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MicroRNAs and Their Impact on Breast Cancer, the Tumor Microenvironment, and Disparities

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Abstract

Breast cancer is a worldwide health issue as it represents the leading cause of cancer in women and the second-leading cause of cancer-related mortality in women, with an increasing incidence. Nothing speaks more clearly to the shocking breast cancer health disparities than the fact that African American (AA) women are as likely to get breast cancer as Caucasian American (CA) women, yet have a higher breast cancer death rate. It is becoming increasingly apparent that racial disparity in cancer exists due to molecular differences in tumor biology as well as, or in addition to, socioeconomic and standard of care issues (Albain, Unger, Crowley, Coltman, & Hershman, 2009). A greater understanding of the risk factors and biological links associated with breast cancer, will significantly impact AA communities due to the higher deaths associated with this disease in this population. microRNAs are small noncoding RNA molecules that were recently discovered as major players in the regulation of many diseases including cancer. Although, there are many studies that have investigated the role of miRNAs in breast cancer, few have investigated their role if any in breast cancer disparities. This review serves to summarize the current published literature that is involved in the study of microRNAs and their impact on breast cancer disparities.

1. INTRODUCTION

1.1 Breast Cancer

Breast cancer is the most commonly diagnosed cancer in women. In 2016, an estimated 234,000 new cases of breast cancer are expected to be diagnosed in women in the United States (Siegel, Miller, & Jemal, 2015). Breast cancer is also the second-leading cause of death among women; in fact, this accounts for 15% of all cancer deaths (DeSantis et al., 2016). Breast cancer is clinically classified into three subtypes based on the expression of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) as (1) hormone receptor positive (ER+/PR+), (2) HER2+, or (3) triple negative (the absence of all three receptors) (Ali et al., 2016; Inoue & Fry, 2016). It is

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becoming increasingly recognized as a heterogeneous disease with multiple subtypes based on molecular profiling that was used to show that breast cancer comprises at least seven different biologic subtypes (Sorlie et al., 2001), that includes luminal A, luminal B, luminal C, HER2-enriched, basal-like, claudin-low, and normal breast-like (for a review, see Kittaneh, Montero, & Gluck, 2013).

1.2 Breast Cancer Disparities

It has been well established that breast cancer affects African American (AA) women at disproportionate rates, AA women now have the same incidence rates as Caucasian American (CA) women, yet they have a higher breast cancer mortality rate (American Cancer Society, 2016; DeSantis et al., 2016). According to 2016 statistics from the American Cancer Society, breast cancer leads the list with 32% for the estimated highest number of new cases (30,700) in AA women. It is expected that one in nine AA women will develop breast cancer in their lifetime, while 1 in 31 will die from the disease (DeSantis et al., 2016). Surprisingly, while the disparity gap is narrowing in colon, lung, and prostate cancer (DeSantis et al., 2016), it is continuing to widen in breast cancer (Siegel, Ward, Brawley, & Jemal, 2011; Smith et al., 2011). Advancements in cancer treatment, screening, and diagnosis are helping women overall, however breast cancer incidence and death rates in AA women are steadily increasing (Zeng et al., 2015). Currently, the 5-year relative survival rate is 80% for AA women compared to 91% among CA women (DeSantis et al., 2016). Indeed, racial disparities in cancer outcomes have been observed in several malignancies. It is believed that biological and nonbiological factors play a major role in breast cancer disparity. Nonbiological factors include socioeconomic factors, access to healthcare, cultural factors, and comorbidities. A study by the Hershman group found that, after controlling for stage, demographics, socioeconomic variables, tumor characteristics, and treatment factors, disparity remained among both premenopausal and postmenopausal women who were diagnosed with early stage breast cancer (Albain et al., 2009). Therefore, it is clear that even with considerations of nonbiological factors, breast cancer racial disparities still exist due to poorly understood inherent molecular and genetic differences in tumor biology. Therefore, a greater understanding of these biological factors is critical for addressing the increased cancer mortality observed in AA women.

1.3 microRNAs

microRNAs (miRNAs) are endogenous 19–25 nucleotide noncoding RNAs that have emerged as a novel class of small, evolutionary conserved gene regulatory molecules involved in key developmental and cellular functions (He & Hannon, 2004; Wiemer, 2007). They primarily regulate gene expression by acting on target mRNAs and promoting either degradation or translational repression, depending upon complementarity (Ambros, 2004; Bartel, 2004; He & Hannon, 2004). They comprise ~3% of the human genome and regulate ~30% of transcripts (Cummins & Velculescu, 2006; Kent & Mendell, 2006). Based on location, miRNAs can be grouped into two classes, intergenic and intragenic. Intergenic miRNAs are located between protein-coding genes while intragenic miRNAs are located within the introns of protein-coding genes (Yao, 2016). A single miRNA can regulate the expression of many genes and each mRNA can be targeted by multiple miRNAs, highlighting the complexity of miRNA biology.

1.4 microRNAs and Cancer

Calin et al. were the first to show involvement of aberrant miRNA expression in cancer progression (Calin et al., 2002). In fact, approximately half of all miRNAs were found to be located in “fragile sites,” regions associated with cancer (Cummins & Velculescu, 2006) with ~73% of breast cancers exhibiting miRNA abnormalities (Zhang et al., 2006). Many studies have now shown miRNAs to function as both tumor suppressors and oncogenes (Bartel & Chen, 2004; Esquela-Kerscher & Slack, 2006; Nelson & Weiss, 2008) and have demonstrated that their dysregulation has implications in invasion, migration, and metastasis in breast cancer (Findlay, Turner, Moussa, & Watson, 2008; Huang et al., 2008; Iorio et al., 2005; Tavazoie et al., 2008). An example of an oncogenic miRNA is miR-21, that has been shown to be dysregulated in many cancers (Chan, Krichevsky, & Kosik, 2005; Slaby et al., 2007; Volinia et al., 2006; Yanaihara et al., 2006) including breast cancer (Iorio et al., 2005; Sempere et al., 2007). Clinically it has been reported that upregulation of miR-21 in primary breast cancer samples is associated with advanced clinical stage, lymph node metastasis, and poor prognosis (Yan et al., 2008). miR-21 has been shown to inhibit many tumor suppressor genes including TPM1 (Zhu, Si, Wu, & Mo, 2007), p53, PDCD4, and maspin (Zhu et al., 2008). An example of a tumor suppressive miRNA is miR-205, which was shown to be significantly downregulated in human breast tumors compared to matched normal (Wu, Zhu, & Mo, 2009). miR-205 suppresses cell proliferation, growth, and invasion by directly targeting HER3 and VEGF-A (Wang et al., 2013; Wu et al., 2009). It has also been shown to negatively regulate epithelial–mesenchymal transition (EMT) by targeting ZEB1 and ZEB2 (Gregory et al., 2008). Most recently, a group demonstrated that secretion of miR-205 from the tumor stroma promotes a cancer-associated stem cell phenotype which illustrates the importance of cellular and tissue context when studying miRNAs (Chao et al., 2014).

1.5 Circulating microRNAs

Recently, it was discovered that extracellular miRNAs circulate in the blood of both healthy and diseased patients, and they are both stable and detectable in human serum and plasma (Kosaka, Iguchi, & Ochiya, 2010; Kosaka, Iguchi, Yoshioka, et al., 2010). This allows miRNAs to be measured repeatedly and noninvasively and has sparked extensive research in miRNAs as therapeutic targets, as well as potential biomarkers of prognosis and diagnosis. The phenomenon of miRNA secretion and its role in intercellular communication has recently gained increased attention. Intensive studies have provided evidence that microvesicles, including exosomes, released from many cell types can transfer miRNAs to neighboring or distant cells, where these exogenous miRNAs function similarly to endogenous miRNAs to regulate target gene expression and recipient cell function (Kosaka, Iguchi, Yoshioka, et al., 2010; Mittelbrunn et al., 2011; Valadi et al., 2007). Therefore, secreted miRNAs may serve as a novel class of signaling molecules for mediating cell-to-cell communication.

1.6 microRNA Therapeutics

Currently, there are several companies involved in the development of therapeutically targeting microRNAs, either by overexpressing tumor suppressive miRNAs (Mirna Therapeutics) or by inhibiting oncomirs (Regulus Therapeutics). Mirna Therapeutics

currently has a mimic of miR-34 in Phase I clinical trials for various solid tumors and hematological malignancies. Regulus Therapeutics has several anti-miRs in clinical trials for various diseases but the clinical initiative for oncology is still in the pre-clinical phase, but includes anti-miR to miR-21 which we described earlier is strongly associated with breast cancer.

2. microRNAs IN BREAST CANCER DISPARITIES

There continues to be controversy surrounding the impact of the biology of tumors from AA women driving aggressive breast cancer disease compared to the impact of socioeconomic factors that can result in higher mortality rates within this racial group. Several studies have shown that the increased mortality still exists in AA women with breast cancer after normalizing for these other factors (Albain et al., 2009; Bauer, Brown, Cress, Parise, & Caggiano, 2007; Lund et al., 2009). Therefore, studies have started to address what these biological differences might be and how they may influence not only the growth of these tumors, but how therapeutically they may be targeted differently. We know that all breast cancers are not the same and we are now beginning to understand the “same” subtype of breast cancer is not the same in women of different race. A pilot study in 2012 on African women in Nigeria with breast cancer showed that the biology was highly aggressive with high grade (III) and hormone receptor negative (65% TNBC) tumors as well as young age (mean age 47 years) at diagnosis (Adisa et al., 2012). This was a similar finding to that of others focused on women from Africa and other developing nations (Bird, Hill, & Houssami, 2008; Desai et al., 2000; Dey et al., 2009; Huo et al., 2009; Lokuhetty, Ranaweera, Wijeratne, Wickramasinghe, & Sheriffdeen, 2009; Mbonde, Amir, Akslen, & Kitinya, 2001; Yarney, Vanderpuye, & Clegg Lamptey, 2008). These studies argue toward more aggressive tumor biology in women of African descent independent of their location or other contributing factors.

There is little that is currently known about the role of microRNAs in breast cancer disparities. However, there are many ways in which a miRNA can be disparate in women with breast cancer (i) up- or downregulated miRNA in AA women; (ii) up- or downregulated gene that is known to be regulated/targeted by a disparate miRNA; (iii) presence of a SNP within a 3′UTR which abolishes or creates a miR-binding site; and (iv) the up- or downregulation of a disparate gene that contains an intronic miRNA. This review will highlight the miRNAs that are disparate that fall into these four categories, some of which overlap. We will also briefly mention published studies that are suggestive of potential disparities as areas of potential future development within the field.

A study in 2012 that performed gene expression profiling of benign tissue and malignant breast tumors from AA and CA women showed 23 differentially expressed genes between tumors and 13 between benign (Field et al., 2012). The genes that were found to be differentially regulated in the AA women are highlighted in Table 1 together with the miRNAs that have been experimentally validated to target them according to miRTarBase (Chou et al., 2016). Of interest the two genes in the signature (CRYBB2 and PSPHL) were also identified in this study as being disparate. However, in subsequent studies it was shown that AA women with invasive breast cancer are less likely (6%) to have deletion of the

genome (7p11) where PSPHL resides (compared to 61% CA with invasive breast cancer). In addition, this study showed that the frequency of the deletion did not differ in AA women with and without invasive breast cancer, and that deletion of PSPHL was not associated with any pathological characteristics (Rummel, Penatzer, Shriver, & Ellsworth, 2014). Therefore, the authors concluded that elevated levels of PSPHL caused by retention of a 30 kb region of 7p11 in AA women does not contribute to cancer disparities, but instead represents population stratification. In contrast to this, another group independently identified both CRYBB2 and PSPHL as being disparate between AA and CA women with luminal A breast cancer (D'Arcy et al., 2015). These two genes were identified along with four others (ACOX2, MUC1, SQLE, and TYMS) that were differentially expressed and associated with survival (Table 2). For all six genes, tumors in AA had higher expression of poor prognosis genes (CRYBB2, PSPHL, SQLE, and TYMS) and lower expression of good prognosis genes (ACOX2 and MUC1). Similar to the previous study, this group also found PSPHL, along with CRYBB2, to be higher in AA normal tissue. However, their interpretation is that this may precede malignancy and contribute to mortality disparities.

As mentioned earlier, circulating microRNAs are of great interest due to their stability within bodily fluids, they have the potential as noninvasive biomarkers of early detection, diagnosis, treatment choice/response, and prognosis. Therefore, many studies have started exploring the differences in miRNA profiles in cancer, including the pilot study by Zhao et al., examining circulating miRNAs as potential biomarkers of early stage breast cancer (Zhao et al., 2010). Of interest, the study samples represented both AA and CA women with early stage breast cancer and race-matched controls. Microarray analysis showed that in women with early stage breast cancer, 9 miRNAs were up- and 9 were downregulated in AAs and 17 were up- and 14 were downregulated in CAs when compared to race-matched healthy controls, with only 2 miRNAs that overlapped between races (Table 3). These results, while preliminary, suggest that it might be necessary to develop race-specific circulating miRNA-based biomarkers in breast cancer early detection. It also suggests that there is validity to performing these same studies in different subtypes of breast cancer as well as in different stages of breast cancer.

Links between these dysregulated miRNAs and implications for breast cancer are highlighted later.

2.1 Upregulated in AA Women

miR-425 was shown to be upregulated in AAs and has been shown to negatively regulate PTEN in breast cancer, a well-established tumor suppressor (Ahir et al., 2016). miR-425 was also shown to be expressed at high levels in breast cancer as part of a nine miRNA signature to detect ER+ breast cancer vs healthy controls (Kodahl et al., 2014). An interesting study in rats showed a downregulation of miR-425 in the mammary glands of once pregnant rats compared to virgin controls in the ALDH+ mammary epithelial cell population, which could suggest an anticarcinogenic or protective role after pregnancy (Nandy et al., 2014). Some studies also suggest its tumor suppressor function, but we highlight here the effects on tumor promotion.

miR-483-5p was shown to be upregulated in cisplatin resistant tongue squamous cell carcinoma (Fan et al., 2015). This could have implications for breast cancer as platinum agents are used to treat TNBC patients, especially as this subtype is more prevalent in AA women, and this study also showed that high levels of miR-483-5p led to poor/lower overall survival (OS) (Fan et al., 2015). Elevated levels of miR-483 were also observed in higher stages (III and IV vs I and II) of ovarian cancer (Zheng et al., 2013). This has implications for cancer disparities as ovarian cancer mortality rates are higher in AA women (American Cancer Society, 2016).

miR-485-3p is generally considered to be a tumor suppressor in breast cancer (Anaya-Ruiz, Bandala, & Perez-Santos, 2013; He et al., 2014; Lou et al., 2016), but is part of a cluster of miRNAs that are dysregulated in chromosomal region 14q32 that have been implicated in cancer.

miR-431 has no published studies directly related to breast cancer, however, elevated levels have been shown to distinguish stage IV colorectal cancer from controls as part of a three circulating miRNA signature (Kanaan et al., 2013). Elevated levels have also been shown to be upregulated in vestibular schwannomas when compared to control nerves (Torres-Martin et al., 2013) and are correlated with OS in pancreatic cancer patients (Schultz et al., 2012). This same pancreatic study showed that miR-431 expression ranked sixth out of nine in the strongest predictive abilities for OS and 5th out of 14 in 2-year follow up. Decreased levels have been shown to inhibit cellular proliferation in glioblastoma by upregulation of its direct target SOCS6 and subsequent suppression of the JAK-STAT signaling pathway (Tanaka et al., 2014).

miR-493 is upregulated in male breast cancer (Lehmann et al., 2010). High levels are also associated with resistance to microtubule drugs (e.g., paclitaxel), advanced forms of ovarian cancer, and reduced survival of ovarian and breast cancer patients with aggressive tumors (Tambe et al., 2016). This study also suggested that intratumoral profiling of miR-493 could have diagnostic value in predicting the efficacy to taxane chemotherapy. In TNBC, miR-493 is part of a four miRNA signature that allowed subdivision of TNBCs into high and low risk groups. They were also able to clearly identify worse outcome patients in the treated and untreated subcohorts, therefore having both diagnostic and prognostic value (Gasparini et al., 2014).

miR-558 has no published studies directly related to breast cancer, however it has been shown to be upregulated in neuroblastoma (Qu et al., 2015; Shohet et al., 2011) and upregulated in response to high doses of radiation in fibroblasts (Maes, An, Sarojini, Wu, & Wang, 2008). This could have implications in the tumor microenvironment as outlined in Section 3.

miR-331-5p has no published studies directly related to breast cancer, however elevated levels in colorectal cancer patients, as part of an eight miRNA signature, can distinguish polyps from controls with high accuracy (Verma et al., 2015). Elevated circulating levels are correlated with hepatocarcinogenic progression in rats (Sukata et al., 2011). Elevated levels are found in acute and chronic lymphocytic leukemia (Zanette et al., 2007) but in acute

myeloid leukemia downregulated miR-331-5p is associated with worse response to therapy and shorter survival (Butrym et al., 2015).

2.2 Downregulated in AA Women

miR-409-5p has no published studies directly related to breast cancer, however stromal-derived miR-409 was shown to drive EMT and tumorigenesis in prostate cancer (Josson et al., 2015). The most well-studied form of this miRNA is the 3p arm (miR-409-3p). miR-409 is located on chromosome 14q32 along with miR-377 which is also downregulated in AA women. Allelic deletions of this region are frequently observed in breast cancer (Kerangueven et al., 1997).

miR-642 has no published studies directly related to breast cancer, however upregulated levels are associated with increased sensitivity to cisplatin in bladder cancer cell lines (Nordentoft et al., 2012), which has potential implications for cisplatin resistance in AA breast cancer patients. miR-642 is downregulated in prostate cancer cell lines compared to normal prostate and upregulation decreased proliferation and the levels of its host gene (DOHH). In prostate cancer patients, the levels of miR-642 and DOHH were inversely correlated (Epis et al., 2012).

miR-505 was identified as part of a six miRNA signature to discriminate BRCA mutation carriers from noncarriers with 92% accuracy (Tanic et al., 2015). This could have implications for disparities based on the lower occurrence of BRCA1 mutation carriers in AA women. Circulating levels of miR-505 were shown to be upregulated in pretreated breast cancer patients compared to healthy controls (Matamala et al., 2015). This is contrary to the reported decreased levels of miR-505 in breast tumor tissue suggesting miR-505 as a tumor suppressive miRNA (Yamamoto et al., 2011). However, this is not unusual as intratumoral levels and circulating levels within the same patient have been shown to not always positively correlate. This study reported the genomic deletion of miR-505 in adriamycin-resistant MCF7 cells (MCF7/ADR), suggesting its role in conferring sensitivity to adriamycin. This could have implications for treatment choice for AA women with breast cancer. Interestingly, the study showing elevated circulating miR-505 levels in pretreated patients also reported its decrease in a group of treated patients (Matamala et al., 2015). Elevated miR-505 levels have been shown to strongly and significantly correlate to high proliferation, ER negativity, and cytokeratin 5/6 positivity in lymph node negative breast cancers (Jonsdottir et al., 2012). These data together support the potential utility of miR-505 to monitor treatment response and highlight its potential clinical value as a noninvasive biomarker for breast cancer detection, typing, and surveillance.

miR-377 was identified as part of a four miRNA signature to identify PR+ status in breast cancer (Lowery et al., 2009). A positive correlation was also observed between miR-377 and recurrence score (RS) from Oncotype DX® (Emmadi et al., 2015). Oncotype DX® testing is for treatment stratification of ER+, lymph node negative breast cancers. The RS is represented by a number 0–100, which correlates to a specific likelihood of breast cancer recurrence within 10 years of initial diagnosis (Paik et al., 2006).

miR-340 has been shown to inhibit migration, invasion, and metastasis of breast cancer by targeting the wnt pathway (Mohammadi-Yeganeh et al., 2016), MYO10 (Chen et al., 2016), and c-met (Wu et al., 2011). Similar to that described earlier for miR-505, miR-340 can distinguish BRCA1 mutation carriers from noncarriers (Tanic et al., 2015). miR-340 loss has been associated with lymph node metastasis, high tumor histological grade, clinical stage, and shorter OS in breast cancer tissue specimens (Wu et al., 2011).

Let-7d expression is correlated with better OS in the ER−/HER2− subtype of breast cancer (Lee et al., 2016). In the hallmark study, characterizing the miRNAs that are dysregulated during breast cancer progression, let-7d was shown to be downregulated during the transition from normal to DCIS and then upregulated during the transition from in situ to invasive breast cancer (Volinia et al., 2012). It has also been shown that LIN28 promotes tumorigenic activity by suppressing let-7d miRNA maturation in breast cancer cells (Sakurai et al., 2012).

The Singh group recently performed cytokine profiling in serum samples from AA and CA breast cancer patients and identified resistin (RETN) and IL-6 as being elevated in AA women (Deshmukh et al., 2015). Although there are no known miRNAs that are validated to target resistin, several have been validated for IL-6 (miR-223-3p, let7a-5p, miR-203a-3p, miR-142-3p, miR-26a-5p, miR-365a-3p, miR-107, let-7c-5p, and miR-149-5p) and although none of these have been specifically linked to be disparate in breast cancer there are many other miRNAs that are predicted to target both of these genes that may be disparate including miR-505, which as described earlier is downregulated in the circulation of AA women with breast cancer and is predicted to target RETN (Agarwal, Bell, Nam, & Bartel, 2015).

Tamoxifen sensitivity varies among breast cancer patients and ~35% of patients are reported to not respond (Clarke, Leonessa, Welch, & Skaar, 2001). In addition, although AA women are less likely to get ER+ breast cancer compared to CA women, most of the pharmacogenomics research on tamoxifen therapy has been conducted in patients of Caucasian ancestry. Therefore, a study was performed to evaluate genetic variants related to tamoxifen therapy in African-derived samples (Weng, Ziliak, Lacroix, Geeleher, & Huang, 2014). This study used an integrative “omic” analysis for tamoxifen sensitivity and identified 50 single nucleotide polymorphisms (SNPs) that were associated with cellular sensitivity to endoxifen (an active metabolite of tamoxifen) through their effects on 34 genes and 30 miRNAs. Of the SNPs identified some were common to both ancestries but others were unique to the African samples, warranting further study.

Another group examined genetic variants in 145 SNPs in 6 miRNA processing genes and 78 miRNAs whose targets are important for breast cancer between AA and CA women and observed that the allele frequencies of most (87%) of the SNPs differed significantly by race (Yao et al., 2013). Of note, no associations were observed in both the AA and CA populations. However, one limitation of the study was a lack of a validation population and therefore further study is needed to validate the findings and to explore the genetic basis and underlying mechanisms of the associations. The Carolina Breast Cancer study also investigated association of germline microRNA SNPs in pre-miRNA flanking regions and

breast cancer risk and survival among AA and CA women (Bensen et al., 2013). They genotyped nine SNPs within six pre-miRNA gene sequences and found two miR-185 SNPs, rs2008591 and rs887205, that were inversely associated with breast cancer risk in AA women. They also identified two SNPs, rs4938723 in miR-34b/34c and rrs6920648 in miR-20b that were associated with breast cancer survival overall. Similar to the previous SNP study described further validation is required to confirm these findings.

3. microRNAs IN TUMOR MICROENVIRONMENT

The impact and significance of the tumor microenvironment (or stroma) on tumor biology is becoming increasingly clear. Many studies are now focused on the different cellular types within the stroma, including immune cells, fibroblasts, and endothelial cells and their impact on tumor “epithelial” cells. However again, few studies have assessed the tumor microenvironment and how it might differ between women of different race. The Nigerian study mentioned earlier also reported a high infiltration of tumor-associated macrophages (TAMs) in these tumors (Adisa et al., 2012). The occurrence of high numbers of macrophages in the tumor stroma has been associated with tumor progression and poor prognosis in breast and other solid malignancies. Tissue sections were stained with CD68 plus PCNA, which marks a subset of TAMs that have been shown to be associated with poor outcomes in breast cancer (Campbell et al., 2011; Mukhtar et al., 2011). They found that 82% of the cases had high levels of CD68/PCNA positive TAMs and that they were more prevalent in hormone receptor (HR) negative or triple-negative cases, compared to hormone receptor positive cases. A second marker, Mac387, was also used and they found 65% of the cases had high numbers of Mac387 cells. As with the CD68/PCNA TAMs, Mac387 cells were most prevalent in HR- or triple-negative tumors. Since then, a study was published showing that macrophage numbers were significantly higher in tumors from AA (90% positive) and Latina (89% positive) than in Caucasian women (40% positive) in the United States (Carrio et al., 2013), although in this study they only used a single marker to identify the TAMs (CD68) and this study was performed in small ER+ breast cancers.

A study looking at the normal breast microenvironment of premenopausal women found that the fibroblasts from AA and CA women differentially influenced the behavior of breast cancer cells both in vitro and in vivo (Fleming et al., 2010). Whole breast extracellular matrix (ECM) was isolated from CA and AA women and they found that ER−/PR− cells were significantly more aggressive when in contact with AA ECM. In contrast ER+/PR+ cells were more aggressive with CAECM contact. They also performed mass spectrometry of the isolated ECM and showed that only 22% of the proteins that were identified were in common. Of interest, the AA proteins associated with breast cancer that they identified were primarily related to tumorigenesis/neoplasia, while CA unique proteins were involved with growth/metastasis.

A study was published in 2009 looking at the tumor microenvironment differences between AA and CA women with breast cancer (Martin et al., 2009). They performed genome-wide mRNA expression analysis specific to the tumor epithelium and stroma and found that many genes were differentially regulated between them. Very few miRNAs that target these genes

have been validated (highlighted in Table 4) but it could be of particular interest therapeutically to identify the miRNAs that target these disparately regulated genes.

Of interest, gene ontology and disease association analyses indicated that pathways related to tumor angiogenesis and chemotaxis could be functionally different between AA and CA women and they further demonstrated higher levels of microvessel density and TAMs in AA tumors, which closely matches the studies described earlier. The authors had previously shown that PSPHL and CRYBB2 could be used as a two gene classifier to differentiate between AA and CA prostate cancer patients (Wallace et al., 2008). Therefore, to test if similar signatures exist in breast cancer, they applied the same prediction analysis and found that the two gene signature could also distinguish between the breast tumor epithelia from AA (94%) and CA (100%) women. They confirmed this result in 55 additional breast tumors (27 AA and 28 CA) and correctly classified 93% of the AA patients and 86% of the CA patients.

The inhibition of let-7d in epithelial cells, one of the miRNAs that was shown to be downregulated in the circulation of AA women with breast cancer, has been shown to cause changes associated with an EMT when inhibited both in vitro and in vivo (Willis et al., 2005). A study then focused on whether the expression of let-7d in fibroblasts was able to alter their mesenchymal features. They showed that expression of let-7d was able to decrease mesenchymal markers α-smooth muscle actin, N-cadherin, fibroblast-specific protein-1 and fibronectin, as well as increase in epithelial markers tight junction protein-1 and keratin 19 (Huleihel et al., 2014). They further went on to show that let-7d expression could phenotypically alter fibroblasts including delaying wound healing and reducing mobility and proliferation. This has implications for the activation of fibroblasts in the tumor microenvironment to cancer-associated fibroblasts which are known to promote aggressive tumor growth and metastasis (Qiao, Gu, Guo, Zhang, & Fu, 2016). Let-7d has also been shown to suppress growth, metastasis, and tumor macrophage infiltration in renal cell carcinoma (Su et al., 2014), suggesting that the loss of let-7d in AA women has implications for the entire tumor population of cells not just the epithelium.

4. SUMMARY AND FUTURE PERSPECTIVES

Although a few studies have begun to investigate the potential role of miRNAs in breast cancer disparities, there is still a lot that is currently unknown. However, it is clear from a review of the literature that we are beginning to understand that miRNAs are a major player in the dysregulation that occurs in women leading to the initiation and progression of breast cancer. It is also clear that the tumor biology of breast cancer in women can differ not only by subtype but by race, explaining, at least in part, the increased mortality observed in AA women with breast cancer. Although there are many issues that can lead to an increase in mortality, and it is critical that these are addressed, one can no longer argue that the tumor biology between different racial groups is the same. If we hope to reduce breast cancer disparities, we must make a concerted effort to study the differences in tumor biology so that we may reduce mortality rates in all women. This information is critical if we want to address the problem of breast cancer and develop treatment strategies with a personalized medicine approach.

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Table 1

miRNAs That Are Validated to Target Differentially Regulated Genes in AA Women with Breast Cancer From the Ellsworth Group (Field et al., 2012)

Gene Symbol	Gene Name	Up- or Downregulated in AA	Validated miRNAs	Intronic RNAs
SOS1	Son of sevenless homolog 1	Up	miR-124-3p	
COIL	Coilin	Up	miR-1-3p let-7b-5p miR-98-5p	
CRYBB2P1	Crystalline beta B2 pseudogene 1	Down	0	MIR6817
EIF2S1	Eukaryotic translation initiation	Down	miR-375	
GOLPH3L	Golgi phosphoproteinn 3-like	Down	miR-16-5p miR-15a-5p	
LTF	Lactotransferrin	Down	miR-214-3p	
RABEP1	Rabaptin, RAB GTPase binding effector protein 1	Down	miR-373-3p	
RYBP	RING1 and YY1 binding protein	Down	miR-9-5p	
ZNF395	Zinc finger protein 395	Down	miR-122-5p miR-525-3p	
AR	Androgen receptor	Down	miR-488-5p, miR-124-3p, miR-185-5p, miR-34a-5p, miR-205-5p	
GPD1L	Glycerol-3-phosphate dehydrogenase 1-like	Down	miR-210-3p	
ABLIM1	Actin-binding LIM protein 1	Down	miR-34a-5p	
INSR	Insulin receptor	Down	miR-195-5p	

Validated miRs are based on those annotated in miRTarBase 2016 with either one or more strong evidence and two or more less strong evidence (Chou et al., 2016).

Table 2

miRNAs That Are Validated to Target Differentially Regulated Genes in AA Women with Luminal A Breast Cancer From the Troester Group (D'Arcy et al., 2015)

Gene Symbol	Gene Name	Up- or Downregulated in AA	Validated miRNAs	Intronic RNAs
SQLE	Squalene epoxidase	Up	0	
TYMS	Thymidylate synthetase	Up	Let-7b-5p miR-196a-5p miR-433-3p	
ACOX2	Acyl-CoA oxidase 2, branched chain	Down	miR-26b-5p	
MUC1	Mucin 1, cell surface associated	Down	miR-145-5p miR-1226-3p miR-125b-5p miR-124-3p miR-455-3p	

Validated miRs are based on those annotated in miRTarBase 2016 with either one or more strong evidence and two or more less strong evidence (Chou et al., 2016).

Table 3

Circulating miRNAs That Are Uniquely Differentially Regulated in AA Women with Early Stage Breast Cancer (Zhao et al., 2010)

microRNA Name	Genomic Location	Up- or Downregulated	Validated Target mRNAs	Intronic/Intergenic
miR-425	3p21	Up	CCND1	DALRD3
miR-483-5p	11p15	Up	SRF, MAPK3, FAM160B2, ALCAM	IGF2
miR-485-3p	14q32	Up	NTRK3, NFYB, SLC40A1, MAT1A	Intergenic
miR-431	14q32	Up	0	RTL1 (as)
miR-493	14q32	Up	RHOC, MAP2K7, FZD4	Intergenic
miR-558	2p22	Up	0	BIRC6
miR-331-5p	12q22	Up	0	Intergenic
miR-409-5p	14q32	Down	0	Intergenic
miR-642	19q13	Down	DOHH	GIPR
miR-505	Xq27	Down	SRSF1	ATP11C
miR-377	14q32	Down	PPM1A, PAK1, SOD1, SOD2	Intergenic
miR-340	5q35	Down	MET	RNF130
Let-7d	9q22	Down	HMGA2, APP, DICER, SLC11A2, PDGFA, IL13, MPL, EIF2C1, TNFRSF10B	Intergenic

Genes that are validated targets of the identified miRNAs are based on those annotated in miRTarBase 2016 with either one or more strong evidence and two or more less strong evidence (Chou et al., 2016).

Table 4

miRNAs That Are Validated to Target Differentially Regulated Genes in AA Women with Breast Cancer From the Ambs Group (Martin et al., 2009)

Gene Symbol	Gene Name	Up- or Downregulated in AA	Validated miRNAs	Intronic miRNAs
PSPHP1 (PSPHL)	Phosphoserine phosphatase pseudogene 1	Up (Epithelium and Stroma)	0	
AMFR	Autocrine motility factor receptor	Up (Epithelium)	miR-376a-5p, miR-29a/b/c-3p	
EDG2 (LPAR1)	Lysophosphatidic acid receptor 1	Down (Epithelium)	miR-200c-3p, miR-23a-3p	
CXCL10	C-X-C motif chemokine ligand 10	Up (Stroma)	miR-21	
SLC38A1	Solute carrier family 38 member 1	Up (Stroma)	miR-16-5p, miR-30a-5p	
PSMA2	Proteasome subunit alpha 2	Up (Stroma)	miR-132-3p	
LASS6 (CERS6)	Ceramide synthase 6	Up (Stroma)	0	MIR4774
SOS1	SOS Ras/Rac guanine nucleotide exchange factor 1	Up (Stroma)	miR-124-3p	
ARF4	ATP ribosylation factor 4	Up (Stroma)	miR-1-3p, miR-7-5p	
GGCT (C7orf24)	Gamma-glutamylcyclotransferase	Up (Stroma)	Let-7b-5p	
PTRF	Polymerase 1 and transcript release factor	Down (Stroma)	miR-124-3p	
NUAK1	NUAK family kinase 1	Down (Stroma)	miR-211-5p	
AQP1	Aquaporin 1	Down (Stroma)	miR-320a	

Validated miRs are based on those annotated in miRTarBase 2016 with either one or more strong evidence and two or more less strong evidence (Chou et al., 2016).