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Review Article

MicroRNA Therapeutics in Triple Negative Breast Cancer

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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

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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 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 imunohistochemical 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 histologiacal 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 (oncomir's), 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 [54] Tanic et al. 2015, miRNA classifiers in order to find out the BRCA germline mutation status of the preserved sample of

Table 1: Potential functions of different miRNAs in triple negative breast cancer progression.

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 SOCS1	Up-regulated	[82]
miRNA-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 LATS	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 maintenace 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 mi-RNAs 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 resistence 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 antagomirs, 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 soncogenic miRNA involved in TNBC and targeting them to stop metastasis. On the other hand to determine the stat 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.

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