MicroRNA-based potential diagnostic, prognostic and therapeutic applications in triple-negative breast cancer

Qian Tanga,*, Hu Ouyanga,*, Dongxiu Heb, Cuiyun Yua,b and Guotao Tanga,b

aInstitute of Pharmacy and Pharmacology, University of South China, Hengyang, Hunan, China; bHunan Province Cooperative Innovation Center for Molecular Target New Drug Study, Hengyang, Hunan, China

ABSTRACT

Triple-negative breast cancer (TNBC) is a distinct subtype of breast cancer characterized by high recurrence rates and poor prognosis compared to other breast cancers. MicroRNAs (miRNAs) are small non-coding RNAs that regulate the expression of various post-transcriptional gene and silence a broad set of target genes. Many recent studies have demonstrated that miRNAs play an important role in the initiation, promotion, malignant conversion, progression, and metastasis of TNBC. Therefore, the aim of this review is to focus on recent advancements of microRNAs-based potential applications in diagnosis, treatment and prognosis of triple-negative breast cancer.

Introduction

Breast cancer (BC) is the most common malignant tumors affecting females worldwide, with an estimated 1,300,000 new cases and 465,000 deaths annually [1,2]. Triple-negative breast cancer (TNBC), which accounts for approximately 10–25% of all BC cases [3], usually show more rapid tumor growth, higher recurrence, poorer prognosis and more aggressive biological behavior compared to other breast cancer subtypes [4]. Based on the gene expression profiles, TNBC can be further classified into six different subtypes including immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL), basal-like 1, basal-like 2 and a luminal androgen receptor (LAR) subtype [5]. In addition, TNBC is characterized by the lack of expression of estrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor-2 (HER2), which are common therapeutic targets [6]. Herein, TNBC does not respond to endocrine therapy or other available targeted drugs [7,8].

Over the past several decades, the basic knowledge of TNBCs morphology, genetic and functional properties and its associated heterogeneity, invasive and metastatic phenotypes is increasingly understood by people [9,10]. Also, the therapeutic strategies including surgery, radiotherapy, chemotherapy, immunological therapy and targeted therapy are currently available for the patients with TNBC [4]. However, TNBC exhibits low survival due to its highly invasive and metastatic cap cells that are associated with higher recurrence behavior in local and distant lymph nodes and have a higher proliferation rate [11]. In addition, patients with TNBC have limited therapeutic options because they do not benefit from the traditional anti-hormonal or anti-HER2-based therapy. Therefore, new approaches for the diagnosis, treatment and prognosis of this breast cancer subtype are required.

MicroRNAs (miRNAs), a family of 21–25 nucleotide small non-protein-coding RNAs, are significantly involved in a variety of pathophysiological processes such as cell migration, invasion, proliferation and differentiation [12,13]. MicroRNAs can silence target genes efficiently and regulate a broad set of genes of interest simultaneously, which are involved in the initiation, progression and survival of TNBC [14–16]. Therefore, miRNAs have the potential to act as therapeutic targets and markers of TNBC [6,17]. However, only a limited number of literature reviews on the miRNAs in TNBC have been published to date [17,18]. Few literature reviews discussing the role of miRNAs in diagnosis, therapy and prognosis of TNBC have been recently published. Herein, this review aims to provide an analysis of miRNA involved in TNBC development as well as potential diagnostic, therapeutic and prognostic applications in triple-negative breast cancer.

Triple-negative breast cancer-linked miRNAs

An increasing number of researches have demonstrated the dysregulated expressions of miRNAs in TNBC. Cascione et al. [18] reported that there were 116 deregulated microRNAs in the first set of primary TNBC and normal tissues. Also, miR-200 family (miR-200a, miR-200b, and miR-200c), miR-21, miR-106b, miR-155 and the cluster miR-17/92 were the most up-modulated while let-7b, let-7c, miR-126, miR-145 and miR-205 were the most down-modulated. The experimental result...
in the second set of TNBC-associated lymph node metastasis and normal tissues revealed a set of six miRNAs (miR-424, miR-125a-5p, miR-627, miR-579, let-7g, miR-101) were differentially expressed in the metastatic tissues. Recent research shows that most oncogenic miRNAs (oncomiRs) were found to be over-expressed and inversely, tumor suppressor miRNAs (tmiRs) were down-regulated, which show the diverse functions in malignant TNBC (Table 1, Figure 1). Among oncomiRs marked oval in Figure 1, we find easily: miR-182 and miR-20a-5p, involved in cell proliferation and invasion; miR-21, which serves as a potent antiapoptotic; 7 miRNAs (miR-25-3p, miR-20a-5p, miR-125b, miR-429, miR-27a, miR-520h and miR-155) involved in drug resistance. Among tmiRs marked rounded rectangle, we find 14 miRNAs can inhibit TNBC cell proliferation; 8 miRNAs can suppress TNBC cell proliferation and invasion; 21miRNAs can suppress TNBC cell invasion; 8 miRNAs induced drug sensitivity in Figure 1. The data given in Table 1 acquired through individual study has potential bias and limits, so expression patterns of some miRNAs associated with TNBC were retrieved from dbDEMC (a differentially expressed miRNA database in human cancer, http://www.picb.ac.cn/dbDEMC/) portal for analyses.

In this updated version of dbDEMC, a total of 209 newly released datasets were collected from Gene Expression Omnibus (GEO) and the Cancer Genome Atlas (TCGA). The current version contains 2224 differentially expressed miRNAs out of 36 cancer types, planned by 436 experiments. As shown in Table 2, we utilized the dbDEMC database to screen a total of 122 miRNAs with up-regulation or down-regulation in triple-negative breast cancer, of which 48 miRNAs were up-regulated and 74 miRNAs were down-regulated.

Some miRNAs in Table 1 have been shown to be up-regulated or down-regulated, which were coordinated with data in dbDEMC database, including miR-182, miR-210, miR-146a, miR-155, miR-10b, miR-145, miR-125b, miR-638, and the like. However, expression patterns of three miRNAs (miR-200a/b/c) between data in Table 1 and Table 2 are not matched. The three miRNAs acquired through individual study (in Table 1) that are down-regulated but up-regulated in high-throughput databases (dbDEMC, in Table 2), which may be data obtained by the individual study that is accidental and may require more experiment or other data for analysis.

**microRNA-based potential diagnostic and prognostic implications in TNBC**

**microRNAs distinguish TNBC from other breast cancer subtypes**

Numerous reports suggested that aberrant expression of miRNAs could clearly separate breast cancer specimens versus normal tissues [85]. Some studies confirmed that profiling of miRNAs can help to distinguish TNBC from other breast cancer subtypes [14,86,87]. Crippa et al. [26] demonstrated that miR-342 has negatively regulated the expression of BRCA1 in breast cancer, which may be a diagnostic marker for TNBC. A panel of 4 miRNAs(miR-155, miR-493, miR-30e and miR-27a) was found to act as a diagnostic and prognostic tool through sub-classifying TNBC into basal-like or core basal (CB) and five negative (SNP). This classification using miRNA could help in predicting the outcome of TNBC since BC subdivision tends to have a poor prognosis compared to SNP [29]. Hu et al. assessed the expression of miR-93 by in situ hybridization in 119 cases of breast cancer. Also, the miR-93 expression level in TNBC tissues was significantly higher than that in non-triple-negative breast cancer tissues, suggesting that miR-93 may be a biomarker associated with the biological and clinical characteristics of TNBC [88]. Altogether, these findings indicate that the up-regulated miRNAs can be considered as a suitable candidate in the diagnosis of TNBC.

In addition, some miRNAs down-regulated in TNBC can also be used as biomarkers for diagnosis. The miR-199a-5p expression is significantly reduced in TNBC patients in comparison with other patients with non-TNBC breast cancer and a healthy group [42]. Also, other studies demonstrated that miR-199a-5p was associated with early stages of TNBC and miR-199a-5p may be a diagnostically valuable TNBC-specific marker in a large number of patients [43,89]. Savad et al. showed that miR-205 and miR-342 expressions were significantly down-regulated in the TNBC group compared to other BC groups in 59 patients with breast cancer. Their results suggested that miR-205 and miR-342 may be used as potential biomarkers for diagnosis of TNBC [90]. Different miRNA-based diagnostic implications in TNBC are summarized in Table 3.

**microRNAs act as potential prognostic markers in TNBC**

Lack of highly sensitive and specific prognostic markers is a major obstacle for effective therapy against TNBC. Recently, several studies found that miRNA signature was correlated with the patients’ overall survival (OS), outcome and recurrence of TNBC and acted as prognostic markers. Kleivi et al. have found that microRNA signature (miR-18b, miR-103, miR-107 and miR-652) was associated with tumor recurrence and reduced OS in TNBC patients as it was exclusively up-regulated in relapsing TNBC compared to non-relapsing TNBC, healthy subjects or ER+ patients [17]. Gasparini et al. [29] also found that upregulation of miR-493 and miR-155 was correlated with better patient outcome, whereas downregulation of miR-30e and miR-27a was correlated with a negative outcome. Liu et al. provided strong evidence that the expression levels of miR-374b-5p, miR-27b-3p, miR-126-3p, and miR-218-5p in tumor tissues were in association with disease-free survival (DFS) and OS of TNBC, which predict TNBC outcomes [91].

MiR-21, one of the most studied oncomiRs in cancer, is predominantly over-expressed in the majority of human tumors. It plays an important role in cancer formation and development, and it has been shown in multiple studies to serve as a potentially prognostic biomarker for TNBC [92–94]. A number of reports confirmed that other up-regulated microRNAs also have potential prognostic value for TNBC patients [38,95–98]. High level of miR-9 expression showed
| MicroRNA   | Target       | Endogenous expression in TNBC | Main biological function(s) in TNBC                                                                 | References |
|-----------|--------------|-------------------------------|------------------------------------------------------------------------------------------------------|------------|
| **Oncogenic miRNAs** |              |                               |                                                                                                      |            |
| miR-181a/b | Bim          | Up-regulate                   | Inhibition of anoikisis                                                                                | [19]       |
| miR-181a/b | ATM          | Up-regulate                   | Impairment of DNA double-strand-breaks repair                                                        | [20]       |
| miR-181a  | BAX          | Up-regulate                   | Promote tumor cell survival, metastasis and chemoresistance to doxorubicin                          | [21]       |
| miR-182   | PFN1         | Up-regulate                   | Promote cell proliferation and invasion, Induction of apoptosis                                       | [22]       |
| miR-210   | Unknown      | Up-regulate                   | Be associated with worse patient disease-free and overall survival                                    | [23]       |
| miR-373   | Unknown      | Up-regulate                   | Downregulate protein expression of the estrogen receptor                                              | [24]       |
| miR-26a   | Unknown      | Up-regulate                   | As biomarkers cancer to predict lymph node metastases (LNM)                                          | [25]       |
| miR-10b   |              |                               |                                                                                                      |            |
| miR-153   |              |                               |                                                                                                      |            |
| miR-342   | ID4          | Up-regulate                   | Regulates BRCA1 expression                                                                            | [26]       |
| miR-146a  | BRCA1        | Up-regulate                   | Control of BRCA1-mediated proliferation and homologous recombination                                 | [25,27]   |
| miR-146b-5p |            |                               |                                                                                                      |            |
| miR-155   | Unknown      | Up-regulate                   | Diagnostic tools                                                                                     | [28]       |
| miR-493   |              |                               |                                                                                                      |            |
| miR-30e   |              |                               |                                                                                                      |            |
| miR-27a   |              |                               |                                                                                                      |            |
| miR-21    | ANKRD46      | Up-regulate                   | Promote proliferation and in vitro migration in MDA-MB-231 cell                                        | [29]       |
| miR-20a-5p| RUNX3        | Up-regulate                   | Promote the migration and invasion                                                                   | [30]       |
| miR-103   | 30-UTR       | Up-regulate                   | Regulation of migration, invasion and MMP 9 expression                                                | [31]       |
| miR-429   | XIAP         | Up-regulate                   | Mediate δ-tocotrienol-induce apoptosis                                                                | [32]       |
| miR-25-3p | BTG2         | Up-regulate                   | Promote the proliferation                                                                            | [33]       |
| miR-455-3p| EL24         | Up-regulate                   | Promote invasion and migration                                                                       | [34]       |
| miR-27a   | CDC27        | Up-regulate                   | Modulate radiosensitivity of TNBC                                                                    | [35,36]   |
| miR-155   | FOXO3a       | Up-regulate                   | Induce chemoresistance                                                                               | [37]       |
| miR-520h  | DAPK2        | Up-regulate                   | Modulate sensitivity of paclitaxel                                                                   | [38]       |
| miR-125b  | Bak1         | Up-regulate                   | Modulate sensitivity of paclitaxel                                                                   | [39]       |
|           |              |                               |                                                                                                      |            |
| **Tumor suppressor miRNAs** |              |                               |                                                                                                      |            |
| miR-10b   | Unknown      | Down-regulate                 | A potential treatment target                                                                           | [22,23]   |
| miR-145   |              |                               |                                                                                                      |            |
| miR-200a/b| Zeb1/Zeb2    | Down-regulate                 | Stimulation of differentiation in undifferentiated mammary epithelial cell line                     | [40]       |
|           | Suz 12      |                              |                                                                                                      |            |
|           | EphA2       |                              |                                                                                                      |            |
| miR-199a-5p| Unknown     | Down-regulate                 | Potential diagnostic marker                                                                            | [41,42]   |
| miR-146a-5p| SOX5        | Down-regulate                 | Inhibit the proliferation and metastasis                                                              | [43]       |
| miR-26a   | Metadherin   | Down-regulate                 | Suppresses tumor proliferation and metastasis                                                        | [44]       |
| miR-136   | RASAL2       | Down-regulate                 | Suppresses tumor invasion and metastasis                                                             | [45]       |
| miR-148a  | WNT1 NRP1    | Down-regulate                 | Suppress metastasis                                                                                  | [46]       |
| miR-203   | BIRC5        | Down-regulate                 | Reduction of proliferation                                                                           | [47]       |
| miR-490-3p| TNKS2        | Down-regulate                 | Inhibit the growth and invasiveness                                                                  | [48]       |
| miR-143-3p| LIM domain kinase 1 | Down-regulate          | Suppresses the growth                                                                                | [49]       |
| miR-101-3p| AMPK         | Down-regulate                 | A key regulator of tumor metabolism                                                               | [50]       |
| miR-145   | ARF6         | Down-regulate                 | Regulate invasion                                                                                    | [51]       |
| miR-940   | Unknown      | Down-regulate                 | Inhibit the growth and migration                                                                       | [52]       |
| miR-205   | ErbB3        | Down-regulate                 | Reduction of proliferation, cell cycle and tumor growth                                              | [53–55]   |
|           | VEGF-A       |                              |                                                                                                      |            |
|           | E2F1         |                              |                                                                                                      |            |

(continued)
significant association with poor disease-free survival and distant metastasis-free survival (DMFS) in TNBC, while a high level of miR-155 expression was associated with better DMFS, which suggests that expression levels of both miR-9 and miR-155 can serve as a candidate for prognostic biomarkers in TNBCs [38]. Shen et al. [95] confirmed that over-expression of miR-27b-3p can act as an independent predictor for distant metastasis of TNBC patients. High expression of miR-210, miR-454 and miR-34b were positively correlated with poor prognosis of TNBC patients [96–98]. Another study also found that miR-301a level was positively correlated with tumor size, depth of invasion, TNM stage and LNM by detecting the expression level of miR-301a in TNBC and adjacent non-cancerous tissues [99].

In addition, some down-regulated miRNAs in TNBC have a potential prognostic value for TNBC patients [100,101]. Deng et al. [101] selected five miRNAs that were differentially expressed in 125 patients with different prognosis for validation. The expression levels of miR-195 and miR-497 were lower in the MDA-MB-231 cell line than in cell line MCF10a. Also, miR-195/miR-497 regulate CD274 expression in TNBC, which may further influence tumor progression and may be able to predict the effect of immunotherapy on patients [102]. The miRNAs with potential prognostic implications in TNBC are listed in Table 4.
microRNA-based potential therapeutic application in TNBC

The therapeutic application of miRNAs involves two strategies. One strategy aims to inhibit oncomiRs by using miRNA antagonists. The other strategy, miRNA replacement, involves the reintroduction of tsmiRs mimic to restore a loss-of-function.

miRNA-based inhibition therapeutic applications

A large number of studies have demonstrated that dysregulation of specific miRNAs can promote tumor cell proliferation, differentiation, migration, invasion and lead to drug resistance (as shown in Table 1, Figure 1), which act as promising therapeutic targets for TNBC. The inactivation of oncomiRs was accomplished successfully through knockdown target oncomiRs or the administration of a synthetic anti-miRNA oligonucleotide. MicroRNA-21, well-known over-expressed oncomiRs, can promote proliferation and migration of MDA-MB-231 cells. Knockdown of miR-21 significantly prevented the proliferation of TNBC cell, in vitro migration and lung metastasis [28]. Some antisense oligonucleotides (antagomiR) can block the function of endogenous micro-RNA and...
normalize the gene regulatory network and signaling pathways and sensitize cancerous cells to chemotherapy. For example, antagomiR-21 could restore trastuzumab sensitivity in resistant breast cancer by inducing PTEN expression [103]. However, miRNAs and antagomiR are easily degraded, some scientists deliver miRNAs into TNBC cells to improve stability through some nanomaterials. Shu et al. [103] developed efficient delivery systems that can specifically deliver antagomiR-21 and improve therapeutic effect in TNBC cells and living animal models. Similarly, Devulapally et al. [104] proved that antisense miR-21-PS and miR-10b can effectively inhibit the proliferation and metastasis of triple-negative breast cancer, which also indicates that multi-target antagonism of endogenous miRNA may be an effective strategy for the treatment of metastatic cancer targeting metastasis and anti-apoptosis. Zhou et al. [105] also reported that a novel calcium phosphate-polymer hybrid nanoparticle system can co-deliver paclitaxel and miRi-221/222 (inhibitors for miRNA-221 and miRNA-222) to their intracellular targets, thereby inhibiting the proliferation mechanism of miR-221/222, thereby significantly improving the therapeutic efficacy of paclitaxel.

miRNA-based replacement therapeutic applications

**Suppress metastasis**

Metastasis is a process in which tumor cell breaks away from the original site and travels through the blood or lymphatic system to the other parts of the body and form new tumors. Some miRNAs such as miR-146a-5p, miR-26a, miR-136 and miR-136 have been proved to inhibit the expression of numerous cancer-related genes that subsequently suppress metastasis in TNBC [43–45].

**Block tumor cell proliferation, invasion and migration**

The tsmiRs can block tumor cell proliferation, invasion, and birth and lead to cancer cell death [46–74] and function of these down-regulated tsmiRs may be replaced by introducing synthetic miRNA mimics. Moreover, miRNA mimics cannot only provide obvious benefits to those cancer cells with low tumor suppressor miRNA expression levels but also show therapeutic benefits in cancer with normal miRNA expression levels. Therefore, miRNA mimics could be a promising treatment for TNBC [106]. For example, miR-542-3p, a potent tumor suppressor, can control cancer aggressiveness through inhibiting cell proliferation, inducing cell cycle arrest and apoptosis and suppressing tumor angiogenesis [107]. It can also directly downregulate the expression of the anti-apoptotic protein Survivin. Herein, Wang et al. developed a nanocarrier system of HA-coated PEI-PLGA NPs for simultaneously delivering chemotherapeutic drug DOX and a tumor suppressor miR-542-3p mimics into TNBC cells. The results indicated that intracellular restoration of miR-542-3p promoted breast cancer cell apoptosis via activating p53 and inhibiting

| Table 3. List of miRNAs with potential diagnostic implications in triple-negative breast cancer. |
|---------------------------------|----------------|----------------|----------------|----------------|
| MicroRNA | Samples | Cohort ethnicity | Endogenous expression in TNBC | References |
|----------|---------|----------------|-------------------------------|------------|
| miR-373  | Serum   | Germany         | Up-regulate                   | [24]       |
| miR-146a | Tumor tissues | France   | Up-regulate                   | [25]       |
| miR-26a  | Tumor tissues | Unknown | Up-regulate                   | [25]       |
| miR-10b  | Tumor tissues | Unknown | Up-regulate                   | [26]       |
| miR-153  | Serum   | Iran            | Up-regulate                   | [25]       |
| miR-342  | Tumor tissues | Chinese | Up-regulate                   | [29]       |
| miR-155  | Serum   | Chinese         | Up-regulate                   | [25]       |
| miR-155  | Tumor tissues | Chinese | Up-regulate                   | [29]       |
| miR-493  | Tumor tissues | Chinese | Up-regulate                   | [25]       |
| miR-30e  | Tumor tissues | Chinese | Up-regulate                   | [25]       |
| miR-27a  | Tumor tissues | Chinese | Up-regulate                   | [25]       |
| miR-199a-5p | Plasma | Chinese | Down-regulate                  | [41,42,89] |
| miR-205  | Serum   | Iranian         | Down-regulate                  | [90]       |

**Table 4. List of miRNAs with potential prognostic value in triple-negative breast cancer.**

| MicroRNA | Samples | Cohort ethnicity | Expression in TNBC | References |
|----------|---------|-----------------|--------------------|------------|
| miR-18b  | miR-103 | Serum           | Up-regulate        | [17]       |
| miR-107  | miR-652 | Serum           | Up-regulate        | [37]       |
| miR-155  | Serum   | Caucasian       | Down-regulate      | [96]       |
| miR-148a | Serum   | Caucasian       | Down-regulate      | [97]       |
| miR-638  | FFPE tissues | Chinese | Down-regulate      | [79]       |
| miR-210  | FFPE tissues | Japanese | Up-regulate        | [96]       |
| miR-454  | Serum   | Chinese         | Up-regulate        | [97]       |
| miR-34b  | FFPE tissues | Chinese | Up-regulate        | [98]       |
| miR-301a | FFPE tissues | Chinese | Up-regulate        | [99]       |
| miR-34c  | Serum   | Chinese         | Down-regulate      | [100]      |
| miR-221-3p | Serum | Chinese | Down-regulate      | [101]      |
| miR-195/miR-497 | Tumor cell | Unknown | Down-regulate | [102]      |

[ARTIFICIAL CELLS, NANOMEDICINE, AND BIOTECHNOLOGY 2805]
surviving [107]. miR-34a is a miRNA that is regulated by the p53 network at the transcriptional level and has been shown to be significantly down-regulated in TNBC. Deng et al. [108] co-wrapped miR-34a with doxorubicin (DOX) in hyaluronic acid – chitosan nanoparticles and into breast cancer cells. The data obtained indicate that intracellular recovery of miR-34a inhibits breast cancer cell migration by targeting Notch-1 signaling, and in addition, co-delivery of DOX and miR-34a can achieve a synergistic effect on tumor suppression. Goyal et al. developed Lbl-NS to deliver tumor suppressor miR-34a to TNBC cells. These constructs were shown to safely and efficiently regulate the expression of SIRT1 and Bcl-2 (two known miR-34a targets) to reduce cell proliferation [109].

### Regulate radiosensitivity and chemosensitivity

Radiotherapy is an effective and well-established cancer treatment. However, radiation resistance poses a major clinical challenge in cancer treatment. Experimental evidence demonstrates that some specific miRNAs play critical roles in modulating radiosensitivity of TNBC [75,110,111]. Liang et al. [112] suggested that miRNA-302 sensitized resistant triple-negative breast cancer cells to irradiation in vitro and in vivo and miRNA-302 could act as a potential sensitizer to radiotherapy.

Multidrug resistance (MDR) is generally considered to be a major factor in the failure of many forms of chemotherapy. Recently, growing body of reports have suggested that several miRNAs are closely associated with MDR and they can modulate drug sensitivity in TNBC [78–84]. Tan et al. [79] found that miR-638 can affect DNA repair and sensitivity to UV and cisplatin. Bockhorn et al. [113] reported that increased miRNA-30c levels did not affect TNBC cell growth but sensitized the drug response of TNBC cell lines to paclitaxel and doxorubicin. They found that miRNA-30c played a pivotal role in chemoresistance via direct targeting of the actin-binding protein Twinfilin 1 which is responsible for the promotion of epithelial-to-mesenchymal transition.

An increasing body of evidence suggests that there has been a tremendous improvement in understanding the mechanisms of miRNAs [43–74] and the development of creative strategies for using miRNA in TNBC therapy [103–105,107–109]. However, there is no currently available miRNA based clinical therapy. There are a few basic reasons for the aforementioned situation. First, naked miRNA antagonists and miRNA mimics are quickly degraded and cleared in the blood circulation [107,108,114]. Second, miRNA probably cause unexpected toxicities and significant undesirable side effects [115,116]. For example, tumor-secreted miR-21and miR-29a can bind to toll-like receptor (TLR) family as agonists, leading to NF-kB signaling activation and secretion of IL-6 and TNF-α, which ultimately may lead to tumor growth and metastasis and may cause systemic immune toxicity. MiRNA let-7b can bind and activate TLR 7 signaling in neurons and cause neurodegeneration [116]. Third, there are probably many off-target effects for miRNAs therapy [117].

### Conclusion and future perspectives

In summary, deregulation of miRNAs is involved in the development of triple-negative breast cancer and these changes have important roles in modulating gene expression and cancer-relevant pathways, which qualify these miRNAs as promising candidate cancer biomarkers for TNBC diagnosis, prognosis and therapy prediction. However, miRNAs have not yet been clinically utilized as disease-specific markers due to the need for an optimized detection strategy. With the development of the times and continued progress with a better understanding of functional involvement of miRNAs, more and more evidence strongly supports miRNAs involved in tumorigenesis and offer the promise of developing a novel approach in the clinical care of TNBC patients.

### Acknowledgement

Financial assistance received from Innovation platform Open Foundation of education department of Hunan province is acknowledged with thanks.

### Disclosure statement

The authors declare that they have no conflict of interest.

### Funding

This work was supported by Innovation platform Open Foundation of education department of Hunan province [contract grant number 16K079, 17K082] and University of South China Innovation Foundation For Postgraduate.

### References

[1] Wang HD, Naghavi M, Allen C, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388:1459–1544.

[2] DeSantis C, Ma J, Bryan L, et al. Breast cancer statistics, 2013. CA Cancer J Clin. 2014;64:52–62.

[3] Shen X, Xie B, Ma Z, et al. Identification of novel long non-coding RNAs in triple-negative breast cancer. Oncotarget. 2015;6:21730–21739.

[4] Wang C, Kar S, Lai X, et al. Triple negative breast cancer in Asia: an insider’s view. Cancer Treat Rev. 2018;62:29–38.

[5] Lehmann BD, Bauer JA, Chen X, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest. 2011;121:2750–2767.

[6] Irvin WJ, Carey LA. What is triple-negative breast cancer. Eur J Cancer. 2008;44:2799–2805.

[7] Croci S, Nanni P, Palladini A, et al. Interleukin-15 is required for immunosurveillance and immunoprevention of HER2/neu-driven mammary carcinogenesis. Breast Cancer Res. 2015;17:70.

[8] Pal SK, Childs BH, Pegram M. Triple negative breast cancer: unmet medical needs. Breast Cancer Res Treat. 2011;125:627–636.

[9] O’Reilly EA, Gubbins L, Sharma S, et al. The fate of chemoresistance in triple negative breast cancer (TNBC). BBA Clin. 2015;3:257–275.
Bartosch R, Ziebierayr R, Zielinski CC, et al. Triple-negative breast cancer. Wien Med Wochenschr. 2010;160:174–181.

Shah SP, Roth A, Goya R, et al. The clonal and mutational evolution spectrum of primary triple-negative breast cancers. Nature. 2012;486:395–399.

Zhang L, Ge Y, Fuchs E. miR-125b can enhance skin tumor initiation and promote malignant progression by repressing differentiation and prolonging cell survival. Genes Dev. 2014;28:2532–2546.

Wang Q, Qin J, Chen A, et al. Downregulation of microRNA-145 is associated with aggressive progression and poor prognosis in human cervical cancer. Tumor Biol. 2015;36:3703–3708.

Kleivi SK, Bottai G, Naume B, et al. A serum microRNA signature profiling identifies a four microRNA signature as a novel diagnostic and prognostic biomarker in triple negative breast cancers. Oncotarget. 2014;5:1174–1184.

Tang W, Zhu J, Su S, et al. MiR-27 as a prognostic marker for breast cancer progression and patient survival. PLOS One. 2012;7:e51702.

Ren YQ, Fu F, Han J. MiR-27a modulates radiosensitivity of triple-negative breast cancer (TNBC) cells by targeting CDC27. Med Sci Monit. 2015;21:1297–1303.

Jang MH, Kim HJ, Gwak JM, et al. Prognostic value of microRNA-9 and microRNA-155 expression in triple-negative breast cancer. Hum Pathol. 2017;68:69–78.

Su CM, Wang MY, Hong CC, et al. miR-520h is crucial for DAPK2 regulation and breast cancer progression. Oncogene. 2017;36:5770.

Zhou M, Liu Z, Zhao Y, et al. MicroRNA-125b confers the resistance of breast cancer cells to paclitaxel through suppression of pro-apoptotic Bcl-2 antagonist killer 1 (Bak1) expression. J Biol Chem. 2010;285:21496–21507.

Aydoğdu E, Katchy A, Tsouko E, et al. MicroRNA-regulated gene networks during mammary cell differentiation are associated with breast cancer. Carcinogenesis. 2012;33:1502–1511.

Abdellatif M. Differential expression of miRNAs in different disease states. Circ Res. 2012;110:638–650.

Shin VF, Kwong A. Response to: Comment on ‘Circulating cell-free miRNAs as biomarker for triple-negative breast cancer’. Br J Cancer. 2016;114:e6.

Li D, Hu J, Song H, et al. miR-143-3p targeting LIM domain kinase 2 (LIMK2) downregulates cell proliferation and migration of breast cancer cells. Oncotarget. 2017;8:51702.

Jia Z, Liu Y, Gao Q, et al. miR-490-3p inhibits the growth and invasiveness in triple-negative breast cancer by repressing the expression of TNKS2. Gene. 2016;593:45–54.

Li D, Hu J, Song H, et al. MiR-143-3p targeting LIM domain kinase 1 suppresses the progression of triple-negative breast cancer cells. Am J Transl Res. 2017;9:2276–2285.

Wang C, Zheng X, Shen C, et al. MicroRNA-203 suppresses cell proliferation and migration by targeting BIRC5 and LASP1 in human triple-negative breast cancer cells. J Exp Clin Cancer Res. 2012;31:58.

Jia Z, Liu Y, Gao Q, et al. miR-490-3p inhibits the growth and invasiveness in triple-negative breast cancer by repressing the expression of TNKS2. Gene. 2016;593:41–47.

Li D, Hu J, Song H, et al. MiR-143-3p targeting LIM domain kinase 1 suppresses the progression of triple-negative breast cancer cells. Am J Transl Res. 2017;9:2276–2285.

Liu P, Ye F, Xie X, et al. MiR-101-3p is a key regulator of tumor metabolism in triple-negative breast cancer targeting AMPK. Oncotarget. 2016;7:20381–20394.

Wang C, Zheng X, Shen C, et al. MicroRNA-203 suppresses cell proliferation and migration by targeting BIRC5 and LASP1 in human triple-negative breast cancer cells. J Exp Clin Cancer Res. 2012;31:58.

Jia Z, Liu Y, Gao Q, et al. miR-490-3p inhibits the growth and invasiveness in triple-negative breast cancer by repressing the expression of TNKS2. Gene. 2016;593:41–47.
metastasis by inhibiting the Src/Vav2/Rac1 pathway. Cancer Lett. 2018;433:199–209.

[56] Li J, Lai Y, Ma J, et al. miR-17-5p suppresses cell proliferation and invasion by targeting ETV1 in triple-negative breast cancer. BMC Cancer. 2017;17:745.

[57] Shyamasundar S, Lim JP, Bay BH. miR-93 inhibits the invasive potential of triple-negative breast cancer cells in vitro via protein kinase Wnk1. Int J Oncol. 2016;49:2629–2636.

[58] Yang ZX, Zhang B, Wei J, et al. MiR-539 inhibits proliferation and migration of triple-negative breast cancer cells by down-regulating LAMA4 expression. Cancer Cell Int. 2018;18:16.

[59] Shi Z, Li Y, Qian X, et al. MiR-340 inhibits triple-negative breast cancer progression by reversing EZH2 mediated miRNAs dysregulated expressions. J Cancer. 2017;8:3037–3048.

[60] Hong L, Pan F, Jiang H, et al. miR-125b inhibited epithelial-mesenchymal transition of triple-negative breast cancer by targeting MAP2K7. Onco Targets Ther. 2016;9:2639–2648.

[61] Zhou W, Song F, Wu Q, et al. miR-217 inhibits triple-negative breast cancer cell growth, migration, and invasion through targeting KLF5. PLOS One. 2017;12:e0176395.

[62] Tsouko E, Wang J, Frigo DE, et al. miR-200a inhibits migration of triple-negative breast cancer cells through direct repression of the EPHA2 oncogene. Carcin. 2015;36:1051–1060.

[63] Humphries B, Wang Z, Oom AL, et al. MicroRNA-200b targets protein kinase Cx and suppresses triple-negative breast cancer metastasis. Carcigenesis. 2014;35:2254–2263.

[64] Rhodes LV, Martin EC, Segar HC, et al. Dual regulation by microRNA-200b-3p and microRNA-200b-5p in the inhibition of epithelial-to-mesenchymal transition in triple-negative breast cancer. Oncotarget. 2015;6:16638–16652.

[65] Ren Y, Han X, Yu K, et al. microRNA-200c downregulates XIAP expression to suppress proliferation and promote apoptosis of triple-negative breast cancer cells. Mol Med Rep. 2014;10:315–321.

[66] Howe EN, Cochrane DR, Cittelly DM, et al. miR-200c targets a NF-xB up-regulated TrkB/NTF3 autocrine signaling loop to enhance anoikis sensitivity in triple negative breast cancer. PLOS One. 2012;7:e49987.

[67] Rogers TJ, Christenson JL, Greene Li, et al. Reversal of triple-negative breast cancer EMT by miR-200c during the invasion-metastasis cascade. Int J Cancer. 2011;42:256–263.

[68] Liang Z, Bian X, Shim H. Downregulation of microRNA-206 promotes invasion and angiogenesis of triple negative breast cancer. Biochem Biophys Res Commun. 2016;477:461–466.

[69] Wang J, Tsouko E, Jonsson P, et al. miR-206 inhibits cell migration through direct targeting of the actin-binding protein corterin 1C in triple-negative breast cancer. Mol Oncol. 2014;8:1690–1702.

[70] Luo LJ, Yang F, Ding JJ, et al. MiR-31 inhibits migration and invasion by targeting SATB2 in triple negative breast cancer. Gene. 2016;594:47–58.

[71] Sossey-Alaoui K, Downs-Kelly E, Das M, et al. WAVE3, an actin remodeling protein, is regulated by the metastasis suppressor microRNA, miR-31, during the invasion-metastasis cascade. Int J Cancer. 2011;129:1331–1343.

[72] Kömer C, Keikilgolou I, Bender C, et al. MicroRNA-31 sensitizes human breast cells to apoptosis by direct targeting of protein kinase C epsilon (PKC epsilon). J Biol Chem. 2013;288:8750–8761.

[73] Xiong H, Yan T, Zhang W, et al. MiR-613 inhibits cell migration and invasion by downregulating Daam1 in triple-negative breast cancer. Cell Signal. 2018;44:33–42.

[74] Moskova P, Buffa FM, Pan Y, et al. miR-182-mediated downregulation of BRC1 impacts DNA repair and sensitivity to PARP inhibitors. Mol Cell. 2011;41:210–220.

[75] Tan X, Peng J, Fu Y, et al. miR-638 mediated regulation of BRC1 affects DNA repair and sensitivity to UV and cisplatin in triple-negative breast cancer. Breast Cancer Res. 2014;16:435.

[76] O’Brien K, Lowry MC, Corcoran C, et al. miR-134 in extracellular vesicles reduces triple-negative breast cancer aggression and increases drug sensitivity. Oncotarget. 2015;6:32774–32789.

[77] Bao L, Hazari S, Mehra S, et al. Increased expression of P-glycoprotein and doxorubicin chemoresistance of metastatic breast cancer is regulated by miR-298. Am J Pathol. 2012;180:2490–2503.

[78] Liu X, Tang H, Chen J, et al. MicroRNA-101 inhibits cell progression and increases paclitaxel sensitivity by suppressing MCL-1 expression in human triple-negative breast cancer. Oncotarget. 2015;6:20070–20083.

[79] Gao J, Li L, Wu M, et al. MiR-26a inhibits proliferation and migration of breast cancer through repression of MCL-1. PLOS One. 2013;8:e65138.

[80] Aakko S, Straume AH, Birkeland EE, et al. MYC-induced miR-203b-3p and miR-203a-3p control Bcl-xl expression and paclitaxel sensitivity in tumor cells. Transl Oncol. 2019;12:170–179.

[81] Toralh EA, Mohammed EA, Farrag S, et al. Pilot study of serum microRNA-21 as a diagnostic and prognostic biomarker in Egyptian breast cancer patients. Mol Diagn Ther. 2015;19:179–190.

[82] Gyparaki MT, Basdra EK, Papavassiliou AG. MicroRNAs as regulatory elements in triple negative breast cancer. Cancer Lett. 2014;354:1–4.

[83] Farazi TA, Horlings HM, Ten HJ, et al. MicroRNA sequence and expression analysis in breast tumors by deep sequencing. Cancer Res. 2011;71:4443–4453.

[84] Hu J, Xu J, Wu Y, et al. Identification of microRNA-93 as a functional dysregulated microRNA in triple-negative breast cancer. Tumor Biol. 2015;36:251–258.

[85] Ebrahimi A, Nikokar I, Zokaei M, et al. Design, development and evaluation of microRNA-199a-5p detecting electrochemical nanobiosensor with diagnostic application in triple negative breast cancer. Talanta. 2018;189:592–598.

[86] Savad S, Mehdipour P, Miryounesi M, et al. Expression analysis of MiR-21, MiR-205, and MiR-342 in breast cancer in Iran. Asian Pac J Cancer Prev. 2012;13:877–877.

[87] Liu Y, Cai Q, Bao PP, et al. Tumor tissue microRNA expression in association with triple-negative breast cancer outcomes. Breast Cancer Res Treat. 2015;152:183–191.

[88] Dong G, Liang X, Wang D, et al. High expression of miR-21 in triple-negative breast cancers was correlated with a poor prognosis and promoted tumor cell invasion in vitro. Med Oncol. 2014;31:57.

[89] Yang L, Feng Y, Qi P, et al. Mechanism of serum miR-21 in the pathogenesis of familial and triple negative breast cancer. J Biol Regul Homeost Agents. 2016;30:1041–1045.

[90] MacKenzie TA, Schwartz GN, Calderone HM, et al. Stromal expression of miR-21 identifies high-risk group in triple-negative breast cancer. Am J Pathol. 2014;184:3217–3225.

[91] Shen S, Sun Q, Liang Z, et al. A prognostic model of triple-negative breast cancer is regulated by miR-21 identifies high-risk group in triple-negative breast cancer. Cancer Lett. 2018;398:3225.
Cao Z-G, Li J-J, Ya L, et al. High expression of microRNA-454 is associated with poor prognosis in triple-negative breast cancer. Oncotarget. 2016;7:64900–64909.

Svoboda M, Sana J, Redova M, et al. MiR-34b is associated with clinical outcome in triple-negative breast cancer patients. Diagn Pathol. 2012;7:31.

Yu H, Li H, Qian H, et al. Upregulation of miR-301a correlates with poor prognosis in triple-negative breast cancer. Med Oncol. 2014;31:283.

Zeng Z, Chen X, Zhu D, et al. Low expression of circulating microRNA-34c is associated with poor prognosis in triple-negative breast cancer. Yonsei Med J. 2017;58:697–702.

Deng L, Lei Q, Wang Y, et al. Downregulation of miR-221-3p and upregulation of its target gene PARP1 are prognostic biomarkers for triple negative breast cancer patients and associated with poor prognosis. Oncotarget. 2017;8:108712–108725.

Si H, Sun X, Chen Y, et al. Circulating microRNA-92a and microRNA-21 as novel minimally invasive biomarkers for primary breast cancer. J Cancer Res Clin Oncol. 2013;139:223–229.

Shu D, Li H, Shu Y, et al. Systemic delivery of anti-miRNA for suppression of triple negative breast cancer utilizing RNA nanotechnology. ACS Nano. 2015;9:9731–9740.

Devulapally R, Sekar NM, Sekar TV, et al. Polymer nanoparticles mediated codelivery of antimiR-10b and antimiR-21 for achieving triple negative breast cancer therapy. ACS Nano. 2015;9:2290–2302.

Zhou Z, Kennell C, Lee JY, et al. Calcium phosphate-polymer hybrid nanoparticles for enhanced triple negative breast cancer treatment via co-delivery of paclitaxel and miR-221/222 inhibitors. Nanomedicine. 2017;13:403–410.

Tomao F, Papa A, Zaccarelli E, et al. Triple-negative breast cancer: new perspectives for targeted therapies. Onco Targets Ther. 2015;8:177–193.

Althoff K, Lindner S, Odersky A, et al. miR-542-3p exerts tumor suppressive functions in neuroblastoma by downregulating Survivin. Int J Cancer. 2015;136:1308–1320.

Deng X, Cao M, Zhang J, et al. Hyaluronic acid-chitosan nanoparticles for co-delivery of MiR-34a and doxorubicin in therapy against triple negative breast cancer. Biomaterials. 2014;35:4333–4344.

Goyal R, Kapadia CH, Melamed JR, et al. Layer-by-layer assembled gold nanoshells for the intracellular delivery of miR-34a. Cell Mol Bioeng. 2018;11:383–396.

Wang S, Zhang J, Wang Y, et al. Hyaluronic acid-coated PEL-PGLA nanoparticles mediated co-delivery of doxorubicin and miR-542-3p for triple negative breast cancer therapy. Nanomedicine 2016;12:411–420.

Huang X, Taeb S, Jahangiri S, et al. miRNA-95 mediates radioreistance in tumors by targeting the sphingolipid phosphatase SGPP1. Cancer Res. 2013;73:6972–6986.

Liang Z, Ahn J, Guo D, et al. MicroRNA-302 replacement therapy sensitizes breast cancer cells to ionizing radiation. Pharm Res. 2013;30:1008–1016.

Bockhorn J, Dalton R, Nwachukwu C, et al. MicroRNA-30c inhibits human breast tumour chemotherapy resistance by regulating TWF1 and IL-11. Nat Commun. 2013;4:1393.

Garzon R, Marcucci G, Croce CM. Targeting microRNAs in cancer: rationale, strategies and challenges. Nat Rev Drug Discov. 2010;9:775–789.

Fabbri M, Paone A, Calore F, et al. MicroRNAs bind to Toll-like receptors to induce prometastatic inflammatory response. Proc Natl Acad Sci U S A. 2012;109:E2110–E2116.

Lehmann SM, Kruger C, Park B, et al. An unconventional role for miRNA: let-7 activates Toll-like receptor 7 and causes neurodegeneration. Nat Neurosci. 2012;15:827–835.

Wen D, Danquah M, Chaudhary AK, et al. Small molecules targeting microRNA for cancer therapy: promises and obstacles. J Control Release. 2015;219:237–247.