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# MicroRNAs in triple-negative breast cancer

*Minireview*

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Triple-negative breast cancer (TNBC) is a molecular subtype of breast cancer with one of the worst prognoses. Current treatment is based on chemo- and/or radiotherapy and surgery. New targets, however, offering other therapeutic approaches, have been identified. These involve poly (ADP-ribose) polymerase (PARP), vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor (EGFR), androgen receptor (AR), long non-coding RNAs (lncRNAs) and microRNAs (miRs). The latter are non-coding RNAs which control the expression of more than 50% of human genes via regulation of basic cellular processes at post-transcriptional level and dysregulation of miRs is found in many types of tumors. The role of dysregulated miRs in carcinogenesis lies in their acting as tumor suppressors or oncogenes, and in resistance to treatment (chemotherapy, hormonal and targeted therapy or radiotherapy). Circulating miRs are also promising prognostic and predictive biomarkers in patients with breast cancer. The aim of this review is to analyze recently published data on miRs and therapeutic targets potentially influenced by miRs in TNBC.

*Key words: triple-negative breast cancer, microRNA, biomarkers, therapeutic targets*

Triple-negative breast cancer (TNBC) is a breast cancer molecular subtype characterized by low or negative hormone receptor expression (estrogen and progesterone receptor), as well as HER2 protein expression and HER2 gene amplification. Usually, it is determined using standard immunohistochemistry (IHC) and in situ hybridization (ISH). About 12 to 17% of all invasive breast cancers are found to be triple-negative and they are usually associated with higher histological grade [1]. Histological types comprise high-grade invasive ductal carcinoma, no special type carcinoma, invasive ductal carcinoma with a large central fibrosis, typical and atypical medullary carcinoma, metaplastic carcinoma and carcinoma with basaloid cell differentiation [2, 3]. The main risk factors for development of TNBC are younger age at time of diagnosis (women less than 50 years old), race (predominantly African-American, followed by Hispanic women compared with other racial and ethnic groups), genetic predisposition (positive BRCA1 mutation, p53 mutations), early age at menarche and higher body-mass index in premenopausal years [1, 4]. Moreover, the basal-like breast cancer with gene expression profile similar to basal-myoepithelial layer of the normal breast (expression of cytokeratin 5) can imitate TNBC because it is also accompanied by negativity or low levels of estrogen receptor (ER), as well as HER2 protein [5].

The treatment of TNBC is based on chemotherapy and radiotherapy due to the absence of estrogen and progesterone receptors and HER2 protein expression as the potential targets of pharmacotherapy (antiestrogens, aromatase inhibitors or anti-HER-2 human monoclonal antibodies) [6]. However, several molecular and therapeutic targets have been explored (Figure 1). These include the androgen receptor (AR), epidermal growth factor receptor (EGFR), poly (ADP-ribose) polymerase (PARP), vascular endothelial growth factor (VEGF), microRNAs (miRNAs) and long non-coding RNAs (lncRNAs). miRNA-based therapeutic approaches include inhibition of oncogenes (oncomiRs) by antisense oligonucleotides, restoration of tumor suppressors using miRNA mimics, and chemical modification of miRNAs. The lncRNA HOTAIR, a new player in tumor development and prognosis may also have diagnostic and therapeutic applications in breast cancer [7].

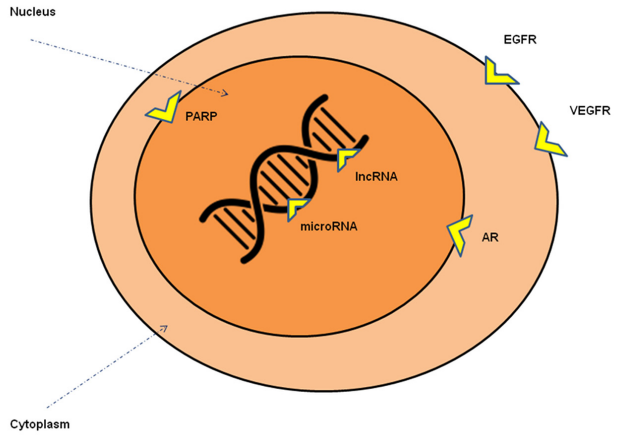


**Figure 1. Potential therapeutic targets in TNBC.**

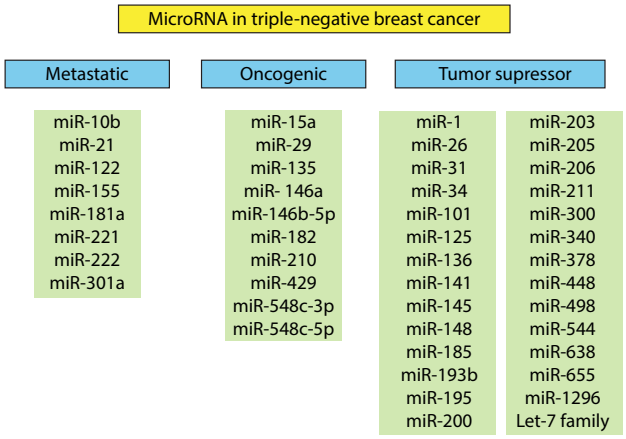


**Figure 2. List of microRNAs involved in tumor suppression, oncogenesis and metastatic process.**

MicroRNAs control more than 50% of human genes via regulation of the basic cellular and developmental processes at the post-transcriptional level [8]. They are found to be deregulated in many types of cancers and have been found to play an important role in carcinogenesis (independence of growth signals, lost cell regulation by inhibitory signals, apoptosis block, unlimited replication potential, defect of DNA reparation and genome instability, angiogenesis, invasion ability and metastasis) and drug resistance including chemotherapy, hormonal or targeted therapy and, radiotherapy [9, 10]. Recent studies have also shown the role of circulating miRNAs as potential prognostic and predictive biomarkers in patients with breast cancer [11]. Along with genes or their regulation pathways, they can act as tumor suppressors or oncogenes (oncomiRs) (Figure 2). Oncogenic miRNAs show anti-apoptotic activity and are found to be over-expressed in neoplastic cells. In contrast, miRNAs as tumor-suppressor genes display anti-proliferative and pro-apoptotic activity and are underexpressed in tumor cells.

MiRNAs are noncoding RNA molecules, differing in length from 18 to 25 nucleotides. Transcription by RNA polymerase II leads to the production of primary transcripts (pri-miRNA) which are transformed by RNase III Drosha into precursor RNA (pre-miRNA). Subsequently, exportin-5 transports the pre-miRNA from the nucleus into the cytoplasm to be modified by RNase III Dicer into short double helix and mature RNAs. The mature RNAs bind to the 3' untranslated region of messenger RNAs (mRNAs) or to sites in the open reading frame (ORF) of the target genes (Figure 3). This results in a down-regulation of target proteins through mRNA degradation or through translational inhibition. However, it is known that some miRNAs are able to bind to the 5' untranslated region of mRNAs or the ORF in order to stimulate the translation of target genes. Deregulation of miRNA occurs at genetic and epigenetic levels through the single-nucleotide polymorphisms within miRNA sequences or polymorphism in an mRNA binding site or because of aberrant DNA methylation and histone modification [12]. Numerous identified specific targets of miRNA action offer new perspectives and targets in breast cancer therapy.

Recently, several reports on the role of miRNAs in TNBC have been published. These focus, in particular, on miRNAs participation in tumorigenesis and their prognostic and predictive potential.

The aim of this review is to summarize recent knowledge on miRNA detection, analysis and the role of specific miRNAs and other prognostic and predictive biomarkers with therapeutic potential in TNBC.

## Methods used for miRNA analysis

miRNA can be examined in native as well as archived formalin fixed paraffin-embedded (FFPE) tissue samples and in body fluids. The most commonly used methods are:

**miRNA extraction.** Total RNA can be extracted from fresh and frozen tissues, FFPE or body fluids using kits according to the manufacturer's protocol [13–15]. The concentration and quality of the isolated RNA can be measured in various ways depending on the downstream application, for example by spectrophotometry, fluorometry or electrophoresis. Kits are also available for miRNA enrichment which enables us to obtain a higher percentage of miRNA molecules in isolated samples.

**Reverse transcription.** During reverse transcription (RT), a complementary DNA (cDNA) is synthesized from isolated RNA using microRNA reverse transcription kits. There are several approaches for performing reverse transcription of mature miRNA molecules. One option is based on polyadenylation of mature miRNAs using poly(A)polymerase with subsequent reverse transcription with oligo-dT primers. Another example of preparing cDNA from mature miRNAs is the use of specific stem-loop RT primers. The products

can be used in different downstream applications, such us quantitative real-time polymerase chain reaction (RT-qPCR) or sequencing analysis.

**Real-time PCR (RT-qPCR).** Real-time PCR (RT-qPCR) systems enable fluorescence-based detection and analysis of PCR products in real time (Figure 4). This is considered to be the gold standard of microRNA quantification because of its higher sensitivity and specificity compared to other methods. There are two possible strategies for fluorescence-based quantification by RT-qPCR. The first is based on a non-specific fluorescence using an intercalating dye such as SYBR Green binding to the minor groove of dsDNA. The second strategy makes use of specific fluorescently-labeled oligonucleotide probes which emit light at a detectable wave-length only after specific binding to their target molecules. The most commonly used probe designs include hybridization probes and hydrolysis probes [15–17]. This approach increases the sensitivity and enables multiplexing of reactions. The advantages of RT-qPCR are the production of quantitative data with an accurate dynamic range of six orders of magnitude not requiring post-amplification manipulation, less time consumption, lower quantity of input RNA and more cost effectiveness than RNA sequencing. However, Redshaw et al. emphasized that the final microRNA measurement can be significantly influenced by short RNA enrichment as well as by quantification strategy [18].

**Digital PCR.** Digital PCR is a single DNA molecule amplification detected through a fluorescence signal and absolutely quantified by counting the number of reactions with a positive amplification [15]. The sample of DNA or complementary DNA is serially diluted and partitioned into many individual, parallel PCR reactions. In contrast to the traditional and quantitative PCR, digital PCR measures in the linear phase of the reaction enabling discrimination of low-fold copy number variation. There is also no need for pre-amplification, relying on references and standards or PCR optimization. The droplet has greater precision, higher day-to-day reproducibility and it reduces the impact of preanalytical and analytical variables in comparison to qRT-PCR. Digital PCR can be successfully used for monitoring circulating miRNAs as diagnostic and prognostic serum biomarkers in breast cancer patients [19, 20].

**Northern blotting.** Northern blotting is one of the hybridization methods used for microRNA detection and analysis. The protocol includes RNA extraction, polyacrylamide gel electrophoresis (PAGE), northern blotting, and hybridization and detection of analysed miRNA using specific complementary labeled oligonucleotide probes [21]. These probes can be labeled with radioactive isotopes, chemiluminiscence or with fluorofores and they can be chemically modified for the purpose of better stability and specificity. Northern blotting is a highly sensitive and highly specific method for detection of mature microRNAs but the procedure is labor intensive and time-consuming. For this reason, it is often replaced by microarray technique.

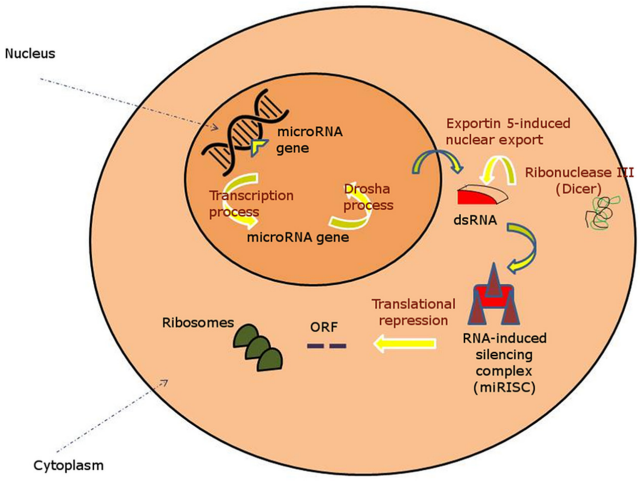


**Figure 3. Processing of microRNA production and translational repression.**

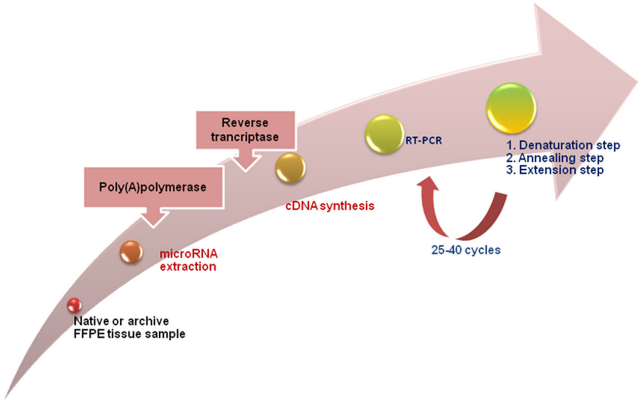


**Figure 4. Scheme of microRNA analysis by RT-qPCR.**

**Microarray.** The microarray technique is akin to the reverse northern blotting with fluorescent labeling enabling simultaneous detection of many miRNAs on one chip. The National Association of Clinical Biochemists (NABC) recommends use of microarrays for high-throughput genotyping, detection of mutation variation in tumor research to evaluate and validate new biomarkers [15, 22]. It is characterized by a dynamic range of four orders of magnitude. Gene expression measurement using microarray is limited by noise at the low end and signal saturation at the high end in contrast to next generation sequencing (NGS), which provides an unlimited dynamic range.

**Next generation sequencing.** NGS enables sequence-based gene expression analysis using the digital nature of sequencing reads. NGS allows for RNA expression quantification with the breadth of a microarray and the resolution of RT-qPCR resulting in increased sensitivity. It is characterized by a dynamic range of five or more orders of magnitude and

can be based on pyrosequencing, sequencing by synthesis (massive parallel sequencing) or oligonucleotide ligation. NGS has a detection accuracy of single nucleotide variants in a frequency of 1% to 2% compared to the traditional Sanger sequencing (10–20%) [15]. However, one run of an NGS experiment is more expensive and time consuming. In contrast, it is possible to analyze multiple samples at the same time and to obtain a large amount of data. These facts favor use of NGS in miRNA discovery and research.

**In-situ hybridization.** In situ-hybridization (ISH) relies on a nucleic acid complementary base pairing between specific labeled oligonucleotide probes and target sequences. It can be used for detection of mRNA as well as microRNA expression in FFPE tissue samples, visualized by fluorescence or bright-field microscope. It enables not only determination of miRNA cellular origin, but if combined with IHC protein detection, it is also able to characterize microRNA expression levels and identify potential targets [23].

## The miRNAs in triple-negative breast cancer with oncogenic effect

**MiR-10b.** MiR-10b is a part of RNA gene family and increased levels have been isolated from metastatic breast cancer. It acts as an activator of pro-metastatic gene RHOC through silencing synthesis of transcription factor homebox D10 (HoXD10)-cell migration. miR-10b along with miR-26a, miR-146a and miR-153 are involved in TNBC development via regulation of BRCA1 expression. MiR-10b and miR-26a are able to down-regulate the expression of BRCA1 not only in TNBC MDA-MB-231 cell lines, but also in luminal epithelial MCF7 breast cancer-derived cells [24]. Apart from metastatic breast cancer, an association of miR-10b with glioblastoma, anaplastic astrocytomas and pancreatic cancer has been found.

**MiR-15a.** MiR-15a targets Cyclin E1 (CCNE1), which regulates the cell cycle and promotes cell proliferation and progression. Low miR-15a expression may be an independent prognostic factor for overall survival especially in TNBC according to multivariate analysis [25].

**MiR-21.** MiR-21 encoded by MIR21 gene and located on chromosome 17 is one of the most frequently up-regulated microRNAs in solid tumors. Its anti-apoptotic ability is responsible for tumor cell growth. The function of miR-21 is in silencing the tumor suppressors tropomyosin1 (tpM1) and programmed cell death gene-4 (pDCD4) and influencing cell growth, angiogenesis, proliferation and invasion. High expression of miR-21 in TNBC correlates with a poor prognosis, tumor cell proliferation and serves as a predictive factor [26, 27]. MiR-21 regulates epithelial-mesenchymal transition (EMT) which exists in three forms. The first described, type one, involves processes during implantation, embryogenesis and organogenesis. Type two is associated with wound healing and finally, type three, describes the role of EMT in cancer progression. Type three can be explained as a process in which epithelial cells lose their adhesive qualities resulting in increased mobility. A significant correlation of miR-21 with advanced clinical stage, lymph node metastasis, and shortened survival of patients with breast cancer was found, indicating that miR-21 may serve as a molecular prognostic and disease progression marker [28]. MiR-21 has also been identified from the serum levels of late-advanced invasive ductal carcinoma (stage III) patients and compared to its expression in age matched healthy individuals and daughters of index cases [29]. Expression of miR-21 in daughters was significantly higher than in healthy controls. These findings strengthen the concept of heritability of disease with prediction of miR-21 as a potentially strong diagnostic and prognostic breast cancer biomarker. The context of altered miR-21 expression provides clinically relevant information. Importantly, miR-21 expression was found to be predominantly up-regulated and potentially prognostic in the tumor stroma of TNBC samples [30]. High levels of miR21 expression were also found in ovarian and cervical cancer, leukemia, lymphoma, cholangiocarcinoma, glioma, head and neck, thyroid, lung, stomach, hepatocellular, pancreas, colorectal and prostate cancer.

**MiR-29.** This microRNA activates EMT by down-regulating cell adhesion molecules, DNA methylation of tumor suppressor genes and by negative regulation of EMT regulator interactor N-myc [31, 32]. The miR-29, miR-30, and miR-200 families have potential target sites in the ADAM12-L 3' untranslated region, one of the major splice variants of human metalloproteinase-disintegrin 12 mRNA. The downregulation of ADAM12-L has prognostic and chemopredictive value in breast [33].

**MiR-122.** High miR-122 levels in the circulation are associated with metastasis in breast cancer patients. The cancer-cell-secreted miR-122 facilitates metastasis by increasing nutrient availability in the pre-metastatic niche [34]. It has been proven that miR-122 suppresses glucose uptake by niche cells in vitro and in vivo by down-regulating the glycolytic enzyme, pyruvate kinase.

**MiR-135.** The up-regulation of miR-135b in breast cancer promotes cell growth and disrupts the cell cycle by regulating LATS2. miRNA-135b can promote proliferation, invasion and migration in TNBC cell lines, especially in MDA-MB-231 and MDA-MB-468 [35]. These findings reveal that the miR-135b and LATS2 axis may be a potential therapeutic target in TNBC. Adenomatous polyposis coli (APC) has been identified as one of miRNA-135b target genes that participate in the process of regulation [36].

**MiR-146.** Generally, miR-146 belongs to microRNA precursors found in mammals. Its physiological function is believed to be an inflammatory mediator along with miR-155 and the innate immune system. The role of miR-146a and miR-146b-5p in down-regulation of BRCA1 was reported in basal-like and triple negative sporadic breast cancers. This was accompanied by an increased proliferation and a reduced homologous recombination rate [37]. In silico analysis of The

Cancer Genome Atlas (TCGA) has confirmed that miR-146a is significantly more highly expressed in TNBC compared to non-TNBC [24]. It has been shown that low expression of miR-146a strongly predicts positive lymph node status and is associated with distinctively poor overall survival of patients [38]. Mi-146 is also reported as an independent prognostic factor in gastric cancer [39].

**MiR-155.** Physiologically, miR-155 plays an important role in hematopoiesis and the immune system (intimate relationship between inflammation induced by viral and bacterial inflammatory mediators, innate immunity and MIR155 host gene expression). The over-expression of miR-155 acts as a trigger of an oncogenic cascade beginning with apoptotic resistance. miR-155 can be regarded as a new marker of TNBC chemoresistance. A negative correlation between miR-155 and von Hippel-Lindau (VHL) tumor suppressor and its association with late-stage, lymph node metastasis and poor prognosis has been found [40]. MiR-155 ectopic expression is linked to extensive angiogenesis, proliferation, tumor necrosis and recruitment of pro-inflammatory cells such as tumor-associated macrophages. Johansson et al. [41] reported the effects of miR-155 on the loss of C/EBPβ which potentiated the TGF-β response of growth inhibition towards EMT and enhanced invasion and metastatic dissemination. Over-expression of miR-155 is also reported in thyroid carcinoma, colon cancer, Lynch syndrome (inactivity of DNA mismatch repair controlling protein), pancreatic ductal adenocarcinomas (decrease in levels of tumor protein-53-induced-nuclear-protein1 (TP53INP1)), cervical, lung cancer and B-cell lymphomas (elevated Bcl-2 controlled by miR-155).

**MiR-181.** MiR-181 is a microRNA that it is regulated by activin and TGFβ growth factors [42]. MiR-181 plays a pivotal role in mediating pro-migratory and pro-invasive effects of these two growth factors in breast and is often over-expressed in tumors [43]. miR-181a expression is selectively up-regulated in metastatic breast cancer, particularly in TNBC and is associated with decreased overall survival.

**MiR-182.** MiR-182 has been found to be up-regulated in MDA-MB-231 TNBC cells. It promotes cell proliferation, invasion and negatively regulates target gene profilin 1 (PFN1) expression [44]. Treatment approaches utilizing inhibition of miR-182 expression or over-expression of the PFN1 gene provide new therapeutic strategies and benefits for TNBC patients.

**MiR-210.** MiR-210 plays a role in breast and renal cancer tumorigenesis by enhancement of the hypoxia-inducible factor (HIF) [45]. The HIF signaling cascade mediates hypoxia effects on the cell which promotes formation of blood vessels in embryos and tumors. Camps et el. [46] found induction of miR-210 over-expression by hypoxia in HIF-1alpha- and VHL-dependent fashion. MiR-210 expression levels in breast cancer samples can serve as an independent prognostic factor.

**MiR-221 and miR-222.** MiR-221/-222 and components of the urokinase-type plasminogen activator system (uPAS) are associated with metastasis and poor prognosis in breast cancer, including TNBC. Falkenberg et al. [47] described an association of uPAR and miR-221/-222 and identified uPAR isoform 2 as a new direct target of miR-221/-222. Inhibition of miR-221 reduces uPAR protein expression and expression of the tumor cell invasion markers, vimentin and gene RHOC. These microRNAs with a common pathogenesis also silence the cell cycle inhibitor $p27^{Kip1}$ [48] which results in cell proliferation and tumor development in luminal breast cancer, thyroid and pancreatic cancer.

**MiR-301.** MiR-301a has clinical significance via positive correlation with tumor size, depth of invasion and TNM stage in patients with TNBC. Multivariate analysis suggested that miR-301a expression is an independent prognostic factor of survival [49].

**MiR-498.** The miR-498 precursor family is found to be over-expressed in TNBC cell line Hs578T. Moreover, its negative correlation with BRCA1 has been demonstrated [50].

**MiR-638.** MiR-638 plays an important role in TNBC progression via BRCA1 gene deregulation, which is one of its direct targets. Enhanced miR-638 expression resulted in a significantly reduced proliferation rate as well as decreased invasive ability of TNBC cells. Moreover, high levels of miR-638 expression increased sensitivity to DNA-damaging agents, ultraviolet light and cisplatin in TNBC cells [51]. The study focused on association of miR-638 and miR-146a with mechanisms leading to reduced expression of BRCA1 in TNBC and showed over-expression of both microRNAs in BRCA1-deficient tumors. They are thus potential biomarkers of better overall survival [52].

## The miRNAs in triple-negative breast cancer with anti-invasive and anti-metastatic potential

**MiR-1.** MALAT1 can be described as a potential therapeutic target in TNBC because of its reciprocal negative control relationship with miR-1 [53]. In this study, down-regulation of MALAT1 increased expression of miR-1, while over-expression of miR-1 decreased MALAT1 expression. Slug was identified as a direct target of miR-1.

**MiR-26.** MiR-26a is down-regulated and associated with lymph node metastasis and overall survival in patients with TNBC [29]. Ectopic expression of miR-26a inhibits TNBC cell proliferation and metastasis by down-regulating MTDH mRNA and protein [54].

**MiR-31.** MiR31 has a pivotal role in cancer metastasis. In breast cancer, decreased miR-31 expression in aggressive basal-cell like and TNBC in comparison to the luminal molecular subtypes has been reported [55]. An inverse relation between miR-31 expression level and late-stage breast cancer has been found. In contrast, the role of miR-31 as a WAVE3 expression regulator and a highly significant correlation between WAVE3 expression and advanced

disease stage has been described [56]. One study on the mechanisms of miR-31 transcriptional regulation showed that miR-31 is transcribed from the intronic sequence of a long non-coding RNA (LOC554202 gene) [57].

**MiR-34.** MiR-34b belongs to the miR-34 family whose members are transcriptionally activated mainly by p53. MiR-34b acts as a tumor suppressive microRNA involved in execution of the p53-driven apoptotic pathways [58, 59]. MiR-34b is also a direct regulator of Notch2 playing an important role in cell differentiation and is under-expressed in breast cancer tumors with poor differentiation. Studies on miRNA-34b expression and association with clinical-pathological features have revealed a negative correlation with disease free and overall survival in TNBC patients and confirm an oncogenic role in tumor cells [60, 61]. The oncogenic feature of this miRNA has also been described in renal cell carcinomas and undifferentiated gastric cancers.

**MiR-101.** MiR-101 inhibits cell progression in TNBC and by suppressing MCL-1 expression, it increases sensitivity to paclitaxel [62].

**MiR-125.** Down-regulation of this microRNA is associated with poor prognosis and resistance to chemotherapy in TNBC. It can serve as a prognostic factor. MAP2K7 has been described as a novel target of miR-125b. Down-regulation of MAP2K7 by miR-125b leads to inhibition of EMT [63].

**MiR-136.** MiR-136 inhibits tumor invasion in TNBC and suppresses mesenchymal invasion and metastasis by targeting RASAL2. Down-regulation of miR-136 in TNBC and an inverse correlation with tumor grade has been demonstrated [64].

**MiR-141.** MiR-141 expression levels are down-regulated in TNBC MDA-MB-231 cell lines, while β-catenin gene (CTNNB1) expression is up-regulated. β-catenin can be considered as one of the main players in tumor pathogenesis and a potential therapeutic target [65].

**MiR-145.** MicroRNA-145 acts as a tumor suppressor by inhibiting growth and migration of breast cancer cells through targeting oncoprotein ROCK1 [66]. The cellular inhibitor of apoptosis (cIAP1) has also been described as a target of miR-145 in MDA-MB-231 TNBC cells [67]. As a result of cIAP1 over-expression, the promotion of miR-145 on TNF-α-induced apoptosis was inhibited. Apart from breast cancer, miR-145 was found to be associated with colorectal cancer and myelodysplastic syndrome.

**MiR-148.** MiR-148a is a suppressor of breast cancer metastasis because of its negative correlation with tumor grade. It may be a prognostic biomarker in patients with TNBC in particular [68].

**MiR-185.** MiR-185 acts as a tumor suppressor in TNBC development. Its ectopic expression inhibits cell proliferation. DNMT1 and E2F6 have been identified as direct targets resulting in a marked increase in the expression of BRCA1 [69].

**MiR-195.** MiR-195 is a tumor suppressor microRNA playing an important role in breast cancer tumorigenesis. Circulating miR-195 with high sensitivity to neo-adjuvant chemotherapy may be a promising biomarker for breast cancer diagnosis and general screening. MiR-195 is able to act as a tumor suppressor by decreasing expression of Wnt3a and may serve as a therapeutic target in non-basal-like type of TNBC (MDA-MB-231 cells) [70].

**MiR-200.** The miR-200 family sensitizes breast cancer cell lines to apoptosis and inhibits metastatic potential. MiR-200a tumor suppressor directly regulates the EPH receptor A2 (EPHA2) oncogene and modulates cell migration in TNBC. EPHA2 expression correlates with poor survival, specifically in basal-like breast cancer [71]. Ectopic expression of miR-200b significantly reduces cell migration in TNBC and inhibits tumor metastasis through inhibition of protein kinase Cα activity [72]. Rhodes et al. [73] described mechanism of microRNA-200b-3p and microRNA-200b-5p dual regulation of EMT inhibition in TNBC. MiR-200c may be involved in invasion and metastasis in TNBC cases with BRCA mutation [74].

**MiR-203.** This tumor-suppressor microRNA inhibits proliferation and migration by targeting BIRC5 and LASP1. MiR-203 and its effect on cell proliferation and migration in TNBC was described by Wang et al. [75]. The data suggest that miR-203 may function as a tumor suppressor in TNBC cells.

**MiR-205.** MiR-205 takes part in down-regulation of EMT by targeting e-cadherin transcriptional suppressors ZeB1 and SIp1. Its ectopic expression is typical for head and neck and breast cancers [76].

**MiR-206.** MiR-206 up-regulation contributes to decreasedmetastatic potential, cell proliferation and invasion through degradation of connexin43 in TNBC [77]. It also inhibits cell migration through direct targeting of the actin-binding protein coronin 1C [78]. In human breast cancers, miR-206 modulates 6-phosphofructo-2-kinase (PFKFB3) expression in MCF-7, T47D and SUM159 cells. Over expression of miR-206 inhibits glycolysis, cell proliferation and migration [79]. MiR-206 can also act as an effector of Kruppel-like factor 4 (KLF4)-mediated pro-survival signaling in mammary cancer stem-like cells (MaCSCs) via repression of programmed cell death 4 (PDCD4) and connexin43 (CX43) in TNBC [80]. Decreased miR-206 expression was found in BRCA1 wild-type TNBC cells after concomitant treatment with gemcitabine and poly(ADP-ribose) polymerase-1 inhibitor [81].

**MiR-211.** MiR-211 is a direct negative regulator of CDC25B phosphatase expression in TNBC [82]. It also alters other related target proteins such as CCNB1 and FOXM1. As a result of this action, miR-211 inhibits breast cancer cell growth, migration, and invasion. The transcriptional loss of miR-211 leading to increase in CDC25B expression facilitates increased genomic instability at an early stage of tumor development. Apart from its role in TNBC, miR-211 suppresses epithelial ovarian cancer proliferation [83] and negatively regulates genes driving invasion of metastatic melanoma [84].

**MiR-300.** MiR-300 plays an important role in regulation of EMT, a key step in the progression of tumor cell metastasis and is negatively regulated by direct targeting of Twist [85].

**MiR-340.** There is an association of tumor suppressor genes and oncogenes with miR-340 in TNBC metastatic cells [86]. The over-expression of tumor suppressor genes such as retinoblastoma and transcriptional factor SOX17 and down-regulation of oncogenes such as SOX2 is in accordance with the inhibitory role of miR-340 causing the blockage of breast cancer metastasis.

**MiR-378.** Ectopic expression of miR-378 in MDA-MB-231 cell lines of TNBC inhibits Runx1 and suppresses migration and invasion, while inhibition of miR-378 in human breast cancer MCF7 cell lines (early stage) increases Runx1 levels and cell migration [87].

**MiR-448.** The findings of Bamodu et al. [88] demonstrated the critical role of Lysine-specific demethylase 5B protein (KDM5B) and its negative regulator hsa-miR-448 in TNBC metastasis and progression. KDM5B under-expression correlated with up-regulation of the hsa-miR-448 and led to suppression of MALAT1 expression with decreased migration, invasion and clonogenic capacity in vitro, as well as poor survival in vivo. Increased expression of KDM5B correlating with disease progression and poor clinical outcome in breast cancer was reversed by hsa-miR-448.

**MiR-544.** Endogenous levels of miR-544 are significantly lower in breast cancer cell lines than in human breast non-tumorigenic and mammary epithelial cell lines. Moreover, the over-expression of miR-544 in TNBC cells down-regulates Bcl6 and Stat3 expression, which in turn severely inhibits cancer cell proliferation, migration and invasion [89].

**MiR-655.** MiR-655 is found to be down-regulated in TNBC, and its expression levels are associated with molecular-based classification and lymph node metastasis in breast cancer. MiR-655 over-expression could inhibit EMT by suppression of Prrx1, thereby inhibiting cell migration and invasion during cancer progression [90].

**MiR-1296.** MiR-1296 expression is significantly suppressed in TNBC cell lines and tissue samples. In contrast, miR-1296 over-expression inhibits Cyclin D1 expression levels and cell proliferation in TNBC and sensitizes TNBC cells to cisplatin treatment [91].

**Let-7 family.** The human let-7 family of 13 members, located on 9 different chromosomes, is found to be deregulated in many human cancers. They are regarded as tumor suppressor microRNAs indicating down-regulation in TNBC. The restoration of let-7 expression may be a useful therapeutic option in cancers where its expression has been lost [92].

## Circulating miRNA in TNBC

MiRNA are stably expressed in human plasma, protected from endogenous RNase activity which results in their uniform amplification and quantification [93]. Moreover, the possible diagnostic value of specific miRNAs, including miR-30a, miR-373, miR-199a-5p, miR-495, provides a new insight into potential targeted therapy [94, 95]. In TNBC, circulating miR-18b, miR-103, miR-107and miR-652 are significantly associated with tumor recurrence and reduced survival [96]. The upregulation of miR-21-5p, miR-375, miR-205-5p, miR-194-5p and downregulation of miR-382-5p, miR-376c-3p, miR-411-5p has also been described in recurrent breast cancer patients [97]. The other way of using miRNAs is based on indications of circulating tumor cells in metastatic breast cancer, especially higher levels of miR-141, miR-200a, miR-200b, miR-200c, miR-203, miR-210, miR-375 and miR-801 [98]. MiR-195 has high sensitivity to neo-adjuvant chemotherapy and can be considered as a promising biomarker for breast cancer diagnosis and general screening [99]. Thus, circulating miRNAs are promising biomarkers that can be used for diagnosis, recurrence monitoring and as indicators of overall survival in TNBC patients.

## Dysregulation of miRNAs in triple-negative breast cancers

Chang et al. [100] documented evidence of seven polycistronic miRNA clusters preferentially deregulated in TNBC. Two of these miRNA clusters (miR-143-145 at 5q32 and miR-497-195 at 17p13.1) were markedly down-regulated, while the other five miRNA clusters (miR-17-92 at 13q31.3, miR-183-182 at 7q32.2, miR-200-429 at 1p36.33, miR-301b-130b at 22q11.21, and miR-532-502 at Xp11.23) were up-regulated. Furthermore, miR-130b-5p from the miR-301b-130b cluster was shown to directly repress the cyclin G2 (CCNG2) gene, a crucial cell cycle regulator in TNBC cells. Another study using multivariate analysis revealed two miRNA signatures (miR-16, 155, 125b, 374a and miR-16, 125b, 374a, 374b, 421, 655, 497) which predicted overall survival ($p=0.05$) and distant-disease free survival ($p=0.009$) in patients with TNBC 50 years old or younger [101]. Guo et al. [102] evaluated the association of soy intake with the expression of 800 microRNAs (miRNAs) and 302 genes via linear regression analysis with adjustments for patient age and TNM stage in 272 TNBC patients. According to this study, long-term pre-diagnosis soy intake may lead to increased expression of tumor suppressors and decreased expression of tumor oncogenes, especially cell growth-related genes, in breast tumor tissues. Boukerroucha et al. [103] analyzed 27 microRNA expression profiles in 69 TNBC samples. miR-548c-5p was in this study emphasized as a new independent prognostic factor. Moreover, a combination of miR-548c expression and tumor size, lymph node invasion and cytokeratin 5/6 expression status allowed for relapse prediction. The study on association of vitamin E δ-tocotrienol anticancer activity with TNBC revealed that inhibition of miR-429 may partially rescue the apoptosis induced by δ-tocotrienol in MDA-MB-231 cells and identi-

fied an X-linked inhibitor of apoptosis protein (XIAP) as one of the miR-429's target genes [104]. Tormo et al. [105] exposed one luminal-A and two TNBC cell lines to doxorubicin and analyzed common and differentially modified microRNAs. They suggested a potential role of miR-548c-3p in doxorubicin resistance. Wahdan-Alaswad et al. [106] provided insight into metformin-induced killing of TNBC by reduction in fatty acid synthase via miRNA-193b.

## Therapeutic targets potentially influenced by miRNAs in triple-negative breast cancer

**Poly(ADP-ribose)polymerase.** The poly(ADP-ribose) polymerase (PARP) is a nuclear enzyme family comprising 17 protein members differing in their function and structure. Using nicotinamide as a substrate, its catalytic domain is responsible for synthesis of poly(ADP-ribose) polymers. PARP participates especially in repair of the single-stranded DNA (base excision repair) and programmed cell death via inactivation by caspase cleavage. PARP is a potential therapeutic target in tumors with homologous recombination repair deficiency, such as TNBC with BRCA1/2 mutation [107–109]. It has been shown that hsa-miR-107 and hsa-miR-222 regulate the DNA damage response and sensitize tumor cells to PARP inhibitor by repressing expression of RAD51. MiR-490-3p as a tumor suppressor inhibits the growth and invasiveness in TNBC by repressing the expression of PARP 5b [110]. In vitro, miR-1 down-regulates proliferation and migration of breast cancer stem cells by targeting the Frizzled 7 and PARP5b to inhibit the Wnt/β-catenin signaling pathway [111].

**Epidermal growth factor receptor.** Epidermal growth factor receptor (EGFR; ErbB-1) belongs to the ErbB transmembrane receptor family with tyrosine-kinase activity along with HER2/c-neu (ErbB-2), HER3 (ErbB-3) and HER4 (ErbB-4). After EGFR activation by binding of specific ligands, it transitions through an inactive monomeric form to an active homodimer. The mutation of EGFR leading to its over-expression results in angiogenesis, apoptosis inhibition, cell proliferation and metastatic spread [107]. It is found to be up-regulated in approximately 80% of TNBC and is associated with decreased disease-free survival [107, 112, 113]. Krüppel-like factor 8 (KLF8) directly represses the promoter of miR141 and miR141 targets the 3'-untranslational region of EGFR transcript to inhibit EGFR translation. The over-expression of miR141 inhibits KLF8-dependent cell invasiveness, proliferation and viability in cell culture, invasive growth and lung metastasis in nude mice [114]. EGFR expression correlates negatively with BRCA1, whereas miR-146a levels increase with BRCA1 which binds to miR-146a promoter and activates its transcription, which in turn attenuates EGFR expression [38].

**Vascular endothelial growth factor receptor.** The vascular endothelial growth factor receptor (VEGFR), activating tyrosine-kinase, occurs in three main forms (VEGFR 1–3) localized on the cell surface. Its ligands, vascular endothelial growth factor (VEGF) A–E, play a pivotal role in the circulatory system formation and the growth of blood vessels which are essential for tumor development. VEGFs also support endothelium proliferation by increasing the expression of the anti-apoptotic proteins (BCl-2, XIAP, surviving) and regulate vascular permeability and migration of endothelial stem cells from the bone marrow. In patients with TNBC, VEGFR up-regulation is associated with decreased disease-free survival, overall survival and distant disease-free survival [107, 115, 116]. It has been found that down-regulation of microRNA-206 promotes invasion and angiogenesis in TNBC. By contrast, miR-141/200c cluster over-expression promotes migration and invasiveness of triple-negative breast cancer cells through activation of the FAK and PI3K/AKT signaling pathways by secreting VEGF-A [117].

**Androgen receptor.** The androgen receptor (AR) is a nucleus receptor activated by androgens and exerts growth inhibitory effects on hormone receptor negative breast cancers with AR expression [118–120]. The AR gene is located on the X chromosome and to date, two AR isoforms have been identified (A and B). The up-regulation of AR in estrogen receptor-negative tumors is found to be associated with lower Nottingham grade and apocrine differentiation. TNBC with androgen receptor expression is characterized by increased sensitivity to AR antagonists, and represents another possible therapeutic target. Patients with AR-positive TNBC have decreased disease-free survival but better prognosis than patients with AR-independent TNBC. One study on the in vitro mechanisms of chemotherapy with drugs used in the treatment of luminal androgen receptor type TNBC, revealed that antitumor miRNAs, miR-122a, miR-145 and miR-205, were significantly elevated in tumor cells treated with 5-fluorouracil together with ixabepilone. By contrast, carcinogenic miR-296 miRNA expression significantly declined, and levels of several other miRNAs such as miR-221, miR-210, miR-21 and miR-10b were also altered [121].

**Long non-coding RNAs.** Long non-coding RNAs (lncRNAs) are RNA transcripts comprising 200 nucleotides or more and are characterized by not encoding for any protein**.** They participate in tumorigenesis by regulating protein-protein, protein-DNA or protein-RNA interactions. Recent studies show that the nonhomologous end joining pathway 1 (LINP 1), which is over-expressed in TNBC, enhances repair of double-stranded DNA and blockage of this pathway, regulated by p53 and EGFR, increases sensitivity to radiotherapy [122–124]. The expression level of the intergenic lncRNA LINC00993 is associated with expression level of ANKRD30A, a marker of disseminated tumor cells. Eades et al. [125] revealed that long intergenic non-coding RNA regulates reprogramming and miR-145 regulates tumor invasion via targeting small GTPase ADP-ribosylation factor 6 (Arf6) which is found to be over-expressed in TNBC cells and breast cancer metastases. Pickard et al. [126]

showed a relationship of arrest-specific 5 (GAS5), a tumor suppressor and apoptosis-promoting gene encoding lncRNA and TNBC. GAS5 is down-regulated in breast cancer and this affects patient prognosis. The dual targeted therapy of TNBC using EGFR inhibitors (lapatinib) and c-ABL inhibitors (imatinib) leads to synergistic repression of up-regulated long non-coding RNA (lncRNA) HOTAIR (HOX Antisense Intergenic RNA) [127]. It is responsible for the regulation of tumor cell proliferation and invasion in breast cancer. Moreover, it has been found that estradiol promotes HOTAIR via its receptor GPER and estrogen-induced breast cancer cell migration is reversed by deleting HOTAIR in TNBC cells MDA-MB-231and BT549. A negative correlation was also found between HOTAIR and miR-148 [128]. Jin et al. [53] revealed that the reciprocal regulation of hsa-miR-1 and lncRNA MALAT1 promotes TNBC development. Lin et al. [129] identified lncRNA localized in the cell cytoplasm and LINK-A (long intergenic non-coding RNA for kinase activation), which activates normoxic HIF1α signaling in TNBC. Latorre et al. [130] showed that a ribonucleoprotein complex including lncRNA MALAT1 and RNA-binding protein HuR decreases CD133 expression and suppresses EMT.

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