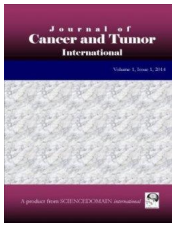

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MiRNA and Target Oncogene Regulation in Triple Negative Breast Cancer: An Age, Ethnic and Environmental Related Neoplastic Event

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Authors' contributions

This work was carried out in collaboration between both authors, Author JOO carried out the literature searches and wrote the manuscript. Author FOO participated in the literature searches. Both authors approved of the final version of the manuscript.

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ABSTRACT

Triple-negative breast cancer is a type of aggressive breast cancer without the immunohistochemical expression of estrogen receptors, progesterone receptors and human epidermal growth factor receptor-2; with poor prognosis, greater relapse risk and worse survival in general. Its proportion in all breast cancer cases ranges from 15 to 20%. Triple negative breast cancer is more prevalent among younger women, particularly African, African-American, Latino and obese women. This observed prevalence, is an age and ethnic related factor which fingers estrogenic agents as a common feature in TNBC occurrence. Inherited variation in the let-7 binding site on the KRAS oncogene has been revealed to confer increased susceptibility to triple negative breast cancer, especially in premenopausal, African-American and Hispanic women. About 15-40% of triple negative breast tumors have BRCA-related epigenetic down-regulation and increased expression of the inhibitors of BRCA1 function, which have be found to be related to indirect

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regulation of ID4 oncogene by miR-342. When compared with wholesome breast tissues, miR-21, miR-210 and miR-221 expression are observed to be elevated in the triple-negative breast cancer; whereas expression of miR-10b, miR-145, miR-205, miR-122a, miR-200a/miR-200b, miR-146b and miR-148a are decreased. Interestingly, eight miRNAs are differentially expressed in metastatic breast cancer tissues (miR-200b, miR- 148a, miR-424, miR-125a-5P, miR-627, miR-579, let-7g and miR-101) when compared with the non-metastatic type. The consequence of differential miRNA expression in triple negative breast is a function of target oncogene modulation which may be related to nutritional, environmental and socio-cultural factors. Insights into the risk factors, miRNA and their validated target may provide novel diagnostic tools and treatment options for triple negative breast cancer.

Keywords: Triple negative breast cancer; age; ethnicity; environmental factor; oncogenes, miRNA; BRCA mutations.

1. INTRODUCTION

Breast cancer afflicts approximately 1 in 8 women and is a leading cause of cancer-related mortality. More than 1 million women worldwide are diagnosed with breast cancer each year of which 170,000 cases are referred to as triple negative breast cancer [1]. According to Reis-Filho and Tutt [2], expression profiles of breast cancer exhibit a systematic variation and allow for the classification of breast cancer into five main groups: two estrogen receptor (ER) positive (luminal A and B) and three ER negative groups (normal breastlike, HER2 positive, and 'basal-like'). Triple-negative breast cancers form 15 to 20% rough estimate of all breast cancer. They are a type of aggressive breast cancer without the immunohistochemical expression of estrogen receptors, progesterone receptors and human epidermal growth factor receptor-2 [3]. TNBC is more prevalent among younger women [1,4], particularly young African, African-American [2,5] and Latino women [2,6]. TNBC is more prevalent in among young obese women [1,6-8]. The fact that TNBC is associated with younger women may be linked to the presence of high estrogen level in their body system. Hence, it is not surprising that TNBC is associated with been obesed women since obesity results in increased estrogen level. So far, the direct cause of the observed high prevalence in the affected age and ethnic groups has not been confirmed. It is suggested that the stated prevalence might be linked to increased *p53* mutations reported in African American women when compared with non-Hispanic white women [9]. It is suggested that the causes may be linked to some environmental or socio-cultural factors. This suggestion is supported by the fact that majority of the familial risk for breast cancer is most likely due to the interaction of low-risk susceptibility genes and non-genetic factors [9].

A study carried out by Heneghan [10] revealed that an inherited variation in the *let-7* binding site on the *KRAS* oncogene conferred increased susceptibility to breast cancer particularly the 'triple negative' subtype. The *KRAS*-variant is found in almost 30% of premenopausal ER/PR/HER2 negative breast cancer patients [11], and in over 20% of unselected TN patients. It has been observed that hormone replacement therapy for postmenopausal women increases the risk of breast cancer 1.2- to 1.7-fold, and administration of progesterone further increases the risk [9]. These reports reinforce the possibility that TNBC may have a strong correlation with hormonal levels in the body, especially estrogen. According to the reports by Minami et al. [11], the KRAS-variant was also observed to be prevalent in African-American and Hispanic women. This higher prevalence in this ethnic group may be adduced to mutations caused by prior generational gene exposure to environmental estrogenic agents. According to Chen and Russo [1], over 80% of BRCA-1 mutation carriers are triple negative and approximately 20% of breast cancer patients with mutations in BRCA-1 and BRCA-2 are incapable of DNA repair, because normal BRCA1 and BRCA2 play pivotal part in DNA repair [1]. Carriers of DNA repair mutations among TNBC patients have higher susceptibility to DNA damaging agents [1]. This further fingers mutations resulting from nutritional and environmental factors, and perhaps herbal concoctions as the leading cause of TNBC in the affected ethnic groups. However, such nutritional and environmental factors are yet to be extensively studied and elucidated.

The term triple negative breast cancer encompasses basal-like breast cancer (BLBC) [12] and other uncommon tumors for example, metaplastic tumors and adenoid-cystic tumors [1,13]. MicroRNAs (miRNAs) are involved in the regulation of key cellular process including

development, differentiation, cell proliferation, apoptosis, fat metabolism, angiogenesis, and inflammation [14]. MicroRNAs are a class of endogenous, small, non-coding RNAs that control gene expression by interacting with target mRNAs [1], leading to either mRNA degradation or translational repression [15,16]. Mounting proof have shown that microRNAs (miRNAs) have key functions in stem cell biology, differentiation and oncogenesis [4,17,18]. Dysregulation in the expression of Tumor suppressor or oncogenic miRNAs induces tumorigenesis [19,20], metastasis and poor prognosis [21]. Altered miRNAs exert their effects by regulating an array of specific targets (Table 1) which in turn determines migration and invasion as well as tumourigenicity, metastases and poor prognosis. Conformational modifications and expressional levels of the validated targets of these miRNAs may halt the progression of cancer, resulting in better prognosis among TNBC patients. This review article gives an overview on the major roles of miRNA and their validated targets in the emergence, metastases, prognosis and treatment of TNBC.

2. CHARACTERISTIC FEATURES OF TNBC

TNBC posses several clinical and histological patterns [22,23,1,4-6]. Lehmann et al. [24] analyzed over 500 TNBCs categorizing them into six distinct subtypes, with regards to intrinsic gene signature: basal 1 and 2, mesenchymal and mesenchymal stem cell-like, immunomodulatory and androgen pathway enriched [3]. These different subtypes of TNBC posses some common characteristics as discussed below. Due to absence of the ER, PR and HER-2, TNBC patients are insensitive to majority of presently existing hormonal or ER-targeted and HER-2-based therapies [3]. However, TNBC patients have a better response to chemotherapy in the neoadjuvant setting, in comparison to non-TNBC patients [25,26]. TNBC patients that are initially non-responsive have higher relapse risk and worse overall survival at 68% than responders who exhibit pathologic complete response at 94% overall survival [27]. Unfortunately, TNBC cases are controlled solely with standard chemotherapy treatment, leading to local and systemic relapse [1,4].

TNBC patients exhibit many similar characteristics with breast cancer susceptibility gene outcome-associated breast cancer [1,28-31]. According to Sorlie et al. [32], 15-40% of TNBC tumors have *BRCA*-related epigenetic down-regulation and increased expression of the inhibitors of *BRCA1* function. This indicates that the label “triple-negative breast cancer” describes a more heterogeneous subtype than other breast cancer subtypes [33,34]. Hartman et al. [35] who reported a lower prevalence of BRCA1 mutation and higher prevalence of BRCA2 mutation in TNBC patients stated that BRCA1 mutants have a median age of 41.5 years while that of BRCA2 is 52 years. This suggests that TNBC in relation to BRCA mutations are age dependent which probably translates to an age-hormone related event, since estrogenic effects are more pronounced in females of younger age groups.

TNBC are poorly differentiated, highly malignant, more aggressive, and with worse overall survival [36,22]. Women with TNBC have double chance of suffering distant metastases compared to other women [1]. An increased proportion of TNBC patients have higher rates of CNS, visceral; particularly the lungs and brain [37], and to a minor extent in bones [3,25] and overall poor outcome despite therapeutic treatment [26]. This metastatic phenotype of TNBC is due in part to the high nuclear grade of TNBC tumors and results in shorter time to disease recurrence and shorter median survival time in of advanced metastatic TNBC [23,24]. More so, greater proportion of TNBC patients experience early local relapse, mostly between the first and third year following diagnosis [3,38], as a result, TNBC patients have poorer survival rate. In TNBC, expressions of several changes in oncogenes, tumour suppressor proteins and abnormal signaling pathways have been observed [1]. Key mediators of immunological response, proliferation, and neuronal signaling, such as MYC, LYN, EGFR, and CEBPB, are either amplified or overexpressed in TNBC in comparison to other breast cancer subtypes [39]. Epidermal growth factor receptor (EGFR) has been identified as a frequently overexpressed marker in triple-negative breast cancer [40].

3. MICRORNA SYNTHESIS

MicroRNAs (miRNAs) are minute non-coding RNAs that regulate gene expression post-transcriptionally by pairing to 3’ untranslated regions (UTRs), coding sequences or 5’ UTRs of target messenger RNAs (mRNAs), which in most cases leads to translation inhibition or mRNA degradation [41-43]. The mature miRNA molecules are produced in a multi-step process.

The DNA sequence is transcribed by RNA polymerase II into a single stranded RNA molecule by hairpin structures known as primary transcripts or pri-miRNAs [44]. The primiRNAs are processed (cutted) into the nucleus by RNAse III Drosha into 70100 nucleotides long fragments called pre-miRNAs. The pre-miRNA molecule is then actively transported to the cytoplasm by a carrier protein [45]. Here, an additional step mediated by the Dicer, generates a double strand.RNA (dsRNA) approximately 22 nucleotides long, including the mature miRNA guide (3p arm) and the complementary passenger strand (5p arm). Once completed, the processing steps, through this mechanism that is not fully characterized yet, the mature miRNA is able to regulate gene expression at post-transcriptional level, binding through partial complementarity the 3' untranslated region (3' UTR) of the target mRNA, and mainly leading to either mRNA degradation or translation inhibition [44,46]. Depending on the targeted mRNAs, the miRNA action ultimately results in reduced protein levels and profound consequences on cellular homeostasis. In 2004, an in silico study showed that more than half of miRNAs map to genomic regions that are frequently altered in cancer [47]. This include: loss of heterozygosity regions (LOH) (e.g. miR-15a/16-1), amplified regions (e.g. miR-17-92 cluster, miR-155) and breakpoint regions and fragile sites (FRA) (e.g. let-7 family members)

4. MICRORNA AND EPITHELIAL-TO-MESENCHYMAL TRANSITION (EMT)

Tumorigenesis and tumour progression can be seen as evolutionary processes, in which the transformation of a normal cell into a tumor cell involves a number of limiting genetic and epigenetic events that occur in a series of discrete stages [48]. Both functional and observational data implicate alterations in histone modifications, DNA promoter methylation, and non-coding RNA expression in carcinogenesis [49]. On the other hand, due to the wide range of biological functions of miRNAs, analyzing changes in overall miRNA expression levels within human tumors has helped identify miRNA signatures associated with diagnosis, staging, progression, prognosis, and response to treatment [50]. Epigenetics, defined as heritable change in gene activity that is independent of DNA sequence, play a prominent part in cancer initiation and progression [51]. The main epigenetic events that regulate tumor-associated genes are linked to aberrant hypermethylation of tumor-suppressor genes, global DNA hypomethylation item and post-translational modifications of histones and other proteins by acetylation and/or phosphorylation. MiRNAs can be targets of epigenetic events that, in some instances, can explain the perturbation of miRNA expression in cancer [52].

EMT (epithelial to mesenchymal transition) is the process by which epithelial cells convert to mesenchymal cells and is essential in embryonic development. It appears that aberrant activation of EMT later in life drives cancer progression, and is involved in highly aggressive, poorly differentiated breast cancers with increased potential for metastasis and recurrence [53]. This suggests that EMT may play a critical role in the high metastatic rate and tumour progression in TNBC patient. In TBNC biology, miR-200 is the most fascinating factor where its upregulation correlates well with lymph node positivity and metastasis [54], but downregulated in metaplastic carcinoma [3,41]. More so, the miR-200 family, especially miR-200c, inhibits cancer cell migration [55], invasion [56] and reverts the anoikisis resistance [3,57,58] which is commonly seen in aggressive carcinoma cells where it correlates with EMT [59,60]. More so, downregulation of miR-200c is linked to poor response to chemotherapy [61] and radiotherapy [62]. Studies have revealed that MiR-200a and miR-200b play important roles in mammary stem cells [63-65], by inhibiting EMT, which is essential during development, progression and metastasis [66]. Thus, therapeutic modulation of the miR-200 family may inhibit EMT which in turn reduces the rate of metastasis in TNBC patients. A decreased expression of *E-cadherin* signifies EMT [4]. Upregulation of *E-cadherin* by MiR-200a/miR-200b could be adduced to downregulation of its transcriptional repressors *Zeb1*, *Zeb2* and the polycomb complex *Suz12* [65,67,68]. A study carried out by Collin-Burrow [69] demonstrated that HDAC inhibitor (HDACi) regulate microRNAs which in turn regulate the epithelial-to-mesenchymal transition (EMT) [41] in triple-negative breast cancer (TNBC) [3]. This study assessed the microRNA expression profiles of two TNBC cell lines following treatment with HDACi identifying a number of up- and down-regulated microRNAs. The overall microRNA profile after HDACi treatment was indicative of a less aggressive phenotype. In this study, miR-126, miR-146b-5p, miR-192, miR-194, miR-215, miR-342.3p and miR-424 were observed to be increased while miR-100, miR-106b, miR-125b, miR-331-3p, Let-7i were

decreased. Treatment with HDACi also resulted in increased expression of E-cadherin as well as decreased migration of TNBC indicating a reversal of the EMT phenotype (which is associated with metastatic and aggressive disease, of TNBC).

Table 1. miRNA expressions in triple negative breast cancer (TNBC) with relative validated targets and their biological functions [1,3,4,11,83,87-92]

miRNA	Target	Description/Biological function of miRs
miR-9	CDH1	miR-9, identified as a new "metastomiR" and activated by MYC and MYCN, directly targets CDH1, the E-cadherin encoding messenger RNA, leading to increased cell motility and invasiveness, activation of β-catenin signaling and upregulation of VEGF.
miR-10a/10b	HOXD10	TWIST transcription factor stimulates the up-modulation of a specific microRNA that suppresses its direct target and in turn activates another pro-metastatic gene, resulting in tumor cell invasion and metastasis
	TIAM1	A mechanism for the regulation of Tiam1-mediated Rac activation in breast cancer cells
miR-19	TF	It target tissue factor (TF), a known promoter of cancer cell survival, angiogenesis, and metastasis. Therefore, miR19 may also play a tumorsuppressive role in breast cancer.
miR-21	TPM1	Suppression of miR-21 can inhibit tumor growth
	PDCD4	MiR-21 modulates tumor suppressor protein programmed cell death 4 (PDCD4); a functionally key target in breast cancer cells
miR-31	ITGA5, RDX, RhoA, FZD3, M-RIP, MMP16, SATB2	miR-31 uses multiple mechanisms (targets) to oppose metastasis
	WAVE3	Reduction of metastatic potential
	PRKCE	Induction of apoptosis and enhancement of chemo- and radiosensitivity
miR-34a	AXL	Impairment of migration
miR-107/103	DICER	Dicer inhibition drifts epithelial cancer toward a less-differentiated, mesenchymal fate to foster metastasis
Let-7 family	PLC1	The Let-7 family has a tumour-suppressor role in breast cancer by negatively regulating EGF-driven cell invasion, viability, and cell cycle progression
	IL6	Inflammation activates a positive feedback loop that maintains the epigenetic transformed state
miR-146 and miR-146b-5p	BRCA1	control of BRCA1-mediated proliferation and homologous recombination
miR-155	SOCS1	miR-155 is an oncomiR in breast cancer, and it has been suggested that miR-155 may serve as a bridge between inflammation and cancer
	WEE1	miR-155 enhances mutation rates by decreasing the efficiency of DNA safeguard mechanisms by targeting of cell cycle regulators such as WEE1
	FOXO3a	FOXO3a affect cell survival and response to chemotherapy in breast cancer
miR-181a/b	Bim	Inhibition of anoikisis

	ATM	Impairment of DNA double-strand-breaks repair
miR-182	PFN1	Inhibition of cell proliferation and invasion Induction of apoptosis
miR-199a-3p	Caveolin-2	Regulates cell proliferation and survival.Caveolin-2 is a member of a family of scaffolding proteins that coats plasma membrane invaginations (caveolae).
miR-200 family (a/b/c)	ZEB1, ZEB2	miR-200 stimulates differentiation in undifferentiated mammary epithelial cell line and inhibits EMT. Down-regulation of the miR-200 family may be an important step in tumor progression
	PLC1	Tumor-suppressor function by negatively regulating EGF-driven cell invasion, viability, and cell cycle progression in breast cancer
	SUZ12	The miR-200b-Suz12-cadherin pathway is important for cancer stem cell growth and invasive ability
	FN1, LEPR, NTRK2, ARHGAP19	miR-200c actively represses a program of mesenchymal and neuronal genes involved in cell motility and anoikis resistance
	EphA2	It inhibits epithelial–mesenchymal transition (EMT)- a characteristic morphological changes in undifferentiated, non-tumorigenic mammary cells.
miR-203	BIRC5	It reduces proliferation
	LASP1	It inhibits migration
miR-205	E2F1; LAMC1	Reduction of proliferation, cell cycle and tumor growth
miR-221/222	FOXO3a	The miR-221/222 cluster targets FOXO3A to suppress p27kip1 also at a transcriptional level
	ESR1	Modulation of ER is associated with antiestrogen therapy
	TRSP1	miR-221/222 promote EMT and contribute to the more aggressive clinical behavior of basal-like breast cancers
	DICER	Dicer is low in ER-negative breast cancers, since such cells express high miR-221/222
miR-224	PAK4 and MMP-9	It has been associated with cancer progression and enhanced cell migration and invasion by increasing the expression of the proinvasive PAK4 and MMP9.
miR-342	ID4	ID4 is involved in mammalian embryogenesis, angiogenesis and in the maintenance of cancer stem cells. It is associated with loss of differentiation, enhanced malignancy and aggressive clinical behavior.
miR5425p		It is associated with maintenance of the mesenchymal phenotype, an important feature of the TNBC phenotype and driver of cell motility and invasiveness.
miR-17/92	HBP1	miR-17/92 cluster has a critical function in breast cancer cell invasion and migration by suppressing HBP1 and subsequently activating Wnt/-catenin

Recent data described miR-181a, which is overexpressed in TNBC [3,70], as metastamiR. Underexpression of miR-181a have been observed to inhibit TGF-β mediated EMT, invasion and migration, and reverting anoikisis resistance in breast cancer cells; overexpressions are related to shorter disease-free survival of breast cancer patients [70]. Moreover miR-181a/b expression sensitizes to cisplatin [71] and to PARP inhibitors [72] by dampening the DNA double-strand-breaks repair, thus representing a possible marker of BRCAness. Estimated levels of miR-181a could play a part in patient selection for PARP inhibitor treatments [3].

It has been observed that miRNAs such as miR-141-3p, miR-203a, miR-548c-3p, miR-607 and miR-96-5p were appreciably upregulated with concomitant downregulation of miR-181a in triple-negative primary breast cancers when compared with double positive cases [73]. Furthermore, according to the reports of Radojicic et al. [73], the expression of miR-21, miR-210, and miR-221 have been observed to be higher in the triple-negative (TN) subtype of breast cancer compared with corresponding healthy tissues; while the expression of miR-10b, miR-145, miR-205, miR-122a [74], miR-200a/miR-200b, miR-146b and miR-148a has been observed to be lower [4]. More so, significant downregulation of Let-7c, miR- 27b, miR-22, miR-143, miR-30b and miR-30d have been observed in all breast cancer cell lines when compared with non-tumorigenic epithelial MCF-10A cells [4]. In TNBC-associated lymph node metastasis, miRNAs such as miR-424, miR-125a-5P, miR-627, miR-579, let-7g and miR-101 were specifically expressed [3], while miR-424 and miR-125a were specifically expressed only in the metastasis *vs*. primary tumor and in normal tissue *vs*. metastasis, respectively [3,75]. MiR-200b and miR- 148a is suggested to target the E2F pathway that is active in poor-prognosis and metastatic breast cancer [4]. MiR-203 has been shown to inhibit cell proliferation and migration, while miR-141-3p inhibits metastasis; upregulation of miR-548c-3p is linked to poor prognosis [4]. Overexpression of miR-155 is observed in TNBC where it results in angiogenesis, tumor growth, metastasis, late-stage/high grade tumor and poor prognosis [76]. MiR-155 is epigenetically regulated by BRCA1 and up-regulated in BRCA1-deficient or BRCA-mutant breast cancer [77] and initiated by pro-oncogenic stimuli such as hypoxia, both risk factors for TNBC [3]. Targeting these miRNAs involved in tumour metastasis may lead to a better prognosis in TNBC patients.

One of the most studied microRNAs which consistently are found up-regulated in a wide variety of cancers, including breast cancer, is miR-21 [78-80]. Up-regulated expression of miR-21 in breast cancer tissues is linked to advanced clinical stage, lymph node positivity, and low survival rate [3,78,80]. Some of the microRNAs have shown different expressions not only within the specific subtype of breast cancer but between distinct subtypes of breast cancer as well. MiR-21 is an oncogenic microRNA with anti-apoptotic potential which is directly involved in the growth, proliferation, and invasion of the tumor cells by inhibiting the activity of the tumor suppressor genes *PDCD4* (programmed cell death-4) and tumor suppressor tropomyosin-1 (TPM1) [81,82]. Expression levels of miR-21 [83] and miR-29a were significantly higher in triple-negative tumor tissues than in luminal-B tumor tissues [84]. Another microRNA which has been reported as being expressed differentially in the TN tumors is miR-31, which is downregulated as a result of epigenetical hypermethylation of LOC554202 [3,73,85]. MiR-31 play an important part in metastastic process and its upregulation initiates apoptosis and increases chemo- and radiosensitivity in TNBC cell lines by direct inhibition of PRKCE [3,86]. Inverse correlation between miR-31 and Bcl-2 was found by exploiting a public dataset of breast cancer patients [87]. Regulation of Bcl-2 oncogene as a therapeutic measure could alter miR-31 effects and perhaps increase the overall survival of TNBC patients.

5. PROGNOSTIC AND THERAPEUTIC MARKERS IN TBNC

Even though MiRNAs have been proposed as potential therapeutic tool, there are few documented accomplishments in that regard [93]. There are two major strategies to target miRNAs expression in cancer: a) direct strategies employs oligonucleotides or virus based constructs to either block the expression of an oncogenic miRNA or to reintroduce a tumor suppressor miRNA lost in cancer [93]; b) indirect strategy involves the use of drugs to modulate miRNAs expression by targeting their transcription and processing. Glyceollins, antiestrogenic agents, exert antitumor activity in TNBC [89]. Decreased expression of miR5425p, with overexpression of NME1, signifies a reversal of EMT and a suppression of metastasis by glyceollins. A second target identified through proteomics approach is vimentin, whose expression was down regulated more than 13 fold by glyceollins. Vimentin is a marker for epithelial-to-mesenchymal transition and is highly expressed in numerous TNBCs [94]. Vimentin is a proven target of miR30d and a predicted target of miR138, both found to be appreciably elevated by glyceollins [95]. These data suggest that the effects of glyceollins on TNBC cell lines are achieved via regulation of miRs, which in turn regulate known oncogenes and tumor suppressors [89]. Among the most down regulated miRs following treatment with glyceollins were 193a5p, 197, 224, 4865p, and

5425p, all of which have been associated with cancer progression [89]. The link between specific miRNAs with ER, PR and HER2 status reveals the role of miRNAs in disease classification of breast cancer. Decreased expression of miRNA-342 in TNBC tumors, increased miRNA-342 expression in the Luminal-B tumors, and down regulated miRNA-520g in ER- and PR-positive tumors indicate that deregulated miRNA expression is not only an indicator for poorer prognosis of breast cancer, but also future target for therapy [96]. Current studies [1,97-103] have shown that several miRNAs play critical roles in the modulation of ERα expression and ERα-mediated signaling in breast cancer cells.

Some microRNAs have been recognized as prognostic markers in breast cancer. For instance, overexpressions of miR-16, miR-155 or miR-374 are associated with better prognosis while underexpression of miR-125b is linked to worse prognosis. Three “risk-associated” miRs (miR-125b, miR-655 and miR-421) and four “protective” miRNAs have been revealed (miR-16, miR-374a, miR-374b and miR-497) are negatively and positively associated with distant disease free survival (DDFS), respectively [104]. MiR-210 over-expressed in TNBC compared to ER+ [105], is an independent prognostic factor in TNBC; decreased levels of miR-210 showed better distant-free-survival (DFS) in TNBC and no relapse 5 years following surgery in node negative TNBC [106]. MiR-34b, a member of the p53-regulated miR-34 family [107], is negatively associated with DFS and overall survival (OS) [3,108].

In TNBC, XBP1 has a critical role in the tumorigenicity and progression. In breast cancer cell line models, decreased levels of XBP1 inhibits tumour growth and tumour relapse and reduced the CD44 high CD24 low population [109]. Tumour cells expressing CD44 high CD24 low have been shown to mediate tumour relapse in some instances [110-112]. XBP1 pathway activation is associated with poor patient survival in TNBC patients, indicating that unfolded protein response (UPR) inhibitors in combination with standard chemotherapy may improve the effectiveness of antitumour therapies [109]. Recent findings suggest that XBP1 branch of the UPR has a major role in TNBC and signify that targeting this pathway may offer alternative treatment strategies for this aggressive subtype of breast cancer [109].

ID4 is a transcription factor of the helix-loop-helix protein family whose expression is inversely correlated with that of ER. ID4 is expressed in breast cancer, particularly triple negative breast cancers [113] and can negatively modulate BRCA1 expression [114]. Increased expression of ID proteins has been reported in several cancer types [115-117] and has been found associated with loss of differentiation, enhanced malignancy and aggressive clinical behavior [117,118]. ID4 is involved in mammalian embryogenesis, angiogenesis and in the maintenance of cancer stem cells [92,119,120]. Furthermore, ID4 overexpression is linked to the anchorage-independent growth exhibited by breast cancer cells [70], while its underexpression dictate their morphological change to large and flat epithelial phenotypes [121]. The finding that ID4 is a negative modulator of the tumor suppressor gene BRCA1 [3,122-124] supports an oncogenic function of ID4. In breast cancer, miR-342 which has been speculated to have a role in reducing the expression of BRCA1 [125] is associated with better prognosis [126,127]. The reports of Crippa et al. [114] reported an inverse correlation between ID4 and miR-342 and also between ID4 and BRCA1 expression [114]. According to their reports [114], overexpression of miR-342 in breast cancer cells depleted ID4 and induced BRCA1 overexpression, suggesting a viable position of this mechanism in breast cancer. The inverse correlation between ID4, miR-342 and BRCA1 expressions in TNBC could be used as a prognostic tool or marker in TNBC management. This review suggests that inhibiting miRNA target oncogenes may provide definite framework for clinical breast cancer therapy [114].

6. CONCLUSION

The correlation between TNBC, BRCA mutation and KRAS oncogene suggests that age, hormone levels and environmental factor play critical roles in the emergence of Triple-negative breast cancer in certain ethnic groups. The age, hormonal, ethnic and environmental factors, one way or the other, directly or indirectly, affect the expressions of some pro-oncogenes and miRNAs in biological systems. The discovery of miRNAs which function by modulation of some target oncogenes have provided prognostic markers and created future possible therapeutic frameworks for TNBC, which is due to the fact that certain target oncogenes have been successfully altered through inhibitory systematic pathways. This review gives knowledge of the

characteristic features of TNBC and its risk factors, especially the BRCA1 mutation, KRAS and ID4 oncogenes, and the place of Epithelial-to-Mesenchymal Transition (EMT) in TNBC progression. However, more studies on nutritional and environmental factors are required to unveil the direct relationship between TNBC and ethnicity.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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