Review Article

MicroRNA Therapeutics in Triple Negative Breast Cancer

Sarmistha Mitra*
Department of Pharmacy, University of Chittagong, Chittagong-4331, Bangladesh

*Address for Correspondence: Sarmistha Mitra, Department of Pharmacy, Faculty of Biological Science, University of Chittagong, Chittagong-4331, Bangladesh, Tel: +8801521484840; Email: sarmisthacu@gmail.com
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ABSTRACT

Breast cancer is a complex disease and one of the main causes of cancer-related mortality in women worldwide. In case of approximately 15% of all breast cancers, three markers i.e. estrogen receptors (ER), progesterone receptors (PR) and human epidermal growth factor receptors-2 (HER2) are not expressed, and is commonly termed as triple-negative breast cancer (TNBC). Particularly, TNBC is associated with a higher percentage of breast cancer related mortality, which is often aggressive and most frequently found with a BRCA1 mutation or increased basal marker expression. However, due to the limitations of chemotherapy and radiation based treatment; the current challenge is to establish a new strategy of diagnosis and treatment of TNBC. The deregulation of a number of microRNAs (miRNAs) in breast cancer has been widely reported. Therefore, this review is directed towards enhancing our understanding of the involvement of various miRNAs in the pathology of TNBC, their upregulations and downregulations and the effects on various factors. From recent studies a number of miRNAs are found to be related with TNBC, which have great potential to be used as a biomarker to determine the disease prognosis and predict the fate of disease. Again miRNA can be targeted to be applied as a therapeutic to provide a great benefit to the patients of TNBC by finding a new, safe, and effective treatment strategy.

INTRODUCTION

Triple-negative breast cancer is one of the most recently identified biological variants [1], which is characterized by tumors that do not express estrogen receptor (ER), progesterone receptor (PR), or HER-2 genes [2,3]. That is why, it represents an important clinical challenge; because these cancers do not respond to endocrine therapy or other available targeted agents [2,3]. These tumors are associated with a shorter median time to relapse and death [4]. Factors like age, ethnicity, BMI are known to affect the survival rate of TNBC [5-7]. There are several unusual characteristics of the triple-negative phenotype that have shifted our understanding of TNBC as a unique entity within the breast cancer classification [8]. The main aim is to find out the prognostic factors and identify the markers in order to differentiate high and low risk subsets of patients with TNBC for various treatment approaches of subtypes with differential responsiveness to various therapeutics.

Many recent studies have proved that aberrantly expressed miRNAs are involved in breast tumors, compared with healthy breast tissues [9]. It is evident that miRNAs mediate the cell fate of TNBC by regulating some biological processes, such as cell survival, cell cycle arrest, and differentiation [10,11]. It is much more significant to study the miRNAs involved in these mechanisms in order to develop an appropriate therapeutic approach for TNBC. As several miRNAs are differently expressed in the patients of TNBC, they can be a potential biomarker for quick diagnosis of the cancer.

From recent studies, it is appeared that TNBC has the worst prognosis among all breast cancer subtypes [4,12]. It is believed that finding appropriate prognostic biomarkers for TNBC patients would allow an optimized treatment selection of
regimens that could be beneficial for the patients. Therefore, in this article the roles of miRNAs on the development and pathophysiology of TNBC are described, exploring the potentiality of miRNAs to be used as ideal biomarkers and therapeutics to find a new era in the field of cancer treatment.

**PATHOPHYSIOLOGY OF TRIPLE NEGATIVE BREAST CANCER**

Triple negative cancers are a heterogeneous group of tumors with a range of different prognostic profiles [13]. Therefore various markers were analyzed to predict and determine the prognosis pattern of triple negative cancer. Studies showed that the majority of triple-negative cancers are of basal-like phenotype [14-17] and the majority of tumors expressing ‘basal’ markers are triple-negative. It was shown that, more than 80% breast cancers occurring in women with BRCA 1 mutation have a basal like profile [18]. Although most basal cancers are sporadic (non-hereditary), they are associated with an abnormal BRCA 1 pathway [19,20].

It is also very important to note that, not all basal-like cancers identified by gene expression profiling lack ER, PR and HER2 gene [17,21,22], and conversely not all triple-negative cancers elicit a basal-like phenotype. Markers which were found to be linked with poor prognostic profile in triple negative breast cancers are CARM1, TTF1 and SBEM [23]. In which, coactivator-associated arginine methyltransferase 1 (CARM1) was found to be expressed in 57% of triple negative cancers and was associated with high tumor grade [24]. While, thyroid transcription factor 1 (TTF1) expression was also reported in basal phenotype breast cancers. TTF1 expression was co-related with high tumor grade, lymph node metastasis and vascular invasion [25]. Similarly, small breast epithelial mucin (SBEM) which has been implicated in tumor genesis and micrometastasis in breast cancer is associated with poor prognostic profile in triple negative breast cancer [26]. Other factors including transmembrane protein 26 (TMEM26) are seen to highly expressed in triple negative breast cancer, particularly in ERα-negative states, associated with unfavorable survival of the tumor and thereby higher risk of recurrence [27]. Another transmembrane protein, the receptor for advanced glycation end products (RAGE) and its ligands are also reported to be an inducer for cell proliferation, as it leads to higher cell division and ultimately promotion of tumor growth [28]. Higher expression of RAGE was found in more aggressive cell type and highly proliferated basal sub-type MDA-MB-231, suggesting an essential role of RAGE in the development of more aggressive clinical behavior, particularly in triple-negative basal sub-type [29].

Apart from immunohistochemical expression of various markers, the roles of microRNAs (miRNAs) were also evaluated in triple negative breast cancers. As an example, miR-34b negatively co-relates with disease free survival and overall survival in triple negative cancers [30]. Laurinavicius A et al. in 2012 reported a high expression of p16 in triple negative breast cancers [31].

Gene expression profiling studies are not possible to be performed on every case of breast cancer. Immunohistochemical studies are relatively less expensive and therefore can be performed for initial segregation of cases into specific expression profiles. Based on morphology and immunohistochemical profile, genetic studies can be performed to identify at risk families as an effective preventive measure. There are some unique histological features of TNBC. Triple-negative tumours are reported to have a higher histologic grade, scant stromal content, elevated mitotic count, central necrosis, pushing margins of invasion, a stromal lymphocytic response and multiple apoptotic cells [32]. From recent studies, it can be also noted that these tumors are histologically ductal. There are also some other histological features like metaplastic [33], atypical or typical medullary [32,34], or adenoid cystic carcinomas [35]. Metaplastic carcinoma itself is a heterogenous group of tumors which includes sarcomatoid [36], squamous cell [37], adenosquamous [38], mucoepidermoid, matrix producing [39], metaplastic
carcinoma with osteoclast like giant cells [40] and low grade fibromatosis like spindle cell carcinoma [41].

ROLE OF MIRNA IN TNBC

MicroRNAs (miRNAs) are a family of small non-coding RNA molecules that are master regulators of many crucial biological processes of cancer like cancer cell growth, apoptosis, invasion, and metastasis [42-44]. During cancer development, progression and metastasis, miRNAs are subdivided in two main categories: tumor suppressor and oncogenic miRNAs (oncomirs), some of them can be correlated with the prognosis of the disease or detected in serum for diagnostic purposes. Multiple studies have revealed that several miRNAs target specifically the three missing receptors ER, PR, and HER2 as well as the BRCA1 in TNBC development (Table 1). From previous researches, it is confirmed that different miRNAs are differently expressed in different molecular subtypes of breast cancers [45,46]. It was revealed by Lehmann et al., in 2011 that TNBC can be classified into at least six distinct molecular subtypes with differing biological characteristics based on mRNA profiling, which are - BL1 subtype, BL2 subtype, IM subtype, M subtype, MSL subtype, LAR subtype [47]. As these are different molecular subtypes of TNBC, so miRNA expression may differ among these subtypes of cancer [48]. Garcia et al. showed that the highest levels of miR-146a and miR-146b-5p were involved in BL subtype which was evident by experimenting in vitro and TNBC patients [49,50]. Reports from Shen et al. represented that genetic polymorphisms in the miR-146a is possibly linked with young age in familial cases of breast cancer [51]. Crippa et al. in 2014 described that miR-342 negatively regulates BRCA1 expression in breast cancer [52]. While, Moskwa et al. in 2011 suggested that miR-182 downregulates BRCA1 expression and found that the manipulation of miR-182 expression in breast cell lines affected their sensitivity to poly-ADP ribose polymerase (PARP) 1 inhibition [53]. It was appeared in the investigation from Tanic et al. 2015, miRNA classifiers in order to find out the BRCA germline mutation status of the preserved sample of

| miRNA | Function | Target | Regulation | References |
|-------|----------|--------|------------|------------|
| miR-146a | Down-regulate the expression of BRCA1 | BRCA1 | Up-regulated | [50,80] |
| miR-146b-5p | Suppress breast cancer metastasis | BRCA1 | Down-regulated | [50] |
| miR-342 | Loss of differentiation, enhanced malignancy and aggressive clinical behavior. | ID4 | Down-regulated | [52,76] |
| miR-182 | Downregulates BRCA1 expression | PFN1 | | [81] |
| miR-155 | Activates the tumor-associated macrophages | FOXO3a | Up-regulated | [82] |
| miR-200 family | miR-200 stimulates differentiation in undifferentiated mammary epithelial cell line and inhibits EMT. | ZEB1,ZEB2, PLC1, SUZ12, FN1 | Down-regulated | [76] |
| miR-29 | Induce metastasis in breast cancer | | Up-Regulated | [79] |
| miR-21 | Important regulator of development and progression | TPM1, PDCD4 | Up-regulated | [77] |
| miR-373 | Increase the cell proliferation, as well as downregulate the protein expression of ER and PR | ER, PR | Up-regulated | [73,75] |
| miR-27b | Involved in attenuating chemoresistance and tumour seeding ability, and also in the breast cancer initiation, invasion and migration | ENPP1, Her2/neu, ST14 | Upregulated | [83,84,78] |
| miR-199a-5p | Plays tumor-suppressive role in TNBC by inhibiting migration/invasion through EMT | CDH1, ZEB1, TWIST | Down-regulated | [64] |
| miR-10b | Down-regulate the expression of BRCA1, promote the invasion and metastasis of tumor cells | BRCA1, HOXD10 | Up-regulated | [85,74] |
| mir-26a | Down-regulate the expression of BRCA1 and stimulated the proliferation | BRCA1 | Up-regulated | [85] |
| mir-153 | Down-regulate the expression of BRCA1 in breast cancer cell | BRCA1 | Lower in triple-negative breast cancers | [85,86] |
breast tumor on the basis of miR-142-3p, miR-505, miR-1248, miR-181a-2, miR-25 and miR-340 [54]. Rodriguez et al. suggested that miR-155 plays a crucial role in regulating homeostasis in the immune system in cancer patients [55]. A report by Zonar group, showed that tumor growth is induced by miR-155, as it activates the tumor-associated macrophages in breast cancer [56]. In 2008, Gregory et al. found that all five members of the miRNA-200 family (miR-200a, miR-200b, miR-200c, miR-141 and miR-429) and miR-205 was markedly downregulated in cells that had undergone EMT in response to ectopic protein tyrosine phosphatase expression [57].

Jiang et al., reported that miR-29 mediated EMT (epithelial mesenchymal transition) and induced metastasis in breast cancer [58,59] miR-21 is an important regulator of development and progression in case of TNBC and miR-21 is highly upregulated in the solid tumor cells of breast cancer [60,61].

Furthermore, Lim et al., showed that exosomal miRNAs which are derived from bone marrow stroma (miR-127, miR-197, miR-222, and miR-223) inhibit breast cancer cell proliferation via direct targeting of the CXCL12 chemokine gene, leading to the induction or maintenance of a dormant state of breast cancer cells [62]. Eichelser et al. demonstrated that upregulation in serum levels of exosomal miR-373 is linked to TNBC, which can downregulate the protein expression of ER [63] While [64]. Abdellatif reported a downregulated level of miR-199a-5p in TNBC when it is compared with non-TNBC samples and healthy controls. Some other miRNAs involved in TNBC are also discussed in further section [65].

From this study, it can be concluded that, these miRNAs can be involved in treatment of TNBC to perform the role of tumor suppressive or protective, because downregulation of the miRNAs involved in pathogenesis of TNBC might have a great therapeutic effect and they can be used as potential biomarker to find out new possible ways of predicting clinical outcome, and to ensure better treatment and assessment.

**FUTURE PROSPECTS OF TNBC THERAPEUTICS USING MIRNA**

In recent times, triple negative breast cancer has created a very challenging situation due to drug resistance and complexity arising from patients not responding to chemotherapy and radiation. That is why new therapeutics must be designed to provide better treatment to the patients. So miRNAs that are upregulated or downregulated and involved in stages of TNBC development can be targeted to design new therapeutics of TNBC. There are many possible approaches to use these miRNAs as therapeutics and biomarker for diagnosis. miRNA can be used as therapeutics mainly by two approaches, one of them is anti-miR therapy and the other one is miR replacement therapy [66]. miR can also suppress the metastatic nature of the tumor by controlling cell migration that is reasoned by EMT [48]. From recent study, it is reported that MiR-34a has the ability to reduce the invasiveness of breast cancer cells by repressing EMT following the Snail pathway [67], so this mechanism of miR-34a can be used as a potential therapeutic approach. Again it is reported by Song et al. that miR-22 triggered EMT which in turn enhanced invasiveness, and promoted metastasis [68]. So MiR-22 can be targeted and its pathway or biogenesis can be blocked as therapeutic approach. Similarly, miR-29 is able to promote metastasis by mediating EMT [58,59], which can also be targeted to prevent metastasis and treating TNBC. It is also found that miR-10b promotes invasion and metastatic programs in human triple negative breast cancer cell lines and it is reported to have higher level of miR-10b in primary tumor tissues [69-70]. So it can be used as a biomarker to monitor the condition or characterization of cancer.

Anti-miRNA therapy may include miRNA sponges and antagonirs, these are miRNA antagonists that affect miRNA-related pathways by binding and blocking oncogenic miRNAs [66]. Antagomirs can bind only one miRNA once, while miRNA
sponges can bind several miRNAs from one family. This specific approach restores the normal expression of genes and reduces the progression of cancer or sensitizes cells to conventional therapies.

MiRNA-replacement therapy generally acts on chemotherapeutics which are designed to inhibit ATP binding (e.g., imatinib, nilotinib, geftinib, erlotinib, and others) as it can sensitize cells, and combinatorial application with other drugs may reduce resistance. MiR-328 expression can increase mitoxantrone sensitivity by targeting ABCG2 [71], therefore, restoring miR-328 downregulated expression as a therapy could improve the outcome since ABCG2 pumps out mitoxantrone and doxorubicine. So it can be very fruitful to use miRNAs as adjuvants to conventional therapies [72], not only as a stand-alone therapy. In order to develop a new validated therapeutic approach using miRNA it is very important to find out suitable and effective delivery method. So future research should be focused to find helpful miRNAs and to increase their expressions or to use them as adjuvants beside the traditional therapy. At the same time future work can also focus on the finding of oncogenic miRNA involved in TNBC and targeting them to stop metastasis. On the other hand to determine the status of cancer the miRNAs that are reported to be overexpressed, can be focused and studied as biomarker.

CONCLUSION

The aim and purpose of the review work is to discuss the histological features of TNBC and to focus on miRNAs, which play a key role on various molecular subtype of triple negative breast cancer. By highlighting these factors we can find out the miRNAs involved and their possibility to be used as a potential therapeutic target and diagnostic biomarker in TNBC treatment. From this short review, it is clearly evident that miRNA can be a promising therapeutic for TNBC to cope with the limitations presently faced in the field of treatments. In present time the mortality rate of TNBC is very high compared to other cancers, and also very challenging to diagnose. Thus it is time to establish a promising, potent and improved biologic therapy and biomarker of TNBC by focusing on the miRNAs.

REFERENCES

1. Akhtar M, Dasgupta S, Rangwala M. Triple negative breast cancer: an Indian perspective. Breast Cancer (Dove Med Press). 2015; 7: 239-243. Ref.: https://goo.gl/qkjztY
2. Hudis CA, Gianni L. Triple-negative breast cancer: an unmet medical need. Oncologist. 2011; 16: 1-11. Ref.: https://goo.gl/rCRpbF
3. Lips EH, Michaut M, Hoogstraat M, Mulder L, Besselink NJ, et al. Next generation sequencing of triple negative breast cancer to find predictors for chemotherapy response. Breast Cancer Res. 2015; 17: 134. Ref.: https://goo.gl/5DVxve
4. Dent R, Trudeau M, Pritchard Ki, Hanna WM, Kahn HK, et al. Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res. 2007; 13: 4429-4434. Ref.: https://goo.gl/ixFkXG
5. Lin NU, Vanderplas A, Hughes ME, Theriault RL, Edge SB, et al. Clinicopathologic features, patterns of recurrence, and survival among women with triple-negative breast cancer in the National Comprehensive Cancer Network. Cancer. 2012; 118: 5463-5472. Ref.: https://goo.gl/C2W1Un
6. Sachdev JC, Ahmed S, Mirza MM, Farooq A, Kronish L, et al. Does race affect outcomes in triple negative breast cancer? Breast cancer(Auckl). 2010; 4: 23-33. Ref.: https://goo.gl/DPyd2R
7. Wei X-Q, Li X, Xin X-J, Tong Z-S, Zhang S. Clinical features and survival analysis of very young (age<35) breast cancer patients. Asian Pacific Journal of Cancer Prevention. 2013; 1: 5949-5952. Ref.: https://goo.gl/MxQDZF
8. Thomas K, Shiao J, Rao R, Minhaiuddin A, Spangler A, et al. Constructing a Clinicopathologic Prognostic Model for Triple-Negative Breast Cancer. American Journal of Hematology/Oncology®, 2017; 13: 11-21. Ref.: https://goo.gl/da2Ue8
9. Iorio MV, Ferracin M, Liu CG, Veronese A, Spizzo R, et al. MicroRNA gene expression deregulation in human breast cancer. Cancer res. 2005; 65: 7065-7070. Ref.: https://goo.gl/AWPv6j

10. Schwarzenbacher D, Balic M, Pichler M. The role of microRNAs in breast cancer stem cells. Int J Mol Sci. 2013; 14: 14712-14723. Ref.: https://goo.gl/2ZLHWG

11. Serpico D, Molino L Di, Cosimo S. microRNAs in breast cancer development and treatment. Cancer Treat Rev. 2014; 40: 595-604. Ref.: https://goo.gl/KNeCPB

12. Stover DG, Winer EP. Tailoring adjuvant chemotherapy regimens for patients with triple negative breast cancer. Breast. 2015; 24: 132-135. Ref.: https://goo.gl/RWURDL

13. Badve S, Dabbs DJ, Schnitt SJ, Baehner FL, Decker T, et al. Basal-like and triple-negative breast cancers: a critical review with an emphasis on the implications for pathologists and oncologists. Modern Pathology. 2011; 24: 157-167. Ref.: https://goo.gl/YYuZYo

14. Banerjee S, Reis-Filho JS, Ashley S, Steele D, Ashworth A, et al. Basal-like breast carcinomas: clinical outcome and response to chemotherapy. J Clin Pathol. 2006; 59: 729-735. Ref.: https://goo.gl/ox1RqW

15. Irvin WJ, Carey LA. What is triple-negative breast cancer? Eur J Cancer. 2008; 44: 2799-2805. Ref.: https://goo.gl/m7Tysk

16. Rakha EA, El-Sayed ME, Green AR, Lee AH, Robertson JF, et al. Prognostic markers in triple-negative breast cancer. Cancer. 2007a; 109: 25-32. Ref.: https://goo.gl/G3oWcS

17. Rakha EA, Tan DS, Foulkes WD, Ellis IO, Tutt A, et al. Are triple-negative tumours and basal-like breast cancer synonymous? Breast cancer research. 2007b; 9: 404. Ref.: https://goo.gl/VKeMR6

18. Sorlie T, Tibshirani R, Parker J, Hastie T, Marron J, et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci USA. 2003; 100: 8418-8423. Ref.: https://goo.gl/XGzMaq

19. Fackenthal JD, Olopade OI. Breast cancer risk associated with BRCA1 and BRCA2 in diverse populations. Nat Rev Cancer. 2007; 7: 937-948. Ref.: https://goo.gl/rqLioJ

20. Fadare O, Tavassoli FA. Clinical and pathologic aspects of basal-like breast cancers. Nat Clin Pract Oncol. 2008; 5: 149-159. Ref.: https://goo.gl/rtDyf

21. Bertucci F, Finetti P, Cervera N, Esterni B, Hermitte F, et al. How basal are triple-negative breast cancers? Int J Cancer. 2008; 123: 236-240. Ref.: https://goo.gl/zLpZxL

22. Calza S, Hall P, Auer G, Bjöhle J, Klaar S, et al. Intrinsic molecular signature of breast cancer in a population-based cohort of 412 patients. Breast Cancer Res. 2006; 8: R34. Ref.: https://goo.gl/zaJs3q

23. Hashmi AA, Edhi MM, Naqvi H, Faridi N, Khurshid A, et al. Clinicopathologic features of triple negative breast cancers: an experience from Pakistan. Diagn Pathol. 2014; 9: 43. Ref.: https://goo.gl/CbeVRJ

24. Cheng H, Qin Y, Fan H, Su P, Zhang X, et al. Overexpression of CARM1 in breast cancer is correlated with poorly characterized clinicopathologic parameters and molecular subtypes. Diagn Pathol. 2013; 8: 129. Ref.: https://goo.gl/YcLpjk

25. Klinge TA, Chen Y, Suhrke P, Stefansson IM, Gundersen MD, et al. Expression of thyroid transcription factor-1 is associated with a basal-like phenotype in breast carcinomas. Diagn Pathol. 2013; 8: 80. Ref.: https://goo.gl/BCFoZv

26. Liu L, Liu Z, Qu S, Zheng Z, Liu, et al. Small breast epithelial mucin tumor tissue expression is associated with increased risk of death and incidence in triple-negative breast cancer patients. Diagn Pathol. 2013b; 8: 71. Ref.: https://goo.gl/Zs3pTt

27. Nass N, Dittmer A, Hellwig V, Lange T, Beyer JM, et al. Expression of transmembrane protein 26 (TMEM26) in breast cancer and its association with drug response. Oncotarget. 2016; 7: 38408-38426. Ref.: https://goo.gl/QVgCfH

28. Yamagishi Si, Matsui T, Fukami K. Role of receptor for advanced glycation end products (RAGE) and its ligands in cancer risk. Rejuvenation Res. 2015; 18: 48-56. Ref.: https://goo.gl/UKVvuy

29. Radia A-M, Yaser A-M, Ma X, Zhang J, Yang C, et al. Specific siRNA targeting receptor for advanced glycation end products (RAGE) decreases proliferation in human breast cancer cell lines. Int J Mol Sci. 2013; 14: 7959-7978. Ref.: https://goo.gl/CmgGy4

30. Svoboda M, Sana J, Redova M, Navratil J, Palacova M, et al. MIR-34b is associated with clinical outcome in triple-negative breast cancer patients. Diagn Pathol. 2012; 7: 31. Ref.: https://goo.gl/YZJ4Rb
31. Laurinavicius A, Laurinaviciene A, Ostapenko V, Dasevicius D, Jarmalaite S, et al. Immunohistochemistry profiles of breast ductal carcinoma: factor analysis of digital image analysis data. Diagn Pathol. 2012; 7: 27. Ref.: https://goo.gl/Cv32X7

32. Livasy CA, Karaca G, Nanda R, Tretiakov MS, Olopade OI, et al. Phenotypic evaluation of the basal-like subtype of invasive breast carcinoma. Mod Pathol. 2006; 19: 264-271. Ref.: https://goo.gl/x6U4g8

33. Fulford L, Easton D, Reis-Filho J, Sofronis A, Gillett C, et al. Specific morphological features predictive for the basal phenotype in grade 3 invasive ductal carcinoma of breast. Histopathology. 2006; 49: 22-34. Ref.: https://goo.gl/wNDjAk

34. Reis-Filho JS, Milanezi F, Steele D, Savage K, Simpson PT, et al. Metaplastic breast carcinomas are basal-like tumours. Histopathology. 2006; 49: 10-21. Ref.: https://goo.gl/7yyofu

35. Cleator S, Heller W, Coombes RC. Triple-negative breast cancer: therapeutic options. Lancet Oncol. 2007; 8: 235-244. Ref.: https://goo.gl/bTe5m9

36. Carter M, Hornick JL, Lester S, Fletcher CD. Spindle cell (sarcomatoid) carcinoma of the breast: a clinicopathologic and immunohistochemical analysis of 29 cases. Am J Surg Pathol. 2006; 30: 300-309. Ref.: https://goo.gl/UYu7xG

37. Wargotz ES, Norris HJ. Metaplastic carcinomas of the breast: IV. Squamous cell carcinoma of ductal origin. Cancer. 1990a; 65: 272-276. Ref.: https://goo.gl/ZhMcrA

38. Rosen PP, Emsberger D. Low-Grade Adenosquamous Carcinoma: A Variant of Metaplastic Mammary Carcinoma. Am J Surg Pathol. 1987; 11: 351-358. Ref.: https://goo.gl/jbrMzF

39. Hanna W, Kahn HJ. Ultrastructural and immunohistochemical characteristics of mucoepidermoid carcinoma of the breast. Hum Pathol. 1985; 16: 941-946. Ref.: https://goo.gl/z1AY4D

40. Wargotz ES, Norris HJ. Metaplastic carcinomas of the breast: V. Metaplastic carcinoma with osteoclastic giant cells. Hum Pathol. 1990b; 21: 1142-1150. Ref.: https://goo.gl/2PUSoL

41. Sneige N, Yaziji H, Mandavilli SR, Perez ER, Ordonez NG, et al. Low-grade (fibromatosis-like) spindle cell carcinoma of the breast. Am J Surg Pathol. 2001; 25: 1009-1016. Ref.: https://goo.gl/JVCmpx

42. Ferracin M, Veronese A, Negrini M. Micromarkers: miRNAs in cancer diagnosis and prognosis. Expert Rev Mol Diagn. 2010; 10: 297-308. Ref.: https://goo.gl/21xJAU

43. Le X-F, Merchant O, Bast RC, Calin, GA. The roles of microRNAs in the cancer invasion-metastasis cascade. Cancer Microenviron. 2010; 3:137-147. Ref.: https://goo.gl/S73wzr

44. Negrini M, Calin GA. Breast cancer metastasis: a microRNA story. Breast Cancer Res. 2008; 10: 203. Ref.: https://goo.gl/H727oi

45. Blenkiron C, Goldstein LD, Thorne NP, Spiteri I, Chin SF, et al. MicroRNA expression profiling of human breast cancer identifies new markers of tumor subtype. Genome Biol. 2007; 8: 214. Ref.: https://goo.gl/J2kvV8

46. Van Schooneveld E, Wildiers H, Vergote I, Vermeulen PB, Dirix LY, et al. Dysregulation of microRNAs in breast cancer and their potential role as prognostic and predictive biomarkers in patient management. Breast Cancer Res. 2015; 17: 21. Ref.: https://goo.gl/eRZ3Dz

47. Lehmann BD, Bauer JA, Chen X, Sanders ME, Chakravarty AB, 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. Ref.: https://goo.gl/JdPQuW

48. Kurozumi S, Yamaguchi Y, Kurosumi M, Ohira M, Matsumoto H, et al. Recent trends in microRNA research into breast cancer with particular focus on the associations between microRNAs and intrinsic subtypes. J Hum Genet. 2017; 62: 15-24. Ref.: https://goo.gl/J2kvrV8

49. Garcia AI, Buisson M, Bertrand P, Rimokh R, Rouleau E, et al. Down-regulation of BRCA1 expression by miR-146a and miR-146b-5p in triple negative sporadic breast cancers. EMBO Mol Med. 2011b; 3: 279-290. Ref.: https://goo.gl/uyDCs7

50. Garcia AI, Buisson M, Bertrand P, Rimokh R, Rouleau E. Down-regulation of BRCA1 expression by miR-146a and miR-146b-5p in triple negative sporadic breast cancers. EMBO Mol Med. 2011a; 3: 279-290. Ref.: https://goo.gl/b6LLyy

51. Shen J, Ambrosone CB, DiCioccio RA, Odunsi K, Lele SB, et al. A functional polymorphism in the miR-146a gene and age of familial breast/ovarian cancer diagnosis. Carcinogenesis. 2008; 29: 1963-1966. Ref.: https://goo.gl/vsxoFy
52. Crippa E, Lusa L, De Cecco L, Marchesi E, Calin GA, et al. miR-342 regulates BRCA1 expression through modulation of ID4 in breast cancer. PloS one. 2014; 9. Ref.: https://goo.gl/hGwK4D

53. Moskwa P, Buffa FM, Pan Y, Panchakshari R, Gottipati P, et al. miR-182-mediated downregulation of BRCA1 impacts DNA repair and sensitivity to PARP inhibitors. Mol Cell. 2011; 41: 210-220. Ref.: https://goo.gl/hcRb6n

54. Tanic M, Yanowski K, Gómez-López G, Rodriguez-Pinilla MS, Marquez-Rodas I, et al. MicroRNA expression signatures for the prediction of BRCA1/2 mutation-associated hereditary breast cancer in paraffin-embedded formalin-fixed breast tumors. Int J Cancer. 2015; 136: 593-602. Ref.: https://goo.gl/grGd5T

55. Rodriguez A, Vigorito E, Clare S, Warren MV, Couttet P, et al. Requirement of bic/microRNA-155 for normal immune function. Science. 2007; 316: 608-611. Ref.: https://goo.gl/GF482e

56. Zonari E, Pucci F, Saini M, Mazzieri R, Politi LS, et al. A role for miR-155 in enabling tumor-infiltrating innate immune cells to mount effective anti-tumor responses. Blood. 2013. Ref.: https://goo.gl/zV0mYo

57. Gebeshuber CA, Zatloukal K, Martinez J. miR-29a suppresses tristetraprolin, which is a regulator of epithelial polarity and metastasis. EMBO Rep. 2009; 10: 400-405. Ref.: https://goo.gl/441YmF

58. Jiang H, Zhang G, Wu JH, Jiang CP. Diverse roles of miR-29 in cancer (review). Oncol Rep. 2014; 31: 1509-1516. Ref.: https://goo.gl/hnLSkJ

59. Gaur AB, Holbeck SL, Colburn NH, Israel MA. Downregulation of Pdcd4 by mir-21 facilitates glioblastoma proliferation in vivo. Neuro Oncol. 2011; 13: 580-590. Ref.: https://goo.gl/byJacU

60. Wang Q, Liu S, Tang Y, Liu Q, Yao Y. MPT64 protein from Mycobacterium tuberculosis inhibits apoptosis of macrophages through NF-kB-miRNA21-Bcl-2 pathway. PloS one. 2014; 9. Ref.: https://goo.gl/aJ5xsF

61. Lim PK, Bliss SA, Patel SA, Taborga M, Dave MA, et al. Gap junction-mediated import of MicroRNA from bone marrow stromal cells can elicit cell cycle quiescence in breast cancer cells. Cancer Res. 2011; 71: 1550-1560. Ref.: https://goo.gl/pvkf4M

62. Eichelser C, Stuckrath I, Muller V, Milde-Langosch K, Wikman H, et al. Increased serum levels of circulating exosomal microRNA-373 in receptor-negative breast cancer patients. Oncotarget. 2014; 5: 9650-9663. Ref.: https://goo.gl/HTpniA

63. Chen J, Shin VY, Siu MT, Ho JC, Cheuk I, et al. miR-199a-5p confers tumor-suppressive role in triple-negative breast cancer. BMC cancer. 2016; 16: 887. Ref.: https://goo.gl/JRTnbS

64. Abbeldatif M. Differential expression of microRNAs in different disease states. Circ Res. 2012; 110: 638-650. Ref.: https://goo.gl/8DbLUY

65. Kaboli PJ, Rahmat A, Ismail P, Ling KH. MicroRNA-based therapy and breast cancer: A comprehensive review of novel therapeutic strategies from diagnosis to treatment. Pharmacol Res. 2015; 97: 104-121. Ref.: https://goo.gl/2KEucF

66. Kim NH, Kim HS, Li XY, Lee I, Choi HS, et al. A p53/miRNA-34 axis regulates Snail1-dependent cancer cell epithelial-mesenchymal transition. J Cell Biol. 2011; 195: 417-433. Ref.: https://goo.gl/16dmCU

67. Song SJ, Poliseno L, Song MS, Ala U, Webster K, et al. MicroRNA-antagonism regulates breast cancer stemness and metastasis via TET-family-dependent chromatin remodeling. Cell. 2013; 154: 311-324. Ref.: https://goo.gl/mFpe5j

68. Graveel CR, Calderone HM, Westerhuis JJ, Winn ME, Sempere LF. Critical analysis of the potential for microRNA biomarkers in breast cancer management. Breast Cancer (Dove Med Press). 2015; 7: 59-79. Ref.: https://goo.gl/MeC42x

69. Ma L, Teruya-Feldstein J, Weinberg RA. Tumour invasion and metastasis initiated by microRNA-10b in breast cancer. Nature. 2007; 449: 682-688. Ref.: https://goo.gl/T2Wbx1

70. Li X, Pan YZ, Seigel GM, Hu ZH, Huang M, et al. Breast cancer resistance protein BCRP/ABCG2 regulatory microRNAs (hsa-miR-328,519c and-520h) and their differential expression in stem-like ABCG2+ cancer cells. Biochem Pharmacol. 2011; 81: 783-792. Ref.: https://goo.gl/AJpbnX

71. Amschler K, Schönb MP, Pletz N, Wabrecht K, Erpenbeck L, et al. NF-κB inhibition through proteasome inhibition or iκBα blockade increases the susceptibility of melanoma cells to cytostatic treatment through distinct pathways. Journal of Investigative Dermatology. 2010; 130: 1073-1086. Ref.: https://goo.gl/4LZLsx
73. Eichelser C, Stückrath I, Müller V, Milde-Langosch K, Wikman H, et al. Increased serum levels of circulating exosomal microRNA-373 in receptor-negative breast cancer patients. Oncotarget. 2014b; 5: 9650-9663. Ref.: https://goo.gl/RhdgD7

74. Gabriely G, Tepliyuk NM, Krichevsky AM. Context effect: microRNA-10b in cancer cell proliferation, spread and death. Autophagy. 2011; 7: 1384-1386. Ref.: https://goo.gl/JeGrJH

75. Lee KH, Goan YG, Hsiao M, Lee CH, Jian SH, et al. MicroRNA-373 (miR-373) post-transcriptionally regulates large tumor suppressor, homolog 2 (LATS2) and stimulates proliferation in human esophageal cancer. Exp Cell Res. 2009; 315: 2529-2538. Ref.: https://goo.gl/pQ5E1y

76. Okoye JO, Okoye FO. miRNA and Target Oncogene Regulation in Triple Negative Breast Cancer: An Age, Ethnic and Environmental Related Neoplastic Event. JCTI. 2015; 2: 66-80. Ref.: https://goo.gl/LAuex9

77. Radojicic J, Zaravinos A, Vrekoussis T, Kafousi M, Spandidos DA, et al. MicroRNA expression analysis in triple-negative (ER, PR and Her2/neu) breast cancer. Cell cycle. 2011; 10: 507-517. Ref.: https://goo.gl/epHQG9

78. Wang Y, Rathinam R, Walch A, Alahari SK. ST14 (suppression of tumorigenicity 14) gene is a target for miR-27b, and the inhibitory effect of ST14 on cell growth is independent of miR-27b regulation. J Biol Chem. 2009; 284: 23094-23106. Ref.: https://goo.gl/d2hUNM

79. Wu Q, Wang C, Lu Z, Guo L, Ge Q. Analysis of serum genome-wide microRNAs for breast cancer detection. Clin Chim acta. 2012; 413: 1058-1065. Ref.: https://goo.gl/rZXH2c

80. Zavala V, Pérez-Moreno E, Tapia T, Camus M, Carvallo P. MiR-146a and miR-638 in BRCA1-deficient triple negative breast cancer tumors, as potential biomarkers for improved overall survival. Cancer Biomarkers. 2016; 16: 99-107. Ref.: https://goo.gl/Tm2PTF

81. Liu H, Wang Y, Li X, Zhang Y-j, Li J, et al. Expression and regulatory function of miRNA182 in triple-negative breast cancer cells through its targeting of profilin 1. Tumour Biol. 2013a; 34: 1713-1722. Ref.: https://goo.gl/hVysfE

82. Mattiske S, Suetani RJ, Neilsen PM, Callen DF. The oncogenic role of miR-155 in breast cancer. Cancer Epidemiol Biomarkers Prev. 2012; 21: 1236-1243. Ref.: https://goo.gl/5FGVmG

83. Ding L, Ni J, Yang F, Huang L, Deng H, et al. Promising therapeutic role of miR-27b in tumor. Tumour Biol. 2017; 39. Ref.: https://goo.gl/DhSVYM

84. Jin L, Wessely O, Marcussen EG, Ivan C, Calin GA, et al. Prooncogenic factors miR-23b and miR-27b are regulated by Her2/Neu, EGF, and TNF-α in breast cancer. Cancer Res. 2013; 73: 2884-2896. Ref.: https://goo.gl/JHqgXT

85. Fkih M’hamed I, Privat M, Ponelle F, Penault-Llorca F, Kenani A. Identification of miR-10b, miR-26a, miR-146a and miR-153 as potential triple-negative breast cancer biomarkers. Cell Oncol (Dordr). 2015; 38: 433-442. Ref.: https://goo.gl/HxFqof

86. Fkih M’hamed I, Privat M, Trimeche M, Penault-Llorca F, Bignon YJ. et al. miR-10b, miR-26a, miR-146a And miR-153 Expression in Triple Negative Vs Non Triple Negative Breast Cancer: Potential Biomarkers. Pathol Oncol Res. 2017. Ref.: https://goo.gl/7y1JFS