Identification of dysregulated microRNAs in triple-negative breast cancer (Review)

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Abstract. Triple-negative breast cancer (TNBC) is defined by the absence of expression of the estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2). TNBC exhibits a more aggressive phenotype and a poorer clinical outcome compared to other breast cancer subgroups, accounting for 15-20% of total breast cancer cases. To date, the treatment strategies for TNBC are limited to surgery, chemotherapy and radiation, owing to the lack of effective therapeutic targets. Therefore, it is important to identify specific targets for TNBCs. MicroRNAs (miRNAs), a family of small non-coding RNAs regulating gene expression, are an emerging class of regulators of various biological processes, including cell proliferation, invasion, epithelial-mesenchymal transition (EMT) and drug resistance. Actually, miRNAs may serve as a novel therapeutic target in TNBC, and here we review current correlated researches and provide our own profiling results for the miRNAs expressed in TNBC cell lines. The present study offers an additional insight into the potential miRNAs involved in the regulation of TNBC.

Contents

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Abbreviations: TNBC, triple-negative breast cancer; miRNA, microRNA; EMT, epithelial-mesenchymal transition; ER, estrogen receptor; 3'UTR, 3' untranslated region

Key words: microRNAs, triple-negative breast cancer, epithelial-mesenchymal transition, metastasis, prognosis

1. Introduction

Breast cancer is a heterogeneous disease which can be classified into four major subtypes: luminal A (ER and/or PR-positive, HER2-negative), luminal B (ER and/or PR-positive, HER2-positive), HER2-amplified (ER/PR-negative, HER2-positive), and triple-negative breast cancer (ER/PR-negative, HER2-negative) (1). Triple-negative breast cancer is the most aggressive and poorly understood subtype due to the absence of well-defined molecular targets. It has been considered to be associated with invasive behavior and worse prognosis. In addition, the intra-tumor heterogeneity challenges the appropriate targeted therapies in TNBC. MicroRNAs are a class of small non-coding RNAs which can reduce the abundance and transcriptional efficiency of mRNAs by targeting the genes. Altered miRNAs expression is common in various human malignancies and associated with tumor initiation, progression and metastasis (2).

Recent studies have shown that a number of miRNAs are correlated with the hormone receptor status in breast cancer. Lowery *et al* (3) identified three classes of miRNA signatures corresponding with ER (miR-342, miR-299, miR-217, miR-190, miR-135b and miR-218), PR (miR-520g, miR-377, miR-527-518a and miR-520f-520c) and HER2 (miR-520d, miR-181c, miR-302c, miR-376b and miR-30e). Furthermore, TNBC can be subdivided into core basal (CB) and five negative (5NP) subgroups, based on a 4-miRNA signature given by miR-155, miR-493, miR-30e and miR-27a expression levels, and deregulation of the four miRNAs has been demonstrated to significantly influence prognosis of TNBC patients (4). Indeed, the prognostic miRNA signatures are distinct according to ER status. For instance, miR-342 and miR-150 are associated with good prognosis and miR-27b with poor prognosis in TNBC, whereas a totally different cluster of miRNAs (miR-135a, miR-767-3p, miR-128 and miR-769-3p) are proven to be the prognostic markers of ER-positive breast cancers (5). Therefore, miRNAs not only play a pivotal role in breast cancer differentiation, but also contribute to the biological process in TNBC. Novel miRNAs are increasingly being investigated, and evidence shows that numerous miRNAs are involved in a variety of processes contributing to tumorigenesis and metastasis in TNBC. However, the complex regulatory network formed by these miRNAs is rarely well-established due to the continuously increasing members. In the present study, we included the

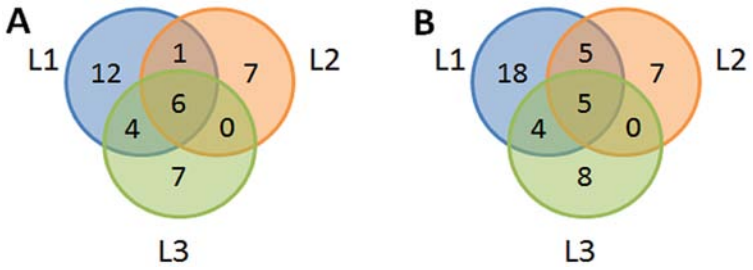

Figure 1. Venn diagram describing miRNA expression patterns in the three independent studies of triple-negative breast cancer cell lines. Venn diagrams representing differentially (A) upregulated and (B) downregulated miRNAs observed in L1, L2 and L3 (for the complete miRNAs list, see Table I).

Table I. Dysregulated microRNAs in TNBC vs. non-TNBC cell lines.

References	Upregulated microRNAs	Downregulated microRNAs
L1 + L2 (7,8)	miR-221, miR-222, miR-29a, miR-29b, miR-100, miR-125b, miR-146a	miR-345, miR-200c, miR-141, miR-375, miR-203, miR-200a, miR-93, miR-205, miR-183, **miR-182**
L1 + L3 (7,9)	miR-221, miR-222, miR-224, miR-29a, miR-100, miR-125b, **miR-138**, miR-146a, miR-23a, miR-503	miR-200a, miR-200b, miR-196a, miR-375, miR-148a, miR-203, miR-200c, miR-141, miR-24a
L2 + L3 (8,9)	miR-146a, miR-100, miR-125b, miR-29a, miR-222, miR-221	miR-200c, miR-141, miR-375, miR-203, miR-200a
L1 + L2 + L3 (7-9)	miR-146a, miR-100, miR-125b, miR-29a, miR-222, miR-221	miR-200a, miR-200c, **miR-141**, miR-375, miR-203

TNBC, triple-negative breast cancer. Bold print indicates the miRNAs consistent with the present study.

differentially expressed miRNAs between TNBC and non-TNBC, and the deregulated ones involved in cell proliferation, cell cycle, apoptosis, EMT, metastasis and others. Moreover, we confirmed certain miRNAs of previous studies, as well as discovered several novel miRNAs. The results from the present study provide additional insight into the miRNA signatures in TNBC.

2. Identification of microRNAs dysregulated in TNBC

miRNAs control gene expression by targeting mRNAs, and are identified to be correlated with specific clinicobiological features. A set of miRNAs were discovered to be differentially expressed between breast cancer and normal breast tissue as the first miRNA signature characteristic of breast carcinoma (6). Since then, more studies have focused on the miRNA expression patterns among subgroups in breast cancer. Making use of miRNA microarray profiling, Cochrane *et al* (7) found 53 miRNAs differentially expressed in luminal A vs. TNBC cell lines. Notably, the miRNAs associated with aggressiveness in lymph node-negative human breast cancer were inconsistent between ER-positive and ER-negative cases. The study further revealed the intrinsic miRNA signatures in these two types of stromal cell lines, and actually the MDA-MB-435 and MDA-MD-231 in ER-negative group are always considered to be triple-negative (8). In a more recent study, 34 miRNAs were observed to be significantly differentially expressed among the luminal A, HER2-amplified and triple negative cell lines (9), and the biologic profiling of miRNA signatures for different subtypes were also extensively explored in breast cancer tissue samples (10-13).

The results from each independent study are consistent for only a few miRNAs, and we summarized the differentially expressed miRNAs observed in the comparison among three independent studies with the Venn diagrams in Fig. 1. Comparing to non-TNBC, six miRNAs (miR-146a, miR-100, miR-125b, miR-29a, miR-222 and miR-221) are upregulated for TNBC in all three studies, while five miRNAs (miR-200a, miR-200c, miR-141, miR-375 and miR-203) are downregulated. Importantly, there are several miRNAs in the overlapping area between each two of the studies (Table I), indicating the reliability of the findings. The inconsistence may be caused by the different cell lines and the different fold-changes in expression in each study.

To further identify differentially expressed miRNAs between TNBC and non-TNBC cell lines, we profiled miRNA expression in luminal A (MCF-7: $ER^+/PR^+/HER2^-$), HER2-amplified (SK-BR-3: $ER^-/PR^-/HER2^+$) and triple-negative (MDA-MB-231 and Hs578T: $ER^-/PR^-/HER2^-$) molecular subtypes, and only twelve miRNAs exhibited a 1.5-fold differential expression between these two groups (Fig. 2). Of these twelve miRNAs, four (miR-138-5p, miR-4324, miR-4800-3p and miR-6836-3p) were observed to be upregulated in TNBC group, and the other eight (miR-363-5p, miR-182-5p, miR-141-3p, miR-339-5p, miR-4655-3p, miR-4784, miR-664b-5p and miR-6787-5p) were downregulated. Among these, however, some miRNAs could be newly discovered ones, which have not been

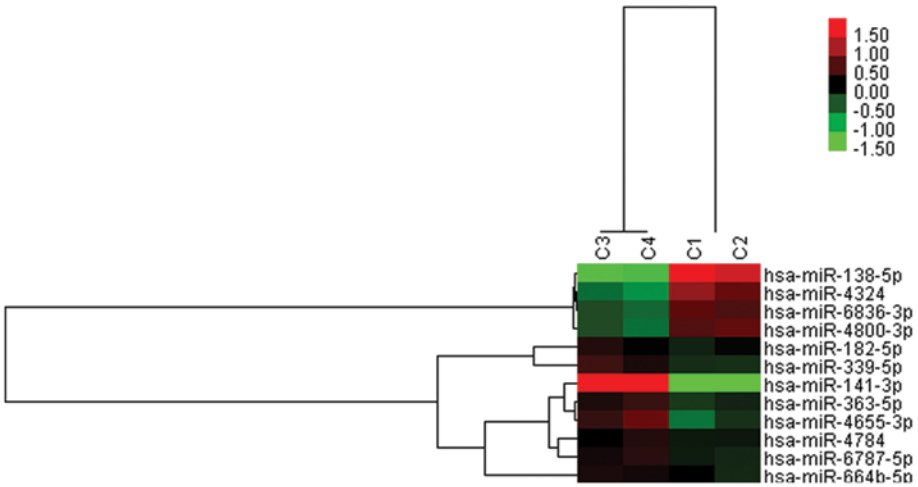

Figure 2. miRNA differential expression in TNBC vs. non-TNBC cell lines. Hierarchical clustering of twelve miRNAs exhibiting a 1.5-fold different expression. Rows, individual miRNAs; colums, individual breast cancer cell lines (C1, MDA-MB-231; C2, Hs578T; C3, MCF-7; C4, SK-BR-3). Pseudo-colors represent transcript levels above, equal to, and below the mean (red, black and green, respectively). The scale represents the intensity of miRNA expression.

identified previously, including miR-4324, miR-4800-3p, miR-6836-3p, miR-4655-3p, miR-4784 and miR-6787-5p. The other miRNAs were validated earlier in other forms, for instance, miR-138-5p was previously identified as miR-138 in the overlap of L1 and L3, and miR-182-5p referred to miR-182 in the overlap of L1 and L2. Likewise, miR-141-3p and miR-363-5p, formerly known as miR-141 and miR-363, were downregulated in L1-3 or only in L3 separately. In the deregulated miRNA set of L1, miR-339-3p was regarded to be downregulated, inconsistent with the miR-339-5p here, and they are the two types of mature sequences from the same stem-loop sequence miR-339.

Given the development in sequencing, our results are partly consistent with previous findings. Moreover, the TNBC cell line Hs578T was derived from carcinoma, while the MDA-MB-231 cells from adenocarcinoma. The different histogenesis of the cell lines may narrow the miRNA profile outcome, contributing to the fewer miRNAs in our results comparing to other researches. Taken together, we validated some previously discovered miRNAs in a precision sequence, providing us additional insight into the miRNA signatures in TNBC. It should be tenable to consider these miRNAs as solid ones being functional in TNBC. However, the observations need to be further confirmed in more cell lines and tissue samples.

3. Functional evidence of microRNAs in TNBC

In general, the miRNAs targeting mRNAs encoding tumor suppressor proteins are defined as oncogenic miRNAs (oncomiRs), while the miRNAs targeting oncogenes exhibiting tumor suppressor properties are defined as oncosuppressor miRNAs. An increasing body of evidence reveals the pivotal role of miRNAs in all stages of TNBC. For instance, miR-221 is one of the best known miRNAs in breast cancer field. Recently, miR-221 was shown to regulate cell cycle progression by targeting *p27* in TNBC, and to modulate cell migration as well as EMT by decreasing the E-cadherin level (14). Another important oncomiR is miR-21 which can promote cell proliferation. In the study by Sharma *et al* (15) miR-21 and miR-206 co-targeted *RASA1* and *SPRED1*, two repressors of RAS-ERK signaling, resulting in resistance to cell death in MDA-MB-231 cells. In addition, miR-21 was proven to regulate *PTEN* by targeting the mRNA 3'UTR, leading to an anti-apoptosis effect in TNBC (16). Specifically, miR-21 exhibits a higher expression level in TNBC than non-TNBC, and it is positively correlated with a poor clinical outcome. In contrast to the miRNAs afore-mentioned, miR-203 is an onco-suppressor miRNA which plays a specific metastic suppressor role by targeting *LASP1* in TNBC, it can significantly inhibit cell proliferation by regulating *BIRC5* (17). Thus, the miRNAs controlling expression of quite a few key genes are likely to affect tumor behavior and progression in TNBC.

microRNA regulation of EMT. An increasing number of miRNAs are demonstrated to be involved in EMT (Table II). Reportedly, miR-181a expression was markedly unregulated in TNBC, and promoted EMT by suppressing the expression of proapoptotic molecule Bim (18). The miR-200 family of miRNAs is comprised of miR-200a, miR-200b, miR-200c, miR-141 and miR-429, and the expression of all the miR-200 family members were absent in invasive breast cancer cell lines with mesenchymal phenotype, cooperatively preventing TGF-β induced EMT by attenuating the expression of *ZEB1* and *ZEB2* (19). Howe *et al* (20) demonstrated that in MDA-MB-231 or BT549 cell lines, miR-200c maintained the epithelial phenotype by targeting *FN1* and *MSN*, encoding proteins normally expressed in mesenchymal or neuronal origin. In our research, miR-141, another member from miR-200 family, was identified down-modulated in TNBC vs. non-TNBC cell lines, which highlights, therefore, the positive role of miR-141 in epithelial phenotype maintenance in breast cancer. Contrary to our expectation, however, all the protective miR-200 family members were shown upregulated in TNBC compared with normal breast tissues (21,22), exhibiting a putative risky role in TNBC initiation. One possible explanation for this phenomenon is that the miR-200 family may act as an entirely inverse effect in tumorigenic TNBC

Table II. MicroRNAs associated with EMT in TNBC.

MicroRNAs	Validated targets	Ref.
Oncosuppressor miRNAs		
miR-200b, miR-107, miR-15b, miR-145, miR-128b	SUZ12, ZEB1/2, KLF4, BMI1	(37)
miR-200a, miR-200b, miR-200c	ZEB1/2, FN1, MSN, N-cadherin, vimentin	(20,38,39)
Oncogenic miRNAs		
miR-181a	Bim	(18)
miR-155	C/EBPβ	(40)
miR-221	E-cadherin	(14)

EMT, epithelial-mesenchymal transition; TNBC, triple-negative breast cancer.

Table III. MicroRNAs associated with metastasis in TNBC.

MicroRNAs	Validated targets	Ref.
Oncosuppressor miRNAs		
let-7	RAS, c-Myc, ERK	(41)
miR-200a/c	UBASH3B, ZEB1/2	(26)
miR-638	BRCA1	(35)
miR-206	CORO1C	(23)
miR-31	LOC554202	(42)
miR-145	ARF6	(24)
miR-200b	PKCα	(25)
miR-34a	AXL	(9)
miR-203	LASP1	(17)
miR-139-5p	HRAS, NFKB1, PIK3CA, RAF, RHOT1	(43)
Oncogenic miRNAs		
miR-181a	Bim	(18)
miR-17, miR-20a	TIMP2/3	(27)
miR-221	E-cadherin	(14)
miR-182	PFN1	(28)

TNBC, triple-negative breast cancer.

vs. EMT. Nevertheless, the actual role of miR-200 family in TNBC deserved to be further verified by well-designed experiments.

microRNA regulation of metastasis. In addition to regulation of EMT, emerging evidence has shown the vital role of miRNAs in cell migration, invasion and metastasis (Table III). Expression of miR-206 was significantly suppressed in TNBC, and the forced expression could markedly inhibit cell migration by targeting 3'UTR of *CORO1C* (23). Similarly, restoration of miR-145 in TNBC resulted in a dramatic decrease in *ARF6*, a known regulator of breast cancer cell invasion (24). Additionally, another study found that miR-200b could suppress TNBC cell migration and tumor metastasis by directly targeting protein kinase Cα (PKCα) (25). Another miR-200 family member miR-200a, is able to inhibit invasion and metastasis in TNBC by reducing the ubiquitin-associated and SH3 domain-containing B (*UBASH3B*) mRNA and protein expression along with *ZEB1* and *ZEB2* (26). Besides the miRNAs mentioned above, miR-139-5p was also validated to repress metastasis in MDA-MB-231 cells, by modulating a network of genes underlying cellular processes involved in metastasis, including *HRAS*, *NFKB1*, *PIK3CA*, *RAF* and *RHOT1*.

In contrast, the miR-17-92 cluster is correlated with a more aggressive behavior in breast cancer, and two members from this cluster, miR-17 and miR-20a, could induce metastasis partially by targeting the extracellular matrix (ECM) proteins TIMP2 and TIMP3 (27). Comparing with normal tissue adjacent to TNBC, miR-182 expression was obviously increased in tumor tissues, which promotes cell invasion by negatively regulating profilin 1 (*PFN1*) (28) and correspondently, miR-182-5p, a mature loop from miR-182, was expressed relatively higher in TNBC tissue vs. normal (12). Whereas, miR-182 or miR-182-5p were found to be specifically expressed in non-TNBC vs. TNBC cell lines based on L1, L2 or our result (Table I and Fig. 2). Taken together, it would be reasonable to treat miR-182 and miR-182-5p as potential therapeutic targets for both TNBC and non-TNBC.

4. MicroRNAs as prognostic markers in TNBC

With the improvement of tumor biology understanding, an increasing number of known miRNAs have been identified to be prognostic in TNBC. Inverse correlation between miR-27b and distant relapse-free survival (DRFS) was found by performing miRNA expression profiles, while miR-342 and miR-150 were correlated with better prognosis (5). A set of seven miRNAs were found to be associated with TNBC clinical prognosis (11), and upregulation of miR-16-2* and miR-766 was correlated with favorable distant metastases-free survival (DMFS), while miR-381 and miR-409-5p correlated with poor DMFS, and miR-409-5p was also negatively associated with breast cancer specific survival (BCSS) along with miR-376b, miR-410 and miR-193a-3p. Cascione *et al* (21) identified further miRNA signatures (miR-16, miR-155, miR-125b, miR-374a and miR-16, miR-125b, miR-374a, miR-374b, miR-421, miR-655 and miR-497) eligible for predicting overall survival (OS) and distant disease-free survival (DDFS), respectively. There are some other miRNAs, such as miR-210 (29), miR-155 (30), miR-27b-3p (31), miR-34b (32)

and miR-21 (16), that could to be poor prognosis indicators in TNBC. However, the prognostic roles of miR-155 in two independent studies were completely the opposite, implying the complexity in miRNA regulation.

It is worth mentioning that the protective miR-497, was identified downregulated in TNBC vs. both normal tissue and non-TNBC cells (9,21,22), indicating its putative positive effect against aggressive malignant phenotype in TNBC. The miR-210, was up-modulated in TNBC vs. both normal and non-TNBC tissues (12,22,33), thereby, providing a potential therapeutic target for TNBC.

5. Conclusion

TNBC is a heterogeneous subgroup in breast cancer characterized by lack of effective targeted therapies, showing an aggressive morphology and poor prognosis, and miRNA profiling studies have shown an additional complexity of signal networks driving the biology of this subtype. There is a need to shed light on the miRNA related pathways to identify biomarkers able to predict prognosis and response to therapy, even probably identify novel therapeutic targets in TNBC. Although no therapeutics targeting specific miRNAs have made into clinic, a few of miRNAs have been implicated in altering sensitivity to treatment. A recent study co-encapsulated miR-34a with doxorubicin into hyaluronic acid (HA)-chitosan (CS) nanoparticles (NPs), and then co-delivered it into TNBC cells or tissues. Surprisingly, the co-delivery of miR-34a enhanced antitumor effects of doxorubicin by suppressing the expression of *Bcl-2* and blocking Notch-1 signaling (34). Furthermore, miR-638 overexpression was associated with increased sensitivity to DNA damaging agents, ultraviolet (UV) and cisplatin in TNBC cells (35), while miR-181a and miR-181b were regarded as negative regulators of the DNA damage response and decreased the sensitivity to poly-ADP-ribose-polymerase 1 (PARP1) inhibition in TNBC cells (36).

The present review has provided a new scenario of the miRNA expression differences between TNBC and normal tissue or TNBC and non-TNBC cells by summarizing previous profiling studies. In our research, we verified some previously proven miRNAs and identified several new ones as well, providing new evidence for investigating the functional miRNAs in TNBC. Such studies will be valuable for gaining better understanding of the role of miRNAs on the pathogenesis of TNBC, and identifying novel biomarkers for diagnosis, treatment and prognosis. However, although quite a few miRNAs showed differences, demonstration of the functions of most molecules has not been validated, and some miRNAs even show the opposite effect among independent studies. Consequently, further studies are required to manifest the underlying mechanism of miRNAs in TNBC progression, including cell proliferation, cell cycle, apoptosis, EMT and metastasis, before taking miRNAs as therapeutic targets in TNBC.

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