Negrini & Calin, 2008). The breast cancer that is connected to the transcription factor GATA3 in metastasis is suppressed by miR-29b upregulation (Chou et al., 2013). But GATA3 is necessary for maintaining the differentiation of luminal epithelial cells, and miR-

29b depletion is associated with a poor prognosis in patients with breast cancer (Chou et al., 2013). In another studies, miR-29b suppresses a network of pro-metastatic regulators linked to angiogenesis, collagen remodeling, and proteolysis to prevent the spread of breast cancer (Yan et al., 2015).

3.4. Tumor Advancement

The CXCL12 chemokine gene is directly targeted by the miRNAs including miR-127, miR-197, miR-222, and miR-223, which prevent breast cancer cells from proliferating and induce or maintain a latent state in breast cancer cells (Takahashi et al., 2015). In another study, interleukin-4 produced from CD4+ T cells activates tumor-associated macrophages, which then deliver miR-223 to breast cancer cells (Cocks et al., 2021). Through direct targeting of myocyte enhancer factor 2C, miR-223 causes the nuclear accumulation of b-catenin, which leads to the development of angiogenesis and invasiveness (Cocks et al., 2021). In another example, high levels of miR-105 secretion and expression are linked to highly metastatic breast cancer cells. By inhibiting the production of the tight junction protein ZO-1 in distant tissues, miR-105, which is produced by cancer, damages tight junctions (Llobat & Gourbault, 2021). As a result, breast cancer cells that overexpress miR-105 exhibit extremely active spreading behavior and increase vascular permeability (Takahashi et al., 2015).

4. Conclusion

We have outlined the functions of miRNAs in the biology of cancer in this chapter, concentrating on breast cancer. A growing amount of research has shown that the patient's health and tumor stage are related to the aberrational expression patterns of miRNAs in breast cancer. Additionally, there are various subtypes of breast cancer, each of which has a distinct molecular profile and functions, and these subtypes are determined and regulated by certain miRNAs. Profiling miRNA expression in breast cancer comprehending the molecular processes behind miRNA expression and release are crucial areas of study in both fundamental and applied research.

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