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Regulation of breast cancer metastasis signaling by miRNAs

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Abstract

Despite the decline in death rate from breast cancer and recent advances in targeted therapies and combinations for the treatment of metastatic disease, metastatic breast cancer remains the second leading cause of cancer-associated death in U.S. women. The invasion-metastasis cascade involves a number of steps and multitudes of proteins and signaling molecules. The pathways include invasion, intravasation, circulation, extravasation, infiltration into a distant site to form a metastatic niche, and micrometastasis formation in a new environment. Each of these processes is regulated by changes in gene expression. Noncoding RNAs including microRNAs (miRNAs) are involved in breast cancer tumorigenesis, progression, and metastasis by post-transcriptional regulation of target gene expression. miRNAs can stimulate oncogenesis (oncomiRs), inhibit tumor growth (tumor suppressors or miRsupps), and regulate gene targets in metastasis (metastamiRs). The goal of this review is to summarize some of the key miRNAs that regulate genes and pathways involved in metastatic breast cancer with an emphasis on estrogen receptor α (ERα+) breast cancer. We reviewed the identity, regulation, human breast tumor expression, and reported prognostic significance of miRNAs that have been documented to directly target key genes in pathways, including epithelial-to-mesenchymal transition (EMT) contributing to the metastatic cascade. We critically evaluated the evidence for metastamiRs and their targets and miRNA regulation of metastasis suppressor genes in breast cancer progression and metastasis. It is clear that our understanding of miRNA regulation of targets in metastasis is incomplete.

Keywords

miRNAs; Breast cancer metastasis; EMT; TGFβ

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1. Introduction

Depending on the breast cancer subtype, primary breast tumors are usually successfully treated by surgery, radiation, and targeted therapies. Where local disease has spread to adjacent lymph nodes or the tumor gene signature derived from multigene assays, *e.g.*, MammaPrint(R) and Oncotype DX(R), show concordance with a high risk of recurrence, specific regimes of chemotherapy are applied [1]. Breast tumors are categorized into three major subtypes based on the expression of specific protein markers: estrogen receptor α (ERα), progesterone receptor (PR), ERBB2 (also referred to as HER2) *versus* triple negative breast cancer (TNBC) which lacks ERα, PR, and ERBB2. The five year survival rate is 94–99% for ERα/PR+ and ERBB2+ breast cancers whereas it is 85% for TNBC [2]. Patients with ERα+ tumors are successfully treated with endocrine therapies that block estrogen synthesis from adrenal androgens using aromatase inhibitors (AI), *e.g.*, letrozole, in postmenopausal patients [3]. For premenopausal patients with ERα+ breast cancer, selective ER modulators (SERMs), *e.g.*, tamoxifen (TAM), that compete with estrogens for ERα, are used in combination with ovarian function suppression therapy, *i.e.*, GNRH/LHRH agonists, *e.g.*, goserelin [4–6]. Patients whose breast tumors are ERBB2+ receive monoclonal antibody therapy: trastuzumab that targets the extracellular domain of ERBB2 or pertuzumab that targets the ERBB2 dimerization domain, or neratinib that is an oral tyrosine kinase inhibitor of ERB2 family members [2]. TNBC patients, proportionally ~ 15% of all breast cancers, receive chemotherapy, but have a high risk of relapse with distant metastasis in the first 3–5 years after diagnosis [2].

Unfortunately, ~ 30% of breast cancer patients succumb to metastatic disease, sometimes decades after initial treatment, highlighting the need to understand and develop anti-metastatic therapies [7]. Mechanisms involved in acquired endocrine-resistant breast cancer have been reviewed and include amplification of growth factor signaling pathways, altered expression of coactivators and corepressors, altered intracellular location and splice variants of ERα, increased G-protein coupled ER (GPER1, also called GPER and GPR30), and dysregulation of non-coding RNAs [8–11]. For patients with ERα+ tumors who receive AI therapy, ~ 25–40% of metastatic tumors from these patients have mutations in *ESR1* (ERα) within the ligand binding domain (LBD) [12]. These LBD ‘hot spot’ mutations activate the mutant ERα in the absence of estrogen binding and reduce the efficacy of selective ER downregulators (SERDs) including fulvestrant, AZD9496, RU-58688, and GDC-0810 to block activation and degrade ERα [13]. *ESR1* Y537S and D538G mutations are associated with shorter survival [14]. Recently, inactivating mutations in *ARID1A*, a subunit of the SWI/SNF chromatin remodeling complex, were identified in metastatic tumors from patients who had received endocrine therapies and these mutations resulted in reduced progression-free survival on SERDs [15]. Knockout of ARID1A in MCF-7 human luminal A (ERα +) breast cancer cells altered chromatin accessibility for transcription factor (TF) binding including reduced ER, FOXA1, and GATA2 sites and increased TEAD4 sites while altering the transcriptome with increased expression of basal-like/stemness genes [15]. FOXA1 is higher in ER+/PR+ vs. ER−/PR− or HER2+ breast tumors and high FOXA1 confers a benefit in OS in breast cancer patients [16].

Current clinically beneficial therapy for patients with metastatic ERα+ breast cancer includes addition of the CDK4/6 inhibitors palbociclib, ribociclib, or abemaciclib in combination with letrozole [17–20]. The combination of PI3K inhibitor alpelisib and fulvestrant is approved for postmenopausal women (and men) with ERα+/HER2− advanced breast cancer [21], including the ~ 40% of patients whose tumors have PIK3CA mutations [22,23]. The mTORC1 (mTOR) inhibitor everolimus is approved in combination with the AI exemestane for ERα+/HER2− postmenopausal women after treatment failure on AIs: letrozole or anastrozole [24]. Clinical trials support the efficacy of everolimus plus fulvestrant in prolonging progression-free survival (PFS) in postmenopausal women with ERα+ primary breast tumors after recurrence on AIs [25]

A variety of non-coding RNAs (ncRNAs) have reported roles in breast cancer progression and metastasis including circular RNAs (circRNAs), PIWI-interacting RNAs (piRNA), microRNAs (miRNAs), and long noncoding RNAs (lncRNAs) [26,27]. Although together these ncRNAs constitute only ~ 1% of total cellular ncRNA, they regulate transcription, post-transcriptional stability, splicing, covalent modification, and mRNA translation [28]. In addition, ncRNA may be packaged into extracellular vesicles (EV) including exosomes [29], thus providing intercellular communication by transfer of miRNA and lncRNA, as well as other molecules, to recipient adjacent and distant cells [30]. Here we will focus on the role of selected miRNAs in regulating gene targets in pathways that contribute to breast cancer metastasis. We have not included the role of metabolic alterations in metastasis as reviewed in [31,32,33{Blücher, 2017 #31679,34].

2. Overview of miRNA in breast cancer

The current miRBase (release 22.1) reports 2,654 mature miRNAs http://www.mirbase.org/ [35]. However, there is debate about how many of these are false positives and a recent study validated ~ 2,300 human miRNAs [36]. miRNAs are short (~ 22 nt), evolutionarily-conserved, single stranded RNAs that base-pair with ~ 7 bp miRNA recognition elements (MREs) in the 3’UTR of their target mRNAs within the RNA induced silencing complex (RISC) [37]. One estimate is that > 60% of human protein-coding genes have been under selective pressure to maintain miRNA binding sites for regulation [38]. One miRNA can directly or indirectly target hundreds of mRNA thus forming a complex miRNA-mRNA network to regulate cellular processes, including breast cancer metastasis.

The biogenesis of miRNAs has been reviewed [27,39]. In brief, most miRNAs are transcribed as primary (pri)-miRNAs by RNA polymerase II. Pri-miRNAs may be co-transcribed within introns of host genes or as independent genes from intergenic regions [40]. Fig. 1 summarizes selected aspects of miRNA biogenesis and their regulation in breast cancer and metastases. Pri-miRNAs are processed to precursor (pre-miRNAs) within the nucleus by the DROSHA-DGCR8 microprocessor complex, which includes additional proteins [41,42]. DROSHA is a class 2 ribonuclease III that cleaves the hairpin-loop pri-miRNA to generate the 60–70 nt pre-miRNA that is exported from the nucleus by the Exportin (*XPO5*) and Ran-GTP (R*AN*) or Exportin1 (*XPO1*) [43]. SNPs in *DROSHA* are associated with elevated risk of breast cancer [44]. DROSHA has oncogenic or tumor suppressor activity, depending on tumor type (reviewed in [45]). Heterogeneous Nuclear

Ribonucleoprotein A2/B1 (HNRNPA2/B1) is a reader of the N(6)-methyladenosine (m6A) post-transcriptional modification of pri-miRNAs and promotes DROSHA processing to pre-miRNAs [46,47]. The DICER (*DICER1*), a Ribonuclease III,-TRBP cytoplasmic complex unwinds the double stranded pre-miRNA, allowing the one miRNA strand (called the 'guide strand') to be incorporated into the RNA-induced silencing (RISC) complex, composed of Argonaute 2 (*AGO2*), DICER, TRBP (*TRBP2*), PACT (*PRKRA*), and TNRC6 (*TNRC6A*) [48]. The other miRNA strand can also be incorporated into RISC or be degraded [49]. Selection of the miRNA strand is mediated by the relative thermodynamic stabilities within RISC [50]. There are data supporting the localization of the DROSHA microprocessor, DICER- TRBP, and RISC complexes with the adherens junction complex protein PLEKHA7 at the apical zonula adherens (ZA) of epithelial cells to regulate the expression of miRNAs, *e.g.*, miR-30, let-7, and miR-24 families, that target *SNAI1*, *MYC*, and *SOX2* to support epithelial homeostasis [51]. Whether this is true in breast ductal epithelial cells and the role for dysregulation of these interactions in breast cancer is unknown.

Among the post-transcriptional modifications of nascent transcripts, N(6)-methyladenosine (m6A) is the most common modification and for mRNAs m6A plays a role in alternative splicing, transcript stability, and translation [52]. The methyl group is added to adenosine (forming m6A) by the RNA methyltransferase complex (WTAP, METTL3, METTL14, VIRMA, and RBM15, plus additional proteins), removed by the dioxygenases ALKBH5 and FTO, with the m6A 'mark' recognized by 'readers', including YTHDC1, HNRNPC,YTHDF1, YTHDF2, and HNRNPA2/B1 [53]. METTL3 methylation of m6A on pri-miRNAs [47] and RNA-dependent interaction of HNRNPA2/B1 with DGCR8, a component of the DROSHA complex, stimulate processing of selected pri-miRNA to pre-miRNAs [46]. *METTL3* transcript expression was reported to be downregulated in breast tumors [54]. HNRNPA2B1 transcript and protein expression was higher in breast cancer cells and tumors compared with non-transformed cell lines and normal breast tissue [55,56]. Using data in Kaplan-Meier plotter (kmplot) for breast tumors [57], we reported that higher *HNRNPA2B1* is significantly associated with lower OS in breast cancer patients [58].. HNRNPA2B1 also interacts with the lncRNA *HOTAIR*, a nuclear scaffold for transcriptional repression by interacting with the PRC2/EZHW and LSD1 complexes [59], in MCF-7 cells [60]. We reported higher expression of HNRNPA2B1 in TAM-resistant LCC9 and LY2 cells compared to parental MCF-7 cells and identified the miRome regulated by overexpression of HNRNPA2B1 in MCF-7 cells [58]. A recent study reported that HNRNPA2B1 expression was lower in breast tumors with LN metastasis than DCIS and high expression correlated with longer OS [61]. The authors reported that HNRNPA2B1 knockout in MDA-MB-231 TNBC cells reduced tumor growth, but stimulated metastasis when injected subcutaneously in nude mice [61]. It is clear that further studies of HNRNPA2B1's role in breast metastasis are needed using additional clinical samples and in other breast cell and animal models.

DICER acts as a tumor suppressor in breast cancer [45]. Amplification of the miR-191/425 locus on chromosome 3p21.31 in breast tumors is associated with lower disease-free survival (DFS), and both miR-191 and miR-424 target the 3'UTR of *DICER1* in breast cancer cells [62]. miR-191 expression was increased in breast tumors relative to normal breast tissue [63] and its expression is stimulated by HIF-1α [64]. In contrast, the miR-424(322)/503 locus on Chr X was deleted from the active allele in ~14% of breast

tumors in METABRIC and TCGA data sets with loss of miR-424(322)/503 associated with poor prognosis, lower OS, and more aggressive tumor subtypes, *i.e.*, basal and luminal B [65]. One study reported higher DICER was associated with TAM-resistance, which is associated with metastatic disease [66].

High AGO2 correlated with luminal B breast cancer in one study [67]. However, another study found higher AGO2 staining in HER2+ and basal breast tumors and the authors reported that reduced AGO2 is associated with poor patient survival [68]. Overexpression of AGO2 in MCF-7 luminal A human breast cancer cells increased levels of an ERα splice variant called ERα36 (36 kDa) and stimulated E_2-induced xenograft tumor growth *in vivo* [67]. ERα36 lacks both N-terminal activation function (AF)-1 and C-terminal AF-2, contains the wildtype DBD, and has a unique 27aa C-terminal domain insertion that regulates coactivator interaction [69]. ERα36 is a plasma membrane-associated protein that is increased in breast tumors and breast cancer cells [70]. High ERα36 in primary breast tumors correlates with increased metastatic disease and reduced DFS and lung and brain metastasis have higher ERα36 IHC staining compared to the primary tumor, suggesting a role for ERα36 in metastasis [71]. ERα36 is activated by estradiol (E2) and 4-hydroxytamoxifen (4-OHT) and plays a role in endocrine resistance and cancer stem cells (CSC) [72]. ERα36 is uniquely targeted by miR-136–5p which is methylated and repressed in breast cancer cells and tumor samples [73]. Although ERα36 is increased in TAM-resistant patient-derived xenografts (PDX) [74], the expression and role of ERα36 in metastases from primary breast tumors is not yet known [70].

3. The metastatic trail in breast cancer

Metastasis is a sequential process that results from the evolutionary acquisition of features that allow tumor cells from a primary site to dissociate, disseminate, migrate, survive, extravagate, infiltrate into a distant site to form a metastatic niche, survive in a new environment, and proliferate. An overview of the pathway including selected gene and miRNA alterations is shown in Fig. 2. Processes involved in these events include activation of oncogenes, altered signaling events, upregulation of matrix metalloproteinases (MMPs), and inactivation of metastasis suppressor genes [75]. The miRNA regulation of MMPs has been reviewed [76]. Changes in the composition of the extracellular matrix (ECM) remodel epithelial-stromal-adipocyte-immune cell interactions and include mechanical stiffening in malignant transformation [77]. Increased expression of the transcription factor FRA-1 (FOSL) increases the transcription of genes in the mesenchymal transition, invasion, and metastasis, *e.g.*, urokinase-type plasminogen activator (uPA, *PLAU*,)-urokinase receptor (uPAR, *PLAUR*), MMP1, MMP9 [78]. uPA is a serine protease that binds its receptor uPAR in breast cancer epithelial cell membranes (not stromal fibroblasts or myofibroblasts) to activate certain MMPs to degrade components of the ECM including fibrin, laminin, and fibronectin (reviewed in [79]). PAI-1 (*SERPINE1*) inhibits uPA by direct binding. Hypoxia activates HIF-1α that stimulates cell proliferation, EMT, and angiogenesis in BCa [80]. Tumors cells form clusters to metastasize [81]. The tumor microenvironment, composed of tumor cells, stromal cells, cancer-associated fibroblast (CAFs), adipocytes, endothelial cells, and infiltrating innate immune cells, *i.e.*, M2-like macrophages, that inhibit or facilitate tumor cell intravasation, is critical in the process of metatastasis [82]. Tumor-associated

macrophages (TAMs) in breast tumors secrete chemokines, cytokines, and growth factors that stimulate tumor cell migration, invasion, and metastasis, *e.g.*, CSCL12, CCL2,IL-4, IL-6, IL-8, IL-13, *NOS2* (to produce nitric oxide), TGFβ, VEGFA, and EGF [83,84]. TAMS also interact with adipocytes to stimulate *CYP19A1* (aromatase) expression in adipose stromal cells (fibroblasts) to increase local estrogen (E_2 and estrone (E1)) production from adrenal androgens [85]. The appearance of metastatic disease can occur many years, even decades after initial breast cancer diagnosis in a process termed “metastatic latency” [86]. Metastatic latency is correlated with ERα expression in the primary breast tumor and ~ 60% of ERα+ breast cancer patients develop bone metastasis, followed by lung, liver and brain [86].

Metastasis is an inefficient process that results from the acquisition of genetic and epigenetic changes that enable tumor cells to survive, migrate, and then survive in a new environment to establish macroscopic foci [87]. Although we usually think of metastatic cells in circulation, either directly or in the lymphatics system, some cancer cells, *e.g.*, pancreatic duct adenocarcinoma, gastric carcinoma, head and neck cancer, prostate cancer, and colorectal cancer, migrate along nerve axons with the support of growth factors and chemokines secreted from cells in the perineural niche [88,89]. Note that higher nerve fiber density was reported in invasive ductal carcinoma (IDC) compared to ductal carcinoma in situ (DCIS) or invasive lobular carcinoma (ILC), suggesting an association with metastatic potential [90].

Only ~ <0.02% of disseminated tumor cells (DTCs) are estimated to successfully seed metastasis [91]. Notably, after colonization, DTCs either proliferate or can enter dormancy in protected niches such as bone marrow for an extended period until ‘awakened’ by intrinsic or extrinsic signals [86]. Interestingly, NR2F1 (COUP-TFI) drives a pro-dormancy gene program in ER+ breast cancer cells after hypoxia that allow cells to evade chemotherapy [92]. Follow-up studies reported that breast cancer patients with low nuclear NR2F1 in DTCs in bone marrow had systemic relapse within 12 month after bone marrow aspiration whereas those with high NR2F1 in DTCs had higher distant disease-free survival, implicating NR2F1’s role in DTC dormancy [93]. NR2F1 is translationally repressed by direct targeting by miR-21 to its 3’-UTR in mouse embryonic stem cell lines [94], but whether the known increase in miR-21 in breast cancer patients is involved in suppressing NR2F1 to release cells from dormancy is unknown.

Evidence supporting the model that metastatic spread occurs early in tumor progression and likely precedes detection of the primary tumor [95,91]. At a molecular level, early tumor cell dissemination results from tumor heterogeneity. Although tumor heterogeneity has long been recognized [96], next-generation sequencing (NGS) with single cell RNA sequencing (scRNA-seq) has revealed that within the non-treated primary tumor resides considerable cellular heterogeneity including small populations of cells already resistant to targeted therapies [97] as well as CSC, also called tumor-initiating cells [98]. Mutations in *MYC*, *TP53*, *PIK3CA*, *HER2*, and *FGFR1* occur early in the development of TNBC [99]. Studies using multiple sublines of MDA-MB-468 TNBC cells identified IL11 and VEGFD (FIGF) as drivers of metastasis in vivo (from the mammary fat pad injection site to lung and bone marrow) by activating ‘effector’ neutrophils, thought to promote the metastatic niche,

although the studies were performed in immunocompromised mice [100]. Chemotherapy can increase the metastatic potential of cancer by selecting those cells with innate resistance as well as driving the development of new mutations that endow chemotherapeutic resistance [101].

Genetic and epigenetic regulatory mechanisms contribute the phenotypic diversity of cells within a tumor, including cells that have undergone epithelial-mesenchymal transition (EMT) and transitioned to the CSC state [102]. CSC are defined by markers, *e.g.*, CD44+/CD24low, EPCAM+, ALDH1+ [103]. Primary tumors also contain what are termed "metastasis-initiating cells (MICs)" that are defined as cancer cells capable of seeding clinically significant metastatic colonies in secondary organs [91]. MICs are highly plastic and retain tumor-initiating cell capabilities, including flexibility between EMT and mesenchymal-to-epithelial transition (MET), resistance to anoikis and apoptosis, evasion of immune surveillance, and metabolic adaptability [91].

A key step in metastasis is colonization of circulating tumor cells (CTCs) in a secondary site or distant organ. CTCs are rare: usually < 1 CTC/10 ml blood in nonmetastatic cancer and 1–5 CTC/7.5 ml blood in breast cancer patients with metastatic breast cancer and have short survival time of 1–3 h in blood [104]. CTC detection in blood has been repeatedly demonstrated to define a subgroup of breast cancer patients at higher risk of relapse [104]. This step is considered the best 'open' therapeutic window in metastasis [7]. For cells to extravasate from the bloodstream and colonize a distant site, primary tumors secrete factors that induce the formation of a "pre-metastatic niche" to support the growth of the CTCs in this distant site. The pre-metastatic niche is a supportive microenvironment, colloquially called the "soil" into which the CTC are the "seeds" which grow into a metastatic tumor [105].

Molecules secreted from the primary tumor regulate pre-metastatic niche formation, thus promoting metastasis. Among the molecules known to be secreted from tumors that stimulate pre-metastatic niche formation are EVs, including exosomes, as well as growth stimulatory factors. The C-X-C motif chemokine ligand 12 (CXCL12):C-X-C motif chemokine receptor 4 (CXCR4) signaling axis promotes breast cancer cell homing and colonization from the primary tumor to the bone [106,86]. Interestingly, in breast tumors, high miR-4784 is a bad prognostic indicator whereas higher expression of its target CXCL12 is a good prognostic indicator [107]. A recent gene expression profiling study of miRNA and mRNA expression in the spontaneous MMTV-NeuT mouse model of mammary carcinogenesis identified pre-invasive changes, *i.e.*, upregulation of circulating miR-29 and miR-23 family prior to invasion of the bone marrow [108]. They determined that the increase in miR-29 family members was coming from circulating immune cells whereas miR-23 family members originated in the mammary epithelium. They found that miR-23a-3p was upregulated in the blood of breast cancer patients [108]. They reported that the increase in miR-29a-3p and miR-29c-3p downregulated *SPARC* (Osteonectin) and protein in the bone marrow which is associated with metastasis. This mouse study demonstrates that circulating miRNAs may impact genes that regulate bone marrow metastasis Interestingly, TGFβ increases miR-23a expression in MCF-7 and MDA-MB-231 cells and miR-23 also directly targets *CDH1* [109]. Knockdown of miR-23a reduced MCF-7

and MDA-MB-231 cell migration and invasion *in vitro* and lung tumor metastases in mice injected with MDA-MB-231-anti-miR-23a inhibitor [109]. These data suggest a role for high miR-23a in breast tumors in invasion and migration *in vivo*.

4. MetastamiRs and their targets in breast cancer

Other investigators have previously [110,111] and more recently reviewed the role of specific miRNAs in pathways in breast cancer invasion and metastasis [112,80,113,114]. miRNAs dysregulated either by upregulation or downregulation and associated with metastasis are called “metastamiRs” and include reported upregulation of 13 miRNAs, *e.g.*, miR-9–5p, miR-10b-5p, miR-21–5p, miR-29 family members, and miR-520–3p, and downregulation of 23 anti-metastatic miRNAs, *e.g.*, miR-141–3p, miR-200 family members, miR-31–5p, and miR-15b-5p [115,110] (Table 1). We reviewed the literature in PubMed with respect to previously reported metastamiR expression in human breast tumors and their metastases, gene targets, and *in vitro* human breast cancer cell line studies to update our understanding of metastamiRs in breast cancer. Some of the papers identifying miRNAs as metastamiRs have been retracted; thus, necessitating reconsideration of the role of certain miRNAs. Specifically, two papers from Weinberg’s lab reporting that levels of anti-metastatic miR-31–5p primary breast tumors were inversely associated with the propensity for metastatic relapse were retracted [116,117]. There is one report of reduced miR-31–5p in invasive ductal carcinomas (IDC) *vs*. ductal carcinoma *in situ* (DCIS) [118]; however, another report came to the opposite conclusion [119]. The anti-invasive phenotype of miR-31–5p is mediated by its suppression of the expression of integrins, including *ITGA2*, *ITGA5*, *ITGAV*, *ITGB1*, *ITGB3*, and *ITGB5* (242) (Table 1). Further study is needed to clarify the role of miR-31–5p in metastatic spread in breast cancer.

The pro-metastatic miRNAs show increased expressing in breast tumors with stage and correlate with reduced DFS, relapse free survival (RFS), and/or overall survival (OS). For example, miR-9–5p is overexpressed in high stage tumors, with high histological grade, and was reported to be higher in HER2+ and TNBC compared to other breast cancer (BCa) subtypes [120]. However, this increase in miR-9–5p was not found in an analysis of TCGA data [121]. Other reports found that patients whose breast tumor have high miR-9 show lower OS and DFS [122,123]. E-Cadherin (*CDH1*) [124] and leukemia inhibitor factor receptor (*LIFR*), a metastasis suppressor [125], are direct targets of miR-9–5p in breast cancer, contributing to EMT and metastasis.

miR-21–5p is a well-established oncomiR [126] that downregulates a number of tumor suppressors notably *PTEN*, *PDCD4*, and *TPM1* (Table 1). The expression of miR-21 is increased in breast tumors and plasma from BCa patients [127]. High miR-21 in breast tumors correlates with lymph node status and tumor stage (150). miR-21–5p is also secreted by CAFs in BCa [128]. miR-21 is a potential plasma/serum biomarker for BCa with a sensitivity of 0.79 [129]. TGFβ and BMP signaling increase miR-21 transcription by activating SMAD2/3 [130]. Transient knockdown of miR-21 in TAM-resistant MCF-7 cells enhanced autophagy in response to TAM or fulvestrant and inhibited the PI3K-AKT-mTOR pathway [131]. miR-21 has been confirmed to maintain the malignant phenotype in various

cancers and thus is of significant interest in the development of therapeutic ablation by DNAzymes, antimiRs, antagomiRs, miRNA sponges, or miRNases [132,133].

In contrast, miR-143–3p was reported to be pro-metastatic in BCa [75] although its expression is downregulated in BCa tissues [127,134]. The decrease in miR-143–3p expression induces RAS signaling to promote aggressive PTEN-deficient basal-like BCa [135]. With the decrease in miR-143–3p expression of its pro-metastatic targets, *e.g.*, *KRAS*, *HRAS*, and *CD44*, would be increased (Table 1).

miR-182–5p was reported to be pro-metastatic [136]; however, overexpression of miR-182–5p inhibited invasively aggressive properties of MDA-MB-231 cells *in vitro* (167). Likewise, miR-182–5p overexpression in MCF-10A immortalized breast epithelial cells increased E-cadherin and decreased vimentin (*VIM*) *in vitro* (168). In agreement with its pro-metastatic role, hsa_circ_0025202 expression is decreased in correlation with histological grade and lymph node status and because circ_0025202 is a miRNA sponge for miR-182–5p, its decrease would increase miR-182–5p levels [137]. In a mouse model of metastatic breast cancer, injection of mouse mammary tumor 4T1 cells in the mammary fat pad resulted in lung metastases that had high miR-182 expression [138].

Overexpression of pro-metastatic miR-520c-3p induces MCF-7 and MDA MB-435 cell migration and invasion *in vitro* and promotes tumor metastasis in a tail vein injection mouse model *in vivo* [139]. In contrast, another paper found that miR-520c-3p overexpression inhibits invasion and migration of MCF-7 and T47D human luminal A breast cancer cells [140]. Overexpression of miR-520c-3p inhibits TGF-β signaling, *i.e.*, phosphorylation of SMAD2 and SMAD3, and decreases target genes *ANGPTL3*, *PTHLH*, and *SERPINE1* (PAI-1) in MDA-MB-231 TNBC cells *in vitro* [141]. lncRNA *HOXA-AS2* acts as a miRNA sponge for miR-520c and its increased expression is detected in patients with distant metastasis [142]. The increase in HOXA-A2A would be expected to reduce miR-520c levels and increase miR-520c targets such as *CD44* and *XPNPEP1* (X-Prolyl Aminopeptidase APP1) (Table 1). *XPNPEP1* is upregulated in BCa, is a predictor or poor prognosis and metastases, and overexpression of *XPNPEP1* in MDA-MB-231, MT474, MCF-7 breast cancer cells increases cell migration [143].

Although miR-373 targets *ESR1* (ERα) [144], it is a pro-metastatic as indicated in experiments demonstrating that its overexpression induces MCF-7 (luminal A) and MDA MB-435 (TNBC) cell migration and invasion *in vitro* and that it promotes tumor metastasis in a tail vein injection mouse model *in vivo* [139]. miR-373 directly targets integrin α2 (*ITGA2*), a collagen receptor on epithelial cells that leads to cell migration in BCa cells and ITGA2 protein is reduced in breast tumors [145]. Transfection of MCF-7 cells with miR-373 induced EMT by inhibiting *TXNIP* resulting in HIF-1α activation and increased TWIST1 [146]. Expression of miR-373 is higher in breast tumors with lymph node positive disease [139] and serum concentrations are higher in patients with metastatic disease at diagnosis [147].

There are four members of the miR-29a/b/c family located on 2 human chromosomes. Chromosome 1q32.2 is the location of miR-29b-2 and miR-29c [148,149]. miR-29b-1 and

miR-29a are encoded on chromosome 7q32.3 [150–152]. All miR-29 family members have the same seed sequence [149]. miR-29 family members were reported to have higher expression in Luminal A and B breast tumors compared with basal and HER2+ tumors {Chou, 2013 #22972}. GATA3 overexpression in MDA-MB-231 TNBC cells increased the levels of luminal gene expression, *e.g.*, *CDH1*, *KRT8*, and miR-29a/b-1 (from a common promoter), while reducing mesenchymal markers, *e.g.*, *ZEB1*, *ZEB2*, *FN1*, *SNAI1*, *SNAI2*, and *VIM*, with miR-29b downregulating *ANGPTL4*, *LOX*, *MMP2*, *MMP9*, *PDGF* and *VEGFA* [153]. miR-29 family members have both tumor suppressor and oncogenic activities in breast cancer (reviewed in [154]). We reported that transient overexpression of miR-29a and miR-29b-1in MCF-7 cells and TAM-resistant LCC9 and LY2 cell lines derived from MCF-7 cells inhibited cell proliferation, migration, and colony formation of LY2 tamoxifen-resistant, luminal A breast cancer cells derived from MCF-7 cells [154].

miR-19a/b were named as metastamiRs by stimulating angiogenesis [136]. However, overexpression of miR-19b inhibited the proliferation of HUVECs, MCF-7, and MDA-MB-231 cells *in vitro* and inhibited MDA-MB-231 xenograft growth and caused growth arrest *in vivo* [155]. In breast tumors, two reports show opposite conclusions with one reporting lower miR-19b in invasive tumors [156]and one reporting higher expression in tumors associated with distant metastasis, TNM stage and reduced OS [157]. A target of miR-19b is Vascular Endothelial Zinc Finger 1 (*VEZF1)* [155], a transcription factor required for vascular system development in mice [158], thus, miR-19b was suggested to inhibit angiogenesis [155]. Thus, further study of the expression and role of miR-19a/b in breast cancer metastases is needed.

Both miR-221 and miR-222 are overexpressed in breast tumors, downregulate ESR1 (ERα), and are associated with endocrine-resistance [159,160] (Table 1). They are considered pro-metastatic and pro-angiogenic. Both miR-221 and miR-222 are involved in regulating genes involved in adherens junctions, PI3K and MAPK signaling, TGFβ signaling, apoptosis, and cell cycle [160] (Table 1). Thus, they contribute to cell proliferation and invasion.

Let-7f was also identified as metastamiR by stimulating angiogenesis [136]; however, members of the Let-7 family are documented tumor suppressors [161] and results of BCa tumor expression show both increased and reduced expression (Table 1). A *bona fide* target of Let-7f is *CYP19A1* [162], the aromatase gene which is a target of AI therapy in postmenopausal BCa patients whose primary tumor is ER+, a result suggesting an inhibitory role for let-7 in this pathway. Indeed Let-7f is upregulated by letrozole treatment in clinical samples [162].

Among the metastamiRs reported to have anti-metastatic activity [136], miR-141–3p would seem to be a good candidate since it targets *ZEB1* and *ZEB2* [163,164]. ZEB1 and ZEB2 are established EMT-inducers downstream of TGFβ, WNT-β-catenin, and RAS-MAPK signaling pathways [165]. However, knockdown of miR-141 inhibited metastatic colonization to brain of SUM149 cells whereas overexpression of miR-141 in non-expressing MDA-MB-231 TNBC enhanced brain metastatic colonization after tail vein injection of mice [166]. Further, reports of tumor and blood expression levels of miR-141 in

BCa patients show both upregulation and downregulation (Table 1). These data suggest the need for further examination of miR-141 as an anti-metastatic metastamiR.

The anti-metastatic activity of miR-193b is supported by a study reporting that mice injected with MDA-MB-231 overexpressing miR-193b cells developed smaller mammary tumors and had a 50% decrease in lung metastasis [167].

Concordant *in vivo* and *in vitro* data support the anti-metastatic roles of miR-200 family members, miR-205–5p, miR-429, miR-146a/b, miR-206, and miR-335 (Table 1). miR-146 is upregulated by BRMS1 [115], a known metastasis suppressor gene that suppresses NFκB-regulated gene transcription [168], interacts with the SIN3-HDAC-ARID4 corepressor complex [169], and with the LSD1-CoREST corepressor complex resulting in demethylation of H3K4me1/2 and histone acetylation on EMT target gene promoters for epigenetic repression, *e.g.*, *VIM* [170]. Overexpression of miR-146a/b in MDA-MB-231 cells increased invasion, migration, and NFκB activity [171]. However, the roles of miR-15b-5p, miR-16, miR-20a-5p, miR-20b-3p and miR-20b-5p as anti-metastatic metastamiRs [136] is uncertain (Table 1). miR-335 is anti-metastatic and suppresses CSC biogenesis [172] and it was reported to be downregulated in BCa cell lines overexpressing BRMS1 [173]. However, miR-335 was increased in exosomes from plasma samples from TNBC patients [174]. miR-20a-5p is part of the miR-17–92 cluster. As reviewed in Table 1, miR-20a has been reported to be downregulated in breast tumors by some investigators and upregulated in ER− vs. ER+ breast tumors and expression correlates with lymph node involvement [175]. miR-20a is upregulated in sera from BCa patients vs normal controls [176]. BCa cell-derived exosomal miR-20a-5p promotes TNBC MDA-MB-231 cell migration and invasion the proliferation and differentiation of osteoclasts by targeting *SRCIN1* [177]. These findings suggest that miR-20a is not anti-metastatic, but further studies are warranted.

Although miR-15b-5p was reported to be anti-metastatic [178], this conclusion needs reconsideration for BCa. In fact, miR-15 is among a 9 serum miRNA signature (miR-15a, miR-18a, miR-107, miR-133a, miR-139–5p, miR-143, miR-145, miR-425, and miR-365) that discriminated early stage ER+ BCa patients from healthy controls [179]. miR-15b-5p targets *MTSS1* (Metastasis suppressor 1) [180] and *MTSS1* expression is inversely associated with OS in breast tumors [181]. Another report found higher miR-15b-5p in aggressive breast tumors than in adjacent normal tissue and inversely correlated with *MTSS1* [180]. Further, miR15b-5p was reported to be upregulated in brain metastasis compared with primary BCa tumors [182]. EGF-induced miR-15b suppresses the translation of MTSS1, and the loss of MTSS1 promotes migration of mammary MCF-10A epithelial cells [180].

5. Metastasis Suppressor regulation by miRNAs

Tumor formation and metastasis formation are distinct, as shown by studies identifying metastasis suppressor genes that block metastasis but not primary tumor formation [75]. Early studies showed that transfection of MDA-MB-435 TNBC cells with an expression vector for the metastasis suppressor KISS1 reduced the number of lung metastases observed, but not the growth of the mammary primary tumor in the mammary fat pad injection site,

separating primary tumor growth vs. metastasis [183]. Further studies identifying and characterizing metastasis suppressors have been reviewed [184] [185] [75,87]. Here we searched the literature for eight identified metastasis suppressors and their potential role in breast cancer and regulation by miRNAs (Table 2). The genes and description of their regulation by miRNAs in breast cancer does not include all the information in Table 2, but focuses on those genes/proteins with clear roles in breast cancer metastasis.

As described above metastasis suppressor BRMS1 interacts with corepressor complexes SIN3-HDAC-ARID4 [169], and LSD1-CoREST [170]. Although BRMS1 has been reported to be targeted by miRNAs in osteosarcoma and hepatocellular carcinoma (Table 2), its regulation by miRNAs in BCa is uncertain. BRMS1 represses expression of miR-10b by inhibiting HOXD10 and inhibits RAC1, a GTPase that is required for cell migration of ER+, TNBC, and HER2+ BCa cells [186], by suppressing TIAM1, which is a target of mTORC2-AKT [110].

Cell adhesion molecule 1 (CADM1, also called TSCL1 and NECL-2) mediates cell-cell adhesion and inhibits metastatic colonization [75]. CADM1 was reported to be a direct target of miR-214 in colorectal cancer cells [187]. Although CADM1 regulation by miRNAs in BCa cells is unknown, miR-214 is a breast tumor suppressor [188].

The *KISS1* transcript encodes a 145 aa peptide that is processed to a number of shorter kisspeptins (kisspeptins 10, 13, 14, and 54) that bind the KISS1 receptor (KISS1, GPCR54) resulting in inhibition of NFκB activation and downregulation of MMP9 and IL8 [189]. Kisspeptins regulate neuroendocrine signaling controlling puberty and reproduction in humans [190]. SIRT1 deacetylates CREB which activates KISS1 transcription in CRC cells [191]. KISS1 expression is reduced in BCa metastasis in brain relative to the breast primary tumor and expression is reduced by CXCL12 from astrocytes [189].

Activation of the bile acid receptor (FXR, gene NR1H4) inhibits cell migration, stress fibers, and contraction of CAFs [192]. FXR is expressed in breast tumors and its expressed correlates with ERα/PR, *i.e.*, the luminal A phenotype [193]. A recent report found that activation of FXR by the FXR agonist GW4064 inhibited the tumor-promoting activities of CAFs, in co-culture experiments with MCF-7 and T47D cells, suggesting that targeting FXR might be a useful molecular target to reduce cell migration and invasion as early steps in metastatic spread [192]. While no miRNAs targeting FXR in BCa have been reported, miR-421 acts as an oncomiR to downregulate FXR in biliary tract cancer [194]. FXR is downregulated by miR-192–3p and miR-192–5p in HCC cells [195]. Experiments examining miRNA regulation in breast cancer are needed.

Lentiviral overexpression of metastasis suppressor Growth arrest specific 1 (GAS1) inhibits MDA-MB-231 xenograft tumor growth in mice [196]. GAS1 inhibits GFRα3-ARTN and MAPK signaling pathways [196]. GAS1 is a positive regulator of CSC maintenance [197]. lncRNA-Hh, was found to directly target *GAS1*, an enhancer of hedgehog signaling to increase the SOX2 and OCT4 expression, thus played a critical role for TWIST-driven EMT cells and TWIST-positive breast cancer cells to gain the CSCs-like characteristics [197].

CD82 KAI1 is a plasma membrane glycoprotein that is a member of the transmembrane 4 superfamily with no intrinsic activity [198]. It is a metastasis suppressor that is associated with metastatic progression in a variety of cancers [184]. It is considered a tumor suppressor by its interaction with multiple protein partners, *e.g.*, DARC (*ACKR1*, Atypical Chemokine Receptor 1 (Duffy Blood Group)) on endothelial cells interacts with KAI1 on cancer cells inhibiting cell proliferation and inducing senescence [199]. KAI1 suppresses cell motility and metastasis of MDA-MB-231 and MDA-MB-435 BCa cells in mouse models [198]

Leukemia inhibitory factor receptor (LIFR), a type I cytokine receptor family member, is in a complex with Gp130 (gene *IL6ST*, Interleukin 6 Signal Transducer) and activates JAK/STAT, MAPK, AKT, and mTOR pathways in BCa [200]. LIFR functions in the Hippo-Yap pathway to suppress metastasis [201]. It is downregulated by miR-9 [125] and miR-629–3p [202]. Novel LIFR inhibitor EC359 blocks binding of ligands, thus attenuating LIFR oncogenic signaling, reduced proliferation, invasion, CSC in TNBC cell lines and PDX assays [200].

Metastasis suppressor Lysine-specific demethylase 1A (LSD1, aka KDM1A) is a histone demethylase for H3K4me2/1 or H3K9me2/1, p53, DMNT, E2F1, HIF-1α, and STAT3 [203]. LSD1 has been reported to exhibit both oncogenic and metastasis suppressor actions in breast cancer. Inhibition of LSD1 strongly inhibits proliferation of breast cancer cells [204]. Thus, increased miR-127, miR-239–3p, and miR-708–5p would be expected to reduce LSD1 in BCa cells and be inversely correlated with LSD1 expression in breast tumors, although no one has yet investigated this. A recent report demonstrated that LSD1 interacts with GATA3, a key luminal-specific transcription factor in BCa, and coregulates 443 genes with 519 overlapping binding sites (determined by ChIP-seq) in MCF-7 cells [205]. LSD1 knockdown in T47D, MCF-7, and MCF-10A cells inhibited proliferation, reduced transcript expression of *CDH1*, and increased MCF-7 cell invasion *in vitro*. LSD1 also downregulated the transcription of *TRIM37*, a histone H2A ubiquitin ligase associated with PRC2 for gene repression. Conditional knockdown of *Lsd1* in the MMTV-PyMT luminal breast cancer mouse model reduced survival with a significant increase in metastatic lung tumors, implicating *Lsd1* as an *in vivo* metastasis suppressor in this model [205]. CARM1, an arginine methyltransferase, dimethylates LSD1 (R838) increasing LSD1 stability by promoting deubiquitylation of LSD1 in MDA-MB-231 TNBC cells by Ubiquitin Specific Protease 7 (USP7), thus blocking proteasome-mediated degradation, and resulting in reduced *CDH1* transcription and increased EMT [206]. The authors reported that CARM1 expression is elevated in malignant breast tumors and positively correlated with LSD1R838me2 and LSD1 protein levels, suggesting a tumor promoting role for CARM1 and LSD1 in breast cancer metastasis [206].

MDM2 Binding Protein (MTBP, aka MDM2BP) suppresses cell migration and metastasis in human HCC [207]; however, it may not be metastasis suppressor in breast cancer. Overexpression was associated with reduced OS in BCa [208] and it was reported to be amplified in 19% of breast tumors with highest amplification in TNBC [209]. No miRNAs are listed as regulating MTBP in miRTarBase.

MAP2K4 plays a role in MAPK-PI3K crosstalk and is associated with drug resistance in several cancers [210]. It is regulated by miR-27a-3p and miR-92a-3p (Table 2), but there are no reports of miRNA regulation in breast cancer. The MAP3K1-MAP2K4-JNK cascade activates JUN for FOS heterodimerization to form AP1 to regulate gene transcription [211]. Loss-of-function mutations in MAPK2K4 sensitize to MAP2K4-mutant BCa cell lines to inhibition by MEK inhibitors selumetinib and dacomitinib *in vitro* and *in vivo* [212]. MAP2K4 interacts with Vimentin in BCa cells to promote cell migration and invasion [213]. Thus, MAP2K4 does not appear to have a role as a metastasis suppressor in BCa.

Transcription of MYCN (N-Myc) downstream regulated gene (*NDRG1*) is increased in response to cellular hypoxia by direct transcriptional regulation by HIF1α and XBP1 and is associated with ERα− BCa [214]. NDRG1 is a metastatic suppressor in prostate and colon cancers (reviewed in [215]). NDRG1 is a direct target of miR-769–3p in MCF-7 breast cancer cells [216]. However, others reported NDRG1 not to be a metastasis suppressor [214]. Elevated expression is correlated with an aggressive metabolic gene signature and *in vitro* studies show that NDRG1 alters lipid trafficking and metabolism in breast cancer [217,214]. Inhibiting lipid and fatty acid (FA) metabolism is a way to block breast cancer metastasis [218,219]. Breast cancer cells with cancer stem cell (CSC) properties show increased FA uptake and oxidation [220]. NDRG1 is targeted by miR-769–3p in MCF-7 cells and stimulates apoptosis [216]. The expression of *NDRG1* is downregulated by the lncRNA *NDRG1-OT1_v4* [221].

Tumor suppressor Nm23-H1, NME/NM23 Nucleoside Diphosphate Kinase 1 (*NME1*) has serine/threonine protein kinase activity, geranyl and farnesyl pyrophosphate kinase activity, histidine protein kinase activity, 3’−5’ exonuclease activity, and granzymeA-activated DNase activity [222]. It was first identified “metastasis suppressor gene” involved in the colonization stage of metastasis [223]. Early studies suggested that NME1 suppresses breast cancer metastasis, at least in part, through down-regulation of Lysophosphatidic Acid Receptor 1 (*LPAR1*, formerly called EDG2) expression [224].

Tissue inhibitors of metalloproteinases (TIMPs) consist of four endogenous proteins: TIMP1, TIMP2, TIMP3, and TIMP4 that are metastasis suppressors (56). TIMPs are regulators of ECM composition and structure. Each is targeted by specific miRNAs (Table 2). TIMPs regulate the enzymatic activity of metzincin proteinases (matrix metalloproteinases (MMPs)) and A disintegrin and a metalloproteases (ADAMs) that are dysregulated in BCa. *TIMP1* transcript levels are increased in breast tumors whereas *TIMP2*, *TIMP3*, and *TIMP4* transcript expression is reduced [225]. TIMP2 and TIMP3 share gene targets in the matrisome, an ensemble of genes that make up the ECM proteome [225].

6. EMT regulation by miRNAs in breast cancer

A number of steps are involved in the initial invasion of tumor cells from the primary tumor into the surrounding ECM including EMT, anoikis, changes in tumor-tumor and tumor ECM adhesion molecules, proteases, and activation of CSC cell pathways [7]. EMT is a reversible process initially characterized in embryonic morphogenesis that allows mesenchymal cells

to migrate to new sites within the embryo and then undergo MET to switch back to an epithelial state [226]. In addition to development, EMT is also important in wound healing and inflammation where cell migration and invasion are needed [227]. In breast cancer, EMT is induced by signaling pathways including receptor tyrosine kinases (RTK, *e.g.*, IL-1-R (*IL1R*1)), TGFβ, TNFα, activation of toll-like receptors (TLR), WNT, and NOTCH with significant correlations between the expression of these genes and metastatic breast cancer risk [228]. In addition, EMT is related to resistance to endocrine and other therapies including conventional chemotherapy in breast cancer [229].

During EMT reprogramming in breast cancer cells there is a disruption of the polarization of epithelial cells and loss of tight cell-to-cell junctions. During EMT, cells acquire the ability to migrate due to repression of epithelial markers including the adherens junction proteins (E-cadherin, *CDH1*), occludins, claudins, α6β4 integrin, and an increase in expression of neural cadherin (N-cadherin (*CDH2*), vimentin (*VIM*), an intermediate filament protein, and fibronectin (*FN1*), a glycoprotein that functions in migration [230]. Thus, markers of EMT include a decrease in *CDH1*, zona occludins protein 1 (ZO-1, *TJP1*), and occludin (*OCLN*) from adherens junctions, and increased *VIM* and *CDH2*). EMT is upregulated by TFs: ZEB family members (ZEB1 and ZEB2) [231], SNAIL (*SNAI1*), SLUG (*SNAI2*), and TWIST (*TWIST1*) (Table 3). These TFs inhibit transcription of genes associated with the epithelial state [230]. A meta-analysis of 14 studies concluded that overexpression of EMT-TFs TWIST (*TWIST1*), SNAIL (*SNAI1*), SLUG (*SNAI2*) was a prognostic factor in advanced MBC, with SLUG (SNAI2) “the most impactful” and demonstrating a higher hazard ratio for Asian MBC patients [228]. A recent study reported that *PRKD1* is a direct target of TWIST1 that is required for cells to disseminate from organoid models of breast tumors by stimulating invasion, loss of adhesion, and cell migration [232]. The authors reported high PRKD1 in basal breast tumors was associated with reduced Distant Metastasis Free Survival (DMFS) [232].

Although EMT is a characteristic of metastatic cells, EMT is not essential for metastasis in every tumor type [87]. EMT is characterized by changes in cell morphology from epithelial, squamous, columnar, cuboidal shapes to fibroblastic-spindle-like elongated cells due to loss of epithelial cell-cell junctions, loss of cell apical-basal polarity, and gain of motility [102]. Activation of EMT also activates MMPs that degrade the extracellular matrix and promote cell invasion.

The role for ncRNA in regulating EMT has been reviewed [233–235]. The EMT Gene database dbEMT 2.0 [236] lists 371 genes that have either oncogenic or tumor suppressor functions in the EMT process. Fig. 3 summarizes aspects of TGFβ and NOTCH signaling, the EMT transition, and roles for miRNA regulation of selected gene/protein targets in this pathway in breast cancer. Cell-to-cell signaling via the NOTCH signaling cascade has been reviewed [237]. Components of NOTCH signaling and downstream targets are upregulated in breast cancer and stimulate EMT (reviewed in [238]). Table 3 lists selected genes from the EMT gene database, their direct miRNA regulation in breast and selected other cancers (if no established role in breast cancer was found in the literature), their roles and regulation in breast cancer, and expression and prognostic value in human breast tumors. This list is not comprehensive since there are a number of other reviews on this topic, as indicated above.

EPH Receptor A2 (*EPHA2*) is an oncogenic cell-surface RTK located at sites of cell-cell contact that is regulated by AKT phosphorylation in the absence of ligand, resulting in enhanced pro-oncogenic signaling [239]. EFNA1 is a ligand for EPHA2 that inhibits cell proliferation and mammary tumor growth in HER2/Neu animal models and is downregulated in breast tumors leading to ligand-independent activation and tumor progression by activing glutaminolysis and lipid metabolism [240]. miR-200a targets EPHA1 [241].

ETS2 is an oncogenic transcription factor that is downstream of MAPK and PI3K/AKT pathways and regulates genes involved in apoptosis, cell cycle, and tumor progression [242]. ETS2 was reported to be a direct effector of CSF-1 signaling in TAMs that decreased primary and tail-vein injection lung “metastases” of BCa cell line growth in mice [243]. Activation of the CSF1-ETS2 pathway in TAMs represses TIMP3 and increases miR-21 and miR-29a that stimulates metastatic tumor growth and angiogenesis in mouse models of BCa [244]. Direct interaction between coactivator SRC-1 (*NCOA1*) and ETS2 increased expression of *MYC* and *MMP2* in aromatase inhibitor (AI)-resistant MCF-7 cells [245]. Although miR-320 and miR-320b target *ETS2* (Table 3), there were no reports of lower expression of these miRs in endocrine-resistant breast cancer [10,11]. An interesting observation is that higher nuclear phospho-ETS2 was detected in patients with AI-resistant lung metastasis (n =3) compared to matched primary breast tumor [245]. One might speculate that miR-320 might be a therapeutic in AI-resistant metastatic breast cancer and design appropriate experiments to test this hypothesis.

EZH2 is the catalytically active methyltransferase component of the polycomb repressive complex (PRC2) that represses gene transcription via methylation of H3K27me3 [246]. EZH2 was reported to interact with 276 chromatin-interacting lncRNAs including *MEG3*, which downregulated genes in the TGFβ pathway in BT-549 BCa cells [247]. EZH2 expression is increased in breast cancer (Table 3). EZH2 activates RAF1-β-catenin signaling to promote CSCs in BCa [248]. EZH2 activates *NOTCH1* transcription in BCa cells and increases CSC [249]. EZH2 is induced by hypoxia in TNBC cells and high HIF1A, EXH2, and FOXM1 expression correlates with OS in BCa patients [250].

FOXO1 is a member of the Forkhead transcription factor gene family containing a 110 aa conserved DNA binding motif [251]. FOX family members regulate embryogenesis, organogenesis, metabolism, and are involved in cancer [251]. FOXO1 is a tumor suppressor whose expression is lower in breast tumors than normal breast [252]. FOXO1 suppressed β-catenin expression and nuclear localization, thus downregulating WNT and JUN signaling, cancer stemness, and metastasis in xenograft models of MCF-7 and MDA-MB-231 [253]. FOXO1 is downregulated by a number of miRNAs (Table 3) including miR-5188 which is elevated in BCa and predicts reduced DFS [253]. Overexpression of miR-5188 enhances tumorigenesis, CSC, metastasis, and chemoresistance *in vivo* in MCF-7 and MDA-MB-231 xenografts [253]. Interestingly, *FOXO1*’s 3’UTR acts as a competitive endogenous RNA (ceRNA) for miR-9 binding to the *CDH1* 3’UTR, thus increasing E-cadherin and inhibiting EMT in BCa cells [254].

RHOA is a GTP binding protein that activates cytoskeletal reorganization and stimulates BCa cell invasion [255]. miR-155 is an oncomiR that facilitates EMT through repressing *RHOA* expression (125). RHOA is also downregulated by other miRNAs in BCa, including miR-150 and miR-155 (Table 2). Expression of miR-150 and miR-155 was higher in invasive breast cancer (IBC) and lympho-vascular invasion (LVI) compared to DCIS in microdissected tumors and corresponded with reduced *RHOA* expression [119]. *RHOA* is targeted by miR-146a. miR-155 (Table 3) which are in a network of miRNAs, including miR-125b, miR-21, and miR-27a, that contribute to antiestrogen resistance [256]and reviewed in [10].

SKP2 (S-phase kinase-associated protein) is a component of the Skp1-Cul1-Roc1 (SCF) ubiquitin ligase complex [257]. SKP2 is an oncogene that specifically recognizes phosphorylated cell cycle regulator proteins, *e.g.*, PDCD4 [258] and $p27^{Kip1}$ (*CDKN1B*) [259], and mediates their ubiquitination and degradation, resulting in increased cell cycle progression and proliferation. SKP2 ubiquitylates AKT, resulting in its activation - independent of PI3K, providing a mechanism for resistance to PI3K inhibitors [260]; however, how SKP2 is increased in PI3K resistance is unknown [261]. High SKP2 was associated with increased risk of distant recurrence in breast cancer patients treated with radiation therapy [262] (Table 3), but no miRNAs have been reported to target SKP2 in breast cancer. Interestingly, miR-30d-5p was reported to target SKP2 in lung cancer [263] (Table 3) and miR-30d (as well as miR-30a/b/c/e) were identified as suppressors of breast cancer bone metastasis whose expression was downregulated in human osteotropic BCa cell lines [264].

Kruppel-like factor 4 (*KLF4*) is a zinc-finger transcription factor that has both oncogenic and tumor suppressor functions and inhibits ERα-DNA binding by direct interaction with the DBD [265]. KLF3 is upregulated by MYB in luminal breast cancer [266]. KLF4 is highly expressed in CSC-enriched populations of MCF-7 and MDA-MB-231 breast cancer cells [267]. KLF4 is downregulated by CpG island methylation in anti-estrogen resistant LCC9 BCa cells [268]. KLF4 is downregulated by miR-29a/b/c and miR-10b-5 (Tables 1 and 3). miR-10b was the top miRNA identified in exosomes isolated from MDA-MB-231 TNBC cell culture medium [269]. Treatment of miR-10b non-expressing normal human mammary epithelial cells (HMLE) with exosomes from MDA-MB-231 cells increased HMLE miR-10b expression ~ 6-fold and reduced KLF4 and HOXD protein expression (both mIR-10b targets) and increased cell invasion [269].

KLF5 appears to be oncogenic in breast tumors (Table 3). Metformin was reported to target KLF5 for degradation in TNBC cells, thus decreasing CSC [270]. KLF5 increased lncRNA *RP1 −5O6.5* that repressed p27Kip1 (CDKN1B) translation in TNBC cells [271]. KLF5 is targeted by miR-590–5p [272] in breast cancer cells.

STAT3 is a transcription factor activated by phosphorylation downstream of TGFβ, IL-6, WNT, NOTCH, and Hedgehog (HH) signaling pathways [273]. More recent studies showed the leptin stimulated STAT3 activation, suggesting a pathway by which obesity stimulates breast cancer [274]. Cell stress activates p38 MAPK that phosphorylates EGFR leading to its internalization in endosomes which leads to STAT3 phosphorylation and triggers a TWIST1-

dependent EMT transcription program [275]. STAT3 is targeted by miR-519d, which is reduced in breast tumors [276]. Phospho-STAT3 increased the transcription of *MCL1* and *BIRC4* [277]. STAT3 is constitutively active in TNBC and ChIP-seq identified 22 common transcripts in 5 TNBC cell lines that included upregulation of *ANKRD2*, *BEAN1*, *CPA3*, and *GDF15* and downregulation of *STAT3*, *NNMT*, *CPT1C*, and *C4A* expression [278]. Activation of STAT3 in TNBC cells stimulates cell processes including actin cytoskeleton, adherens junction, extracellular vesicular exosome, basement membrane, and stress fibers [278].

SALL4 is a zinc finger-containing transcription factor that increases transcription of *CCND1*, *CCND2*, *TWIST1*, *BMI1*, and represses *CDH1* to promote EMT (477). SALL4 is directly activated by TCF/LEF in the canonical WNT signaling pathway [279]. SALL4 interacts with OCT4 and NANOG [280] and enhances stemness and CSC in TNBC cell lines [281]. This is modeled in Fig. 3. miR-33b directly suppresses SALL4 translation and miR-33b expression is downregulated in breast tumors and is inversely correlated with lymph node metastatic status [282], providing a mechanism for upregulation of SALL4 in breast cancer progression and metastasis. SALL4 is directly activated by TCF/LEF in the canonical WNT signaling pathway [279].

GLI1 is a member of the Kruppel family of zinc-finger transcription factors that is activated by HH signaling [283]. GLI1 directly interacts with STAT3 and stimulates CSC [284]. Results examining GLI1 in breast tumors appear to be divergent in terms of association with luminal status (Table 3). Overall, increased GLI1 is reported in breast tumors. miRNA regulation of GLI1 in breast tumors has not been reported.

SIRT1 (Sirtuin 1) is an NAD+-dependent deacetylase for histones H1, H2, and H4 as well as p53, E2F1 [285], NFκB, selected NRs, *e.g.*, AR, ERα, and LXRα (reviewed in[286]) and FOXO family members [287]. SIRT1 is involved in a range of cellular processes including aging, circadian rhythm, metabolism, and cancer [288]. SIRT1 transcription is induced by E2F1 and repressed by P53 [289]. SIRT1 is downregulated in aggressive breast tumors [290] and in TNBC compared to normal breast tissue [291]. SIRT1 is directly regulated by miR-22, miR-200a, miR-34a, and miR-211–5p (Table 3) and is a putative target of metastamiR miR-520c-3p (Table 1). Low miR-34a and high levels of SIRT1 have been reported in breast CSC (495). SIRT1 seems to have both pro- and anti-metastatic activity in breast cancer depending on the model system used. For example, SIRT1 suppresses EMT in breast cancer by suppressing TGF-β-driven EMT in SV40,h-*ras*V12-h,*TERT* immortalized normal human mammary epithelial cells (HMLER cells [292]) [293]. On the other hand, SIRT1 upregulates MMPs in BCa cells and interacts with SMAD proteins downstream of TGFβ signaling [288]. Knockdown of SIRT1, inhibited lysosomal activity and promoted exosome release from MDA-MB-231 TNBCs with the released exosomes promoting proliferation and an invasive phenotype of immortalized MCF-10A breast epithelial cells [291]

CCN2/CTGF is a secreted growth factor that is increased ~ 2-fold by TGFβ signaling in fibroblasts where it simulates angiogenesis, but it inhibits the migration and invasion of ovarian and CRC cancer cells [294]. CTCF is an oncogene in gastric cancer [295], glioma

[296] and melanoma, but acts as a tumor suppressor lung adenocarcinoma [297]. Elevated *CCN2* (CTGF) was reported in stroma-rich, TNBC tumors with poor clinical prognosis [298,299]. In breast tumors, CCN2 expression was correlated with EMT markers, *i.e.*, increased *CDH2*, *FN1*, *VIM*, *GSC*, *SNAI1*, and *TWIST1*, and with downregulation of *CDH1*, *KRT18*, and *KRT8* [299]. CTGF acts both as a paracrine factor to stimulate collagen fiber deposition and an autocrine factor by activing TNF receptor (TNFR1, *TNFRSF1A*) signaling and activating NFκB to increase the transcription of genes that stimulate EMT. Inhibiting miR-221 in MDA-MB-231 cells decreased the expression of CTGF by suppressing the expression of the ubiquitin-editing enzyme, A20, that ubiquitinylates CTGF for proteosomal degradation [300].

TP63 is a member of the p53 TF family with cell-specific oncogenic and tumor suppressor activities [301]. There are 6 protein isoforms of TP63 due to differential promoter use and alternative splicing [302]. The isoform TAp63 provides pro-apoptotic and senescence-inducing properties, whereas ΔNp63 isoforms stimulate cell survival [303]. Increased expression of ΔNp63 was associated with metaplastic and medullary TNBC tumors, and with a basal phenotype, whereas TAp63 was associated with AR, BRCA1/2 wild-type status, PTEN positivity, and with improved OS [303]. miR-196a2* targets TP63 and is upregulated by E_2-stimulated ERα-ERK transcriptional activation in BCa cells [304].

Cyclin dependent kinase inhibitor 1 B (*CDKN1B*) encodes the protein referred to as p27 (p27Kip1). p27Kip1 is a tumor suppressor that inhibits cell cycle progression is regulated by the PTEN/AKT pathway [305]. Low levels of p27Kip1 in breast tumors is associated with lower OS [306]. Mutating the *CDKN1B* gene in MCF-7 cells results in increased proliferation and re-expressing p27Kip1 inhibits proliferation [307]. miR-222 targets PTEN resulting in increased phospho-AKT and decreased p27Kip1 [308]. Overexpressing miR-203 in MCF-7 cells suppresses p27Kip1 expression, resulting in increased cell growth, migration and invasion [309].

Wilms' tumor 1 (WT1) is a transcription factor that regulates transcription of numerous human genes involved in WNT signaling, *e.g.*, *DKK2*, *JUN*, and *DACT1*; cell growth, *e.g.*, *AREG*, *CX3CL1*, *EREG*, *VDR*, *IGF1*, *CCNE*, *PDGF1*, *SLC6A2*, and MAPK signaling, *e.g.*, *DUSP16* and *MAPKAPK2*; epigenetic regulation, *e.g. DNMT3A* and *SRPK1*; and Apoptosis, *e.g.*, *BCL2A1*, *BCL2*, and *JUN* [310]. WT1 inhibits transcription of *STIM1* (Stromal Interaction Molecule 1) that triggers store-operated calcium channels to increase Ca+ entry which stimulates BCa cell progression and EMT [311]. WT1 interacts directly with ERα to suppress IGF-I receptor (*IGR1R*) transcription in BCa cells [312]. WT1 is a target of miR-193a in BCa [313] and miR-193a-5p was decreased BCa [314]. Accordingly, WT1 expression is increased in breast tumors (Table 3).

As described above, the loss of CDH1 is a marker of EMT. Reduced CDH1 expression in breast tumors is a poor prognostic marker (Table 3). Patients whose primary breast tumors showed loss of E-cadherin had increased CTCs with a mesenchymal phenotype and LN metastasis with increased expression of *TWIST1, SNAI1* (SNAIL), and *SNAI2* (SLUG) accompanied by decreased Ki67 labeling index [315]. C*DH1* transcription is stimulated by EP300, FOXA1/2, and RUNX1 [316] and repressed by ZEB1/2 [317]. *CDH1* is targeted by

miR-9–5p [124], miR-199a-5p [318], miR-544a [319], miR-888–5p [320], and miR-421 [321].

Another marker of EMT is increased Vimentin (*VIM*) [322,323] and VIM promotes cell migration [324]. In breast cancer, VIM is targeted by miR-124 [325], miR-17–3p [326], and miR-378g [327] (Table 3).

Transforming Growth Factor Beta 1 (TGFβ1) is a secreted protein that binds TGFβ receptor type II (TβRII) receptor which then heterodimerizes with TGβRI to activate SMAD family transcription factors to regulate development and homeostasis [328]. TGFβ signaling in EMT is modeled in Fig. 3. *TGFB1* transcript was upregulated and associated with low recurrence score in breast tumors, e.g., higher in non-metaplastic TNBC [329]. *TGFB1* is an inhibitor of proliferation of primary HMECs and many breast cancer cell lines - thus acting as a tumor suppressor [330]. *TGFB1 is a target of* miR-675 [331] and represses miR-29b/c expression [332–334]. The repression of miR-29b/c may play a role in breast cancer progression since miR-29 has tumor suppressor targets (Table 1), although miR-29 has oncomiR targets as well (reviewed in [335,154]).

Sprouty (SPRY2) is a negative regulator in the EGF and FGF signaling that is a tumor suppressor downregulated in breast tumors and associated with poor RFS and OS (Table 3). In TNBC, increased EGF induced the expression of c-MYC, which increased the expression of mature miR-23a, miR-24–2, and miR-27a that decreased the expression of SPRY2; and promoted cell migration and invasion through activation of p44/42 MAPK [336]. SPRY2 is targeted by miR-27a/b, miR-23a, miR-24–2 [337]; and miR-128a (632) (Table 3).

NOTCH signaling promotes the self-renewal of CSC in various cancers and participates in tumor-stroma and tumor-endothelium interactions in CSC niches in primary and metastatic tumors [338,339]. Low *NOTCH1* in breast tumors correlates lower OS [340] and high levels of EZH2 were associated with activated NOTCH1 protein and increased tumor initiating cells (TICs) in TNBC invasive carcinomas [249]. EZH2 increases NOTCH1 transcription and CSC in TNBC [249]. NOTCH1 is upregulated by EGF and ERBB3 in ERBB2/HER2+ BCa cells [341]. IL6 and hypoxia increase NOTCH1 transcription in MCF-7 cells in a C/EBPδ (*CEBPD*)-dependent manner [342]. NOTCH1 is targeted by miR-34a-5p [343]; miR-30a [344]; miR-139–5p [345]; miR-3178 [346] in breast cancer. The miR-106b-25 cluster represses the E3-ubiquitin ligase *NEDD4L*, thus increasing NOTCH1 in ERα+ and TNBC cells [347].

Mucin1 (*MUC1*) is a high MW, PM-bound, heavily O-glycosylated protein that has a single transmembrane domain and a 72 aa C-terminal domain (CD) that is cleaved forming an intracellular C-terminal domain (MUC1-C) that is regulated by tyrosine phosphorylation [348]. The N-terminal domain (NTD) of MUC1 protrudes from the apical surface of glandular epithelial cells in breast and other cell types [349]. Studies (at least 55 papers in PubMed) from the Kufe lab have identified roles for MUC1 and MUC1-C in EMT and CSC and as a target for breast cancer treatment [350,351]. The cellular distribution of the MUC1-C subunit (C-terminal) is dysregulated in cancer with a loss of cell polarity and a distribution of MUC1-C over the entire surface of the breast cancer cell where it interacts with EGFR

and HER2 [352]. MUC1-C interacts with NFκB p65, acting as a coactivator to increase *ZEB1* transcription [353,354]. MUC1-C interacts with other TFs including C/EBPβ [355] and ERα [356] as a coactivator. MUC1-C also interacts with EZH2 to decrease gene-specific H3K27me3 and repress transcription of *CDH1* and *BRCA1* in BT-549 and MDA-MB-468 TNBC cells [357]. MUC1-C interacts with STAT3 to increase *TWIST1* transcription and with TWIST1 protein to increase transcription of EMT and CLC stemness genes, *e.g.*, *ZEB1*, *SNAI1*, *SOX2*, *BMI1*, *ALDH1*, and *CD44* [358]. MUC1-C interacts with MYC to drive stemness and with components of the NuRD complex on the *ESR1* promoter to suppress transcription in TNBC cells [359]. miRNAs that regulate MUC1 are listed in Table 3. miR-145 is a *bona fide* regulator of MUC1 with reduced expression in breast cancer cells corresponding to increased MUC1 [360].

7. TGFβ signaling in breast cancer and metastasis

TGFβ has tumor suppressor roles in normal breast epithelial cells by activating cyclin-dependent kinase (CDK) inhibitors, *e.g.*, *CDKN2B* (P15 CDK inhibitor) and *CDKN1A* (P21, in normal and pre-malignant cells, TGF-β inhibits proliferation [361]. However, after epigenetic and genetic changes occur that convert normal ductal epithelial cells to primary breast cancer cells, TGFβ takes on an oncogenic role driving EMT, motility, invasion, and metastasis (reviewed in [362]). Higher levels of TGFβ in serum of patients with advanced breast cancer is a prognostic indicator of cancer progression associated with lower OS [363].

Fig. 3 summarizes selected aspects of TGFβ signaling in breast cancer and EMT for metastasis. The 33 members of the TGFβ family of cytokines in humans includes TGFβ1 (*TGFB1*) that binds TGFβ type I and II receptors (T*GFBR1, TGFBR2*) which are ser/thr kinases that act as heterodimers to initiate an intracellular signaling pathway of SMAD intracellular effectors. *TGFB1R1* transcript expression is higher in breast tumors compared to normal breast and is inversely correlated with miR-133b expression [364]. 3'UTR-luciferase reporter assays demonstrated that miR-133b directly targets TFGB1R1 *in vitro* [364]. miR-133b is downregulated in MCF-7, MDA-MB-231, MDA-MB-453, and MDA-MB-469 cells relative to MCF-10A cells and miR-133b was lower in breast tumors compared to normal breast tissue [364]. Knockdown of *TGFB1R1* in MCF-7 and MDA-MB-231 cells inhibited phosphorylation of SMAD3, increased *CDH1*, and suppressed cell invasion and migration *in vitro* [364]. *TGFB1R2* expression is also higher in breast tumors *versus* normal breast tissues and its expression is inversely correlated with miR-153 that is downregulated in breast tumors [365]. *TFGBR2* 3'UTR-luciferase reporter assays validated TFGB1R2 as a direct target of miR-153 [365]. Transient overexpression of miR-153 in MDA-MB-231 cells inhibited cell migration and invasion, increased protein levels of *CDH1* (E-cadherin) and *VIM* (vimentin) [365]. *TGFBR2* and *RELA* are directly targeted by miR-372, miR-373, miR-520c, and miR-520e, all of which show reduced expression in MDA-MB-231 TNBC cells and ERα− breast tumors [366].

TGFBR1 phosphorylates regulatory SMADs, SMAD2 and SMAD3, that form heterodimeric complexes with each other and SMAD4, translocate to the nucleus, bind DNA, recruit coactivators, and stimulate transcription of genes, *e.g.*, *HMGA2*, *DNMT1*, *SNAI1*, S*NAI2*) *ZEB1*, *ZEB2*, *TWIST1*, and a number of miRs, including miR-155 [367,368] (Fig. 3).

SMAD2 is a *bona fide* target of miR-190 that is decreased in breast tumors [369]. Cell-based studies demonstrated that transiently overexpressed ZEB1, TWIST1, and SNAI1/2 bind the miR-190 promoter to suppress its transcription in MCF-10A cells and overexpression of miR-190 decreased SMAD2 protein levels and inhibited TGFβ-induced MCF-10A migration *in vitro* [369].

HMGA2 binds AT-rich DNA sequences and is a positive effector to increase transcription of *SNAI1, SNAI2*, and *TWIST1* [370]. TGFβ also activates non-SMAD pathways including the PI3K/AKT, MAPK, JNK, and P38 MAPK pathways [368]. Although the three isoforms of AKT (AKT1, AKT2, and AKT3) have ~ 80% similarity, AKT1 is the most mutated form and AKT2 is amplified in breast tumors and promotes migration and invasion by regulating β-integrins, EMT-related proteins and F-actin [371]. Integrins are a family of transmembrane cell adhesion receptors composed of 18 α and 8 β subunits that mediate cellular cytoskeletal interaction with the ECM [372].

SNAIL (*SNAI1*) and SLUG (*SNAI2*) are related C2H2 zinc finger transcriptional repressors that share structural homology, including an N-terminal SNAG (Snai.Gfi1) domain for nuclear localization and repression, and both bind E-box DNA sequences [373]. They have non-overlapping cellular functions in mammary gland development and in breast cancer progression in regulation of EMT and stemness (CSC) [373]. Increased expression of SNAI1/SNAI2 can induce resistance to endocrine therapies in breast cancer cells [374] with findings confirmed for increased SNAI2 in a separate cell-based study and in primary breast tumors and metastases [375].

ZEB1 and ZEB2 are Zinc Finger E-box-binding homeobox transcription factors overexpressed in breast tumors and in the serum of BCa patients compared to healthy controls (Table 2). The expression of ZEB1 and ZEB2 is induced by signaling pathways activated in breast tumor progression, *e.g.*, NFκB, TGFβ, WNT-β-catenin, and RAS-MAPK g [165] and induce EMT by suppression of targets including CDH1 and miR-200 family members [230] [317,376–379]. ZEB1 and ZEB2 are downregulated by common and specific miRNAs (Table 3). GATA3 inhibits TGFβ-induced EMT in breast cancer cells by increasing the transcription of miR-455–3p which directly targets *ZEB1*, *SMAD2*, and *HDAC2* in MCF-7 and MCF-10A cells [380]. ZEB1 reciprocally repressed miR-455 transcription in MCF-7 cells [380]. ZEB1 expression is increased and miR-200abc decreased in TAM-resistant LCC9 and LY2 breast cancer cells [381]. There is an inverse correlation between miR-200 family members and ZEB1 expression in TNBC cells, *i.e.*, MDA-MB-231 and BT549 [163,382,383,164]. Studies in TNBC cells show that treatment with DNA methyltransferase inhibitors (DNMTi, *e.g.*, 5-Azacytidine and Decitabine) and HDAC inhibitors (HDACi, *e.g.*, Vorinostat and Entinostat) can reprogram the cells to a less aggressive phenotype, *e.g.*, MET, by suppressing ZEB1, EZH2, and mutant p53 while increasing CDH1 expression [384]. Entinostat is in Phase I/II clinical trials for TNBC treatment [385].

8. Conclusions

Despite advances in treatment for breast cancer, the survival rate for patients with distant metastasis is only 27% [386]. Thus, a better understanding of dysregulated signaling pathways underlying metastasis is clearly needed. Proteins in the miRNA biogenesis pathway are targets of miRNAs that are dysregulated in breast cancer and contribute to metastatic pathways (Fig. 1). In advanced stage breast cancer, pro-metastatic miRNAs are reported to have increased expression, resulting in decreased expression of their tumor-suppressing targets. I n contrast, miRs that have anti-metastatic activity by targeting oncogenes have decreased expression in more advanced stage breast tumors. Recent research focuses on miRNA participation in crosstalk between signaling pathways that contribute to tumor progression and metastasis when dysregulated, *e.g.*, TGFβ/SMAD/EMT, WNT-β-catenin pathway and CSC pathways. These studies are beginning to elucidate the mechanisms and effects of aberrant miRNA expression, but indicate a need for further investigation.

We reviewed the identity, regulation, human breast tumor expression, and reported prognostic significance of miRNAs that have been documented to directly target key genes in pathways contributing to the metastatic cascade. We critically evaluated the evidence for metastamiRs and their targets in breast cancer. Not all of the roles identified for specific metastamiRs was supported by recent reports as summarized in the text and in Table 1. We evaluated the expression and miRNA regulation of metastasis suppressor genes in breast cancer (Table 2) and identified the need for further studies on specific miRNAs, *e.g.*, miR-31–5p and miR-19a/b in metastatic spread. We reviewed the miRNA regulation of EMT-related genes and their expression and prognostic value in breast cancer (Table 3). Additional miRNAs target proteins involved in TGFβ signaling, a central inducer of EMT, a hallmark of metastasis, were reviewed (Fig. 3, Table 3).

Although the literature on the topic of breast cancer metastasis and miRNAs is vast, our understanding of the complexities of these interactions remains to be resolved and computational modeling of these interactions will provide insight into potential ‘high yield’ targets for further study. Identification and validation of miRNAs that regulate the protein, and RNA levels, of genes that act as metastamiRs, metastasis suppressors, or in pathways including TGFβ signaling, and EMT is incomplete. Finally, the studies reviewed here suggest that miRNAs that are dysregulated in breast tumors or patient sera should be explored as novel diagnostic and potential targets for therapy to reduce metastatic disease and thus suffering and mortality in breast cancer patients..

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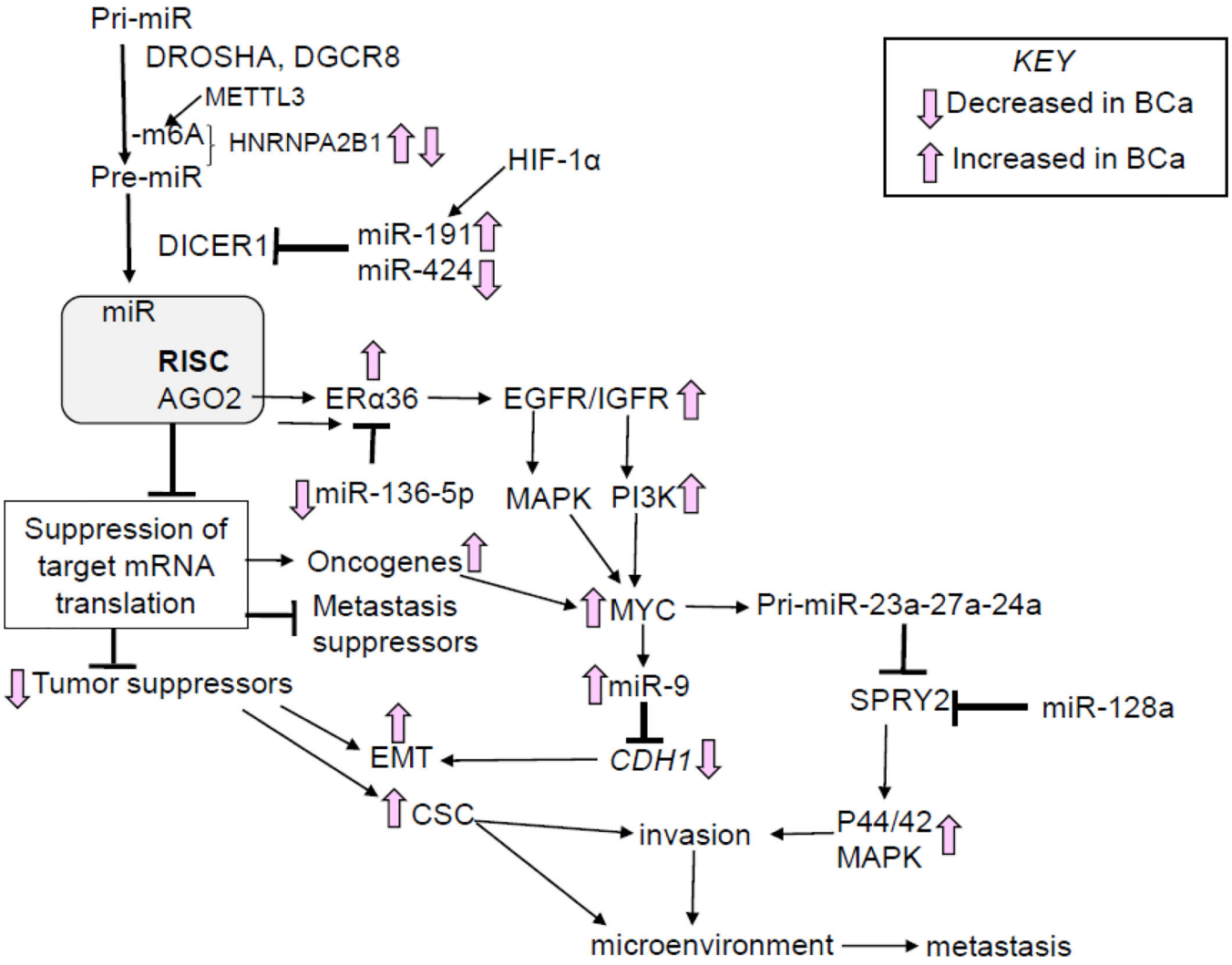

Fig. 1: A brief summary of miRNA biogenesis and aspects of regulation in breast cancer and metastasis.

The pathway and proteins involved are described in the test. The upregulation of ERα36 in breast cancer is reviewed in [72]; the regulation of SPRY2 is reviewed in [336]; and MYC upregulation of miR-9 in [752].

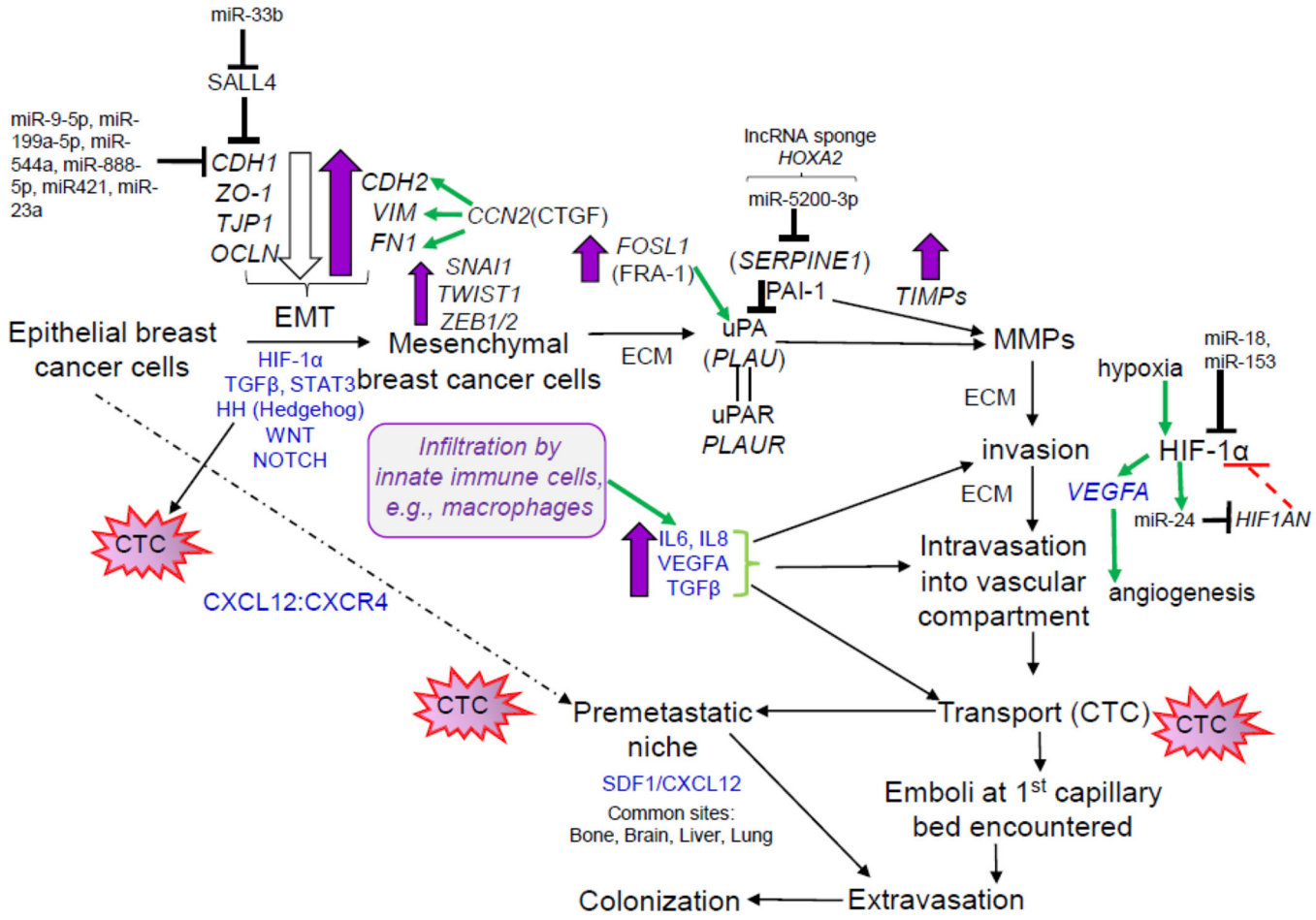

Fig. 2: An overview of the metastatic process in breast cancer.

The overall metastatic pathway was recently reviewed in [87]. Purple-fill arrows indicate upregulation, open arrows indicate downregulation, and green arrows indicate stimulation. Growth factor, cytokine, signaling pathways are in blue.

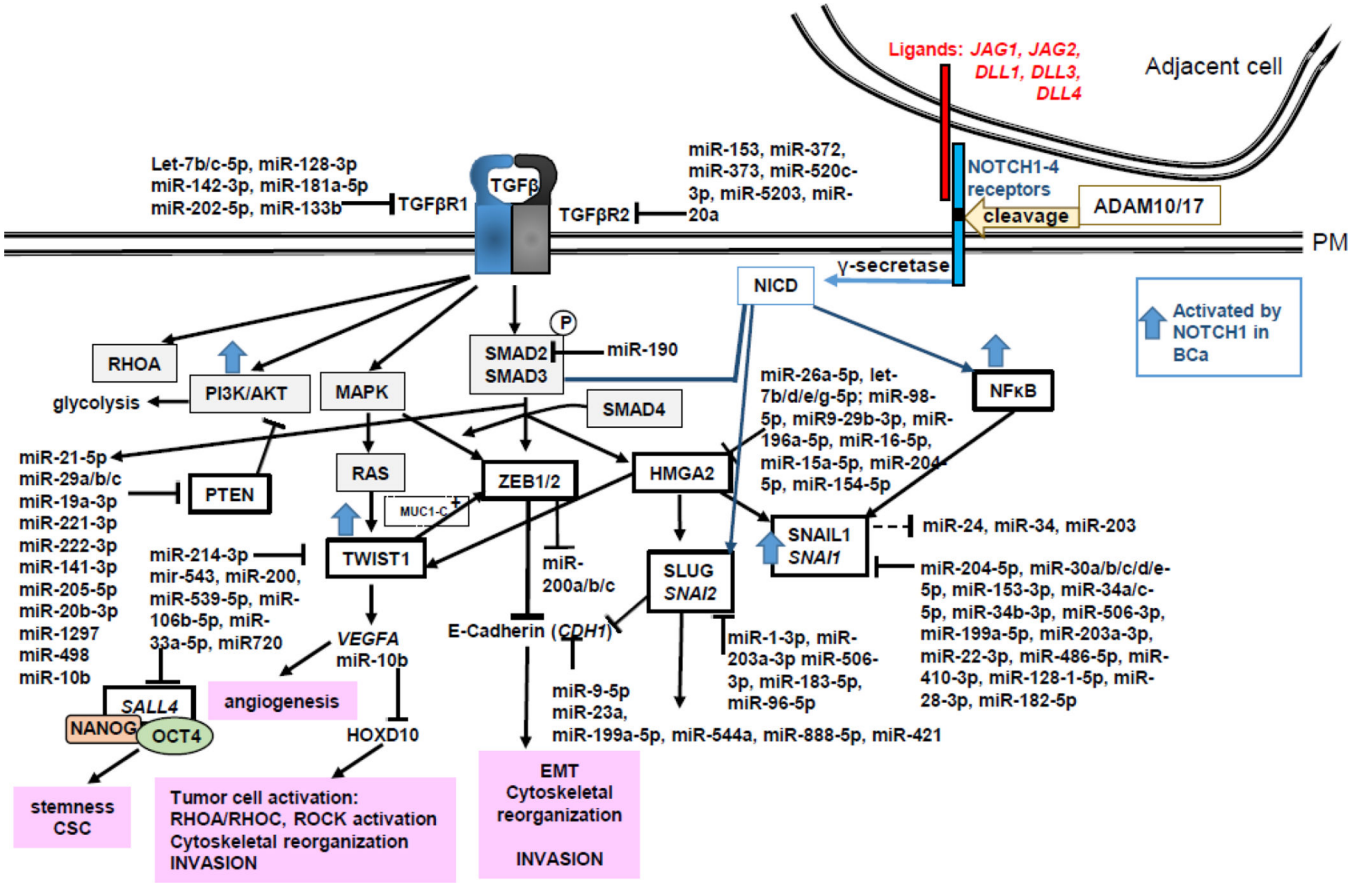

Figure 3: TGFβ stimulation of EMT, angiogenesis, and stemness in breast cancer progression toward metastasis.

TGFβ binds TGFβ type I and II receptors and phosphorylates SMAD2 and SMAD3. SMADs 2/3 form a complex with SMAD4, translocate into the nucleus to bind HMGA2, a chromatin remodeling factor, and activate the transcription of *SNAI1*, *SNAI2*, *ZEB1*/*2* and *TWIST1*. These transcription factors suppress *CDH1* and increase *VEGFA*, in addition to regulating other genes in EMT (not shown). Canonical NOTCH signaling is initiated by interaction of ligands from one cell, *e.g.*, Jagged (*JAG1*, *JAG2*), Delta-like (*DLL1,2,3,4*) and cognate NOTCH (*NOTCH1,2,3,4,5*) receptors on adjacent cells. The interaction activates cleavage of NOTCH receptor(s) by ADAM10 or ADAM17. γ-secretase cleavage releases NOTCH intracellular domain (NICD) that goes to the nucleus and interacts with RBPJ and MAML1 (Mastermind Like Transcriptional Coactivator 1) as a coactivator to stimulate gene transcription, including by interaction with NFκB. NICD also interacts with SMAD3 to regulate gene transcription. The indicated miRNAs and targets in this pathway are summarized in Tables 1–3.

Table 1

MetastamiRs: miRNAs that have reported pro- and anti-metastatic effects [136,114].

miRNA	***Bona fide* validated Gene targets Those miRNA gene targets not cited by reference number were identified as validated targets in miRTarBase [387].**	**Role-Pathways Phrases in red are from [136]. ? = more recent data do not support the original identification.**	**Expression in human breast tumors and roles**
miR-9–5p	*CDH1* [124], *LIFR* [125]	Pro-metastatic oncomiR • EMT • CSC [123]	• Increased in breast tumors [388] • Higher in tumors with high T stage and histological grade and higher in HER2+ and TNBC than other BCa subtypes [120] • Patients whose breast tumor have high miR-9 show lower OS and DFS [122,123].
miR-10b-5p	*TBX5, PTEN, HOXD10* [389], *NF1, KLF4* [114], *TBX5* [390]	Pro-metastatic EMT Adhesion, migration, invasion • Whole-body knockout of miR-induced mammary tumorigenesis and metastasis [114].	• Expression positively correlated BCa tumor stage and higher in the lymph node positive BCa [391] • Overexpression induced migration and invasion and promotes metastasis in xenograft models [390].
miR-21–5p	*PTEN, PDCD4* [392,393]; *NFIB* [394]; *TPM1* [395], *RASA1* and *RASA2* [396]; *BTG2, FBXO11, MARCKS, RECK*, and *TPM1* [397]; *TIMP3* [398]; *LZTFL1* [399]	Pro-metastatic apoptosis • PI3K-AKT signaling-angiogenesis [400] • Links inflammation and cancer [401]. • Knockdown of miR-21 inhibits cell proliferation, EMT markers: decrease in E-cadherin and increased N-Cadherin, • Vimentin, and nuclear β-catenin *in vitro* and *in vivo* in Hs578T BCa cells and xenografts in mice [399]	• High in breast tumors [402] • levels positively correlate with tumor stage and LN status and plasma levels are higher than control or benign breast disease patients [399]. • Overexpression was associated only with reduced DFS, but not with OS [403]. • Overexpression in HER2+ tumors is associated with resistance to trastuzumab [404]
miR-143–3p	*MAPK1* [405]; *DNMT3A* [406]; *CIAPIN1* [407]; *BCL2* [408]; *KRAS, HRAS, CD44, AKT1*	Pro-metastatic • RAS signaling in basal-like BCa [135].	• Downregulated in BCa tumors [127,134];
miR-182–5p	*PFN1* [409] *PLD1* [410] *SNAI1* [138] *FOXO3a* [137]	Pro-metastatic EMT • Tumor suppressor in primary site	• Increased in breast tumors vs. adjacent normal tissue [409] • High expression of miR-182 was correlated with reduced *SNAI1* in metastatic lymph nodes of breast tumor samples [138].

miRNA	***Bona fide* validated Gene targets Those miRNA gene targets not cited by reference number were identified as validated targets in miRTarBase [387].**	**Role-Pathways Phrases in red are from [136]. ? = more recent data do not support the original identification.**	**Expression in human breast tumors and roles**
miR-373	*ESR1* [144]; *CD44* [139] *TXNIP* and *RABEP1* [411]; *RELA* and *TGFBR2* [141]	Pro-metastatic	• Higher in DCIS vs. normal breast epithelium [394]. • Serum concentrations are not higher in patients with metastatic disease at diagnosis vs. non-metastatic BCa [147] • Higher in circulating exosomes from TNBC patients vs. benign breast disease [144].
miR-520c-3p	*RELA* and *TGFBR2* [141] *IL8* [140]; *CD44, MROP, SIRT1, GPC3, MICA, XPNPEP1*	Pro-metastatic	• Upregulated in patients who developed metastasis [118].
miR-29a/b/c	*DICER1, TTP, PTEN, ARP1B1, KLF4, MYP, ANGPTL4, LOX, MMP, PDFGC, VEGFA, ADAM12, SERPINH1* (reviewed in [11,154,26]). *ATP5G1* and *ATPIF1* [335]	Pro-metastatic? • miR-29 family members have both tumor suppressor and oncomiR roles [412]	• Upregulated in BCa tissues [127] • miR-29b-1–5p is decreased in breast tumors of human BRCA1 mutation carriers and BRCA1 binds the miR-29b-1 promoter to increase transcription and processing [413] • High miR-29b-1–5p expression stratified with a better outcome for patients with basal-like tumors and TNBC and miR-29b-1–5p stratified OS greater than any of the tested clinical markers including age at diagnosis and lymph node status [413]
miR-27a/b (share 20/21 nt)	*ZBTB10* [414] *FOXO1* [252] *SPRY2* [336] *FBXW7* [415] miR-27b: *CYP1B1* [416]; *ST14, MMP13* [417]	Pro-metastatic Pro-Angiogenesis	• Higher in tumors with lymph node metastases [336] • Overexpression promotes MCF-7 cell migration and invasion, but not proliferation, *in vitro* and increased liver "metastasis" after tail vein injection of lentivirus transformed miR-27a-infected MCF-7 cells *in vivo* [336]
miR-19a-3p miR-19b-3p (miR-17/20 cluster on chromosome 13q31 encodes six miRNAs [418]).	*FOSL* (Fra-1)[419]; *IMPDH1 & NPEPL1* [420]; *PTEN* [421] *BRCA2* [422] miR-19b: *VEZF1* [155]	Pro-metastatic? Pro-Angiogenesis?	• miR-19a - Higher in TNBC *vs.* luminal tumors [118] • miR-19a - Higher in serum of BCa patients than controls and decreased after radiation or chemotherapy [423] • miR-19b - lower in invasive BCa tumors *vs.* normal breast or DCIS [156] • miR-19b - increased and is associated with distant metastasis, TNM stage and reduced OS [157].
miR-221–3p	*ESR1*/ERα [159], *CDKN1B, FOXO3, KIT, PTEN* and *TIMP3, BRAP, ARIH2, FOS, ICAM1*	Pro-metastatic Angiogenesis	• Increased in tumors of patients who develop TAM-resistance [424]. • Decreased in breast tumors of human BRCA1 mutation carriers [413]
miR-222–3p	*ESR1*/ERα [159], *TIMP3* [425], *STAT5A* [426], *MMP1* [427], *FOXO3, FOX, PTEN, KIT, SOCS1*	Pro-metastatic Angiogenesis	• Increased in breast tumors [430].

miRNA	*Bona fide* validated Gene targets Those miRNA gene targets not cited by reference number were identified as validated targets in miRTarBase [387].	Role-Pathways Phrases in red are from [136]. ? = more recent data do not support the original identification.	Expression in human breast tumors and roles
	and *CDKN1B* [428]; LBR in CAFs [429]		• High expression was associated with short relapse-free time in ER+/PR+ BCa patients [431]. • Increased in CAFs from BCa resection samples using laser microdissection (LMD) [429]
Let-7f	*CYP19A1* [162]	Pro-metastatic Angiogenesis	• Higher in node negative *vs.* positive human breast tumors [432] and higher in ER+ tumors [433]. • Let-7 family members are downregulated in BCa tissues with tumor grade [434] • Let-7f is upregulated by letrozole treatment in clinical samples [162]
miR-141–3p (a member of the miR-200 family [435])	*ZEB1,ZEB2* [163,164]; *TGFB2* [436], *PTEN* [437], *EIF4E* [438], *CTNNB1* [439]; *ANP32E* [440], *CDC25B* [435], *CTBP2, MAPK14, PPARA, BRD3, UBAP1, ZFPM2*	Anti-metastatic? • EMT	• Up-regulated in atypical ductal hyperplasia (ADH), DCIS and IDC compared to normal breast [441] • Higher in the blood of patients with stage I-III, lymph node metastasis, and HER2-negative tumors [442] • Lower in basal vs luminal breast tumors [440] • Higher blood levels were associated with shorter PFS and OS [443] • Higher blood levels are associated with breast tumor metastasis [444] • Downregulated by progesterone in luminal BCa cells [445]
miR-193b	*PLAU* (UPA) [167] *YWHAZ, SHMT2, AKR1C2* [446]	*Anti-metastatic*	• miR-193b expression was lower in BCa patients with lymph node metastasis [167]
miR-200a/b/c	*ZEB1 ZEB2* [317,376–379]; *SLUG*, *BCL2*, *E2F2*, *RND3*, *VEGFA*, *KDR*, *FLT1*, *ETS1*, *SUZ12*, *BMI1*, *NOTCH*, *LIN28B*, *FOXM1* [447]	*Anti-metastatic* • EMT	• Correlated with ERα/PR+ in human breast tumors [432] • Downregulated by TGFβ [448] and by ZEB1/2 [376]
miR-205–5p	*ZEB1, SIP1* [164]; *ERBB2* [449]; *SHP2, PTEN, E2F1,E2F5 PRKCE* (PKC epsilon), *VEGFA, ERBB3* [450]; *NOTCH2* [451]; *ITGA5* [452]	*Anti-metastatic* • EMT • CSC suppressor [451] • Tumor suppressor • ERBB2 signaling epigenetically suppresses miR-205 transcription via the Ras/Raf/MEK/ERK pathway [453].	• Downregulated in BCa tissues [127]; • Downregulation is associated with reduced DFS and OS in early BCa [403]. • Low expression correlates with reduced recurrence free survival (RFS) and distant metastasis free survival [452]. • Loss of miR-205 in poorly differentiated high-grade tumors was positively correlated with increased JAG1, ZEB1, and NOTCH2 in breast tumors[451] • Reduced in serum of BCa patients vs controls [454]

miRNA	***Bona fide* validated Gene targets Those miRNA gene targets not cited by reference number were identified as validated targets in miRTarBase [387].**	**Role-Pathways Phrases in red are from [136]. ? = more recent data do not support the original identification.**	**Expression in human breast tumors and roles**
miR-429 (miR-200 family member [435])	*LRP1* [455], *PLCG1* [456] *ZEB1* & *ZEB2* [435]	*Anti-metastatic* • EMT	• Downregulated in BCa and lower in metastatic BCa [457];
miR-146a/b	*RHOA* [458]	*Anti-metastatic* • Migration/invasion	• Upregulated by BRMS1 [115]
miR-206	*NOTCH3* [459]	*Anti-metastatic* • Migration/invasion	• Expression reduced in metastatic variants derived from the MDA-MB-231 TNBC cells [460]
miR-335	*SOX4, TNC, MERTK, PTPRN2* [460]; *ESR1, IGF1R SP1* [461]	*Anti-metastatic* • Migration/invasion • Tumor suppressor [462]	• Decreased in sporadic breast tumors compared with normal controls and reduced expression correlated with reduced OS [461] • No correlation with pre-miR-335, miR-335–5p, or miR-335–3p to a specific BCa subtype, but lower than normal breast tissue [463].
miR-31–5p	*ITGA2, ITGA5, ITGAV, ITGB1, ITGB3, ITGB5* [464]; *FZD3, ITGA5, M-RIP, MMP16, RDX, RHOA, SATB2* [388]; *DICER1* [465]; SATB2 [466]	*Anti-metastatic* • Migration/invasion by inhibiting the expression of integrins [464]. • Apoptosis • Colonization	• Initial studies reporting that levels in primary breast tumors were inversely associated with the propensity for metastatic relapse were retracted [116] • Lower in invasive ductal carcinomas (IDC) *vs.* ductal carcinoma *in situ* (DCIS) [118] • Lower in DCIS *vs.* invasive breast cancer (IBC) [119] • Lower in TNBC tumors *vs.* normal breast specimen [467] • Encoded in a region with copy number variations in breast tumors [468] • IsomiR-31s have concordant and discordant regulation of target genes in BCa cells [465] • Downregulated by oncogenic EMSY that interacts with KDM5B and ETS-1 to demethylate H3K4me3 in the miR-31 promoter, thus repressing transcription [469,470]
miR-15b-5p	*MTSS1* [180]; *CCNE1, RECK, BCL2, CCND1, VEGFA, EI4A1, AXIN2, IFNG, PURA*	*Anti-metastatic*? [178]	• Downregulated in CSC [172] • Downregulated in macrophages cultured with conditioned medium from ID4-overexpressing BCa cells [471]
miR-16 miR-15a/ miR-16 cluster	*CCDN1, CCNE1* [472], *BCL2* [473]; *EEF1AKNMT* (METTL13) [474]	*Anti-metastatic*	• Detectable in whole blood, serum, and plasma samples from BCa patients, as well as healthy controls- considered a “reliable endogenous control” [475] • Stably expressed in primary BCa tumors and metastasis as a strong “housekeeping candidate” [476]

miRNA	*Bona fide* validated Gene targets Those miRNA gene targets not cited by reference number were identified as validated targets in miRTarBase [387].	Role-Pathways Phrases in red are from [136]. ? = more recent data do not support the original identification.	Expression in human breast tumors and roles
			• upregulated in brain metastasis compared with primary BCa tumors [182] • Upregulated in plasma of BCa patients *vs.* healthy controls [477]
miR-20a-5p (part of the miR-17–92 cluster)	*TGFBR2* [478]; *E2F1* [479]; *CCND1* [418], *CXCL8* (IL-8) [480], *ZBTB4* [481]; *BECN1, ATG16L1, SQSTM1* [482]; *RUNX3* [483]; *HMGA2* [484];	*Anti-metastatic?* • LncRNA HOTAIR is upregulated in breast tumors, targets miR-20a-5p, and represses its expression [484]	• miR-20a is downregulated in breast tumors [478] • miR-20a-5p expression is higher in high grade breast tumors and higher in TNBC *vs.* other BCa tumors (n = 102() [485] • Downregulated in TNBC vs. ER+/PR+ breast tumors. [486]
miR-20b-3p and miR-20b-5p (from pri-mir-106a-363 on Chromosome X)	For 3p: *ESR1* [487]; *EPAS1* [488]; *NCOA3* (SRC-3, AIB-1) [489]; *BRCA1, PTEN* [490]; For 5p: *ARID4A, MYLIP* [491]; *HIF1A, VEGFA* [492]; *PPARG, BAMBI, CRIM1* [493] *EPHB4, EFNB2* [494]; *PTEN* [495]; *SOS1, ERK2* [496].	*Anti-metastatic?* • Expression is stimulated by EGR1 [490].	• Lower expression in taxol-resistant breast tumors and cells [55]. • Down-regulated in tumors from patients with early recurrence [497] • Downregulated in TNBC vs. ER+/PR+ breast tumors. [486] • miR-20b-5p was increased in plasma and serum from BCa patients vs controls [498]

Abbreviations: BCa = breast cancer; ceRNA = competing endogenous RNA (‘miRNA sponge’); CSC = cancer stem cells; DCIS = ductal carcinoma *in situ*; DFS = disease-free survival; EMT = epithelial-to-mesenchymal transition; LN = lymph node; OS = overall survival; RFS = relapse-free survival; TNBC = triple negative breast cancer;

Table 2:

Metastasis suppressors identified by Welch and colleagues [75], their regulation by miRNAs, and roles in breast cancer.

Metastasis suppressor genes do not prevent primary tumor cell growth, but inhibit metastasis. Those miRNA gene targets not cited by reference number were identified as validated targets in miRTarBase [387].

Metastasis suppressor	miRNA regulation	Role	Breast cancer
BRMS1	None reported for BCa; miR-3200–5p in osteosarcoma [499]; miR-346 in hepatocellular carcinoma (HCC) [500]	• Breast cancer metastasis suppressor 1 (BRMS1) interacts with HDAC corepressor complexes [501], ARID4A [169] • Upregulates miR-146a/b in TNBC cells that target EGFR and CXCR4 to block metastasis [115]	• strong correlation between loss of BRMS1 protein expression and reduced DFS ER− and HER2+ breast tumors [502]
CADM1	None reported for BCa; miR-10b in HCC [503]; miR-214 in colorectal cancer cells [187]	• Suppresses ERB2/ERB3 signaling [504]	• Gene is methylated and protein IHC staining is low in primary BCa tumors with lower expression in ~ 72% of invasive lesions from the same patients [505]. • miR-214 is a breast tumor suppressor [188]
KISS1 [75]	None experimentally reported for BCa; however, miR-137and miR-345 were identified as putative targets *in silico* [506]	• Suppresses invasion and maintains dormancy in BCa cells [506]	• higher in breast tumors vs. normal tissue and correlated with reduced DFS [507] • reduced in BCa metastasis to the brain relative to the breast primary tumor and expression is reduced by CXCL12 from astrocytes [189].
NR1H4 = FXR	None reported for BCa; miR-421 in biliary tract cancer [194]; miR-192–3p and miR-192–5p in HCC cells [195]	• FXR = bile acid receptor, heterodimerizes with RXR to regulate gene transcription [508]	• Higher expression is associated with improved DFS and OS in BCa patients [192]
GAS1	miR-34a-5p in papillary thyroid carcinoma cells [509]	• Growth arrest specific 1 (GAS1) is a 37 kDa protein that has structural homology with receptors for the GDNF family of ligands that promote cell proliferation by activating MAPK and PI3K7AKT signaling (reviewed in[196] • Overexpression of GAS1 in MDA-MB-231 TNBC cells inhibited xenograft tumor growth in vivo [196]. • An enhancer of HH signaling via binding to SHH protein and acts as a positive regulator of CSC maintenance [197]	•
CD82 KAI1	miR-203 in H1299 lung adenocarcinoma cells [510]; miR-97 in gastric cancer [511].	• membrane glycoprotein that is a member with no intrinsic activity [198] • Tumor suppressor: interacts with multiple protein partners, suppresses cell motility and metastasis of MDA-	• KAI1 protein was downregulated in highly malignant BCa cell lines and tumors and only 19% of infiltrating tumor specimens retained KAI1 staining [512]

Metastasis suppressor	miRNA regulation	Role	Breast cancer
		MB-231 and MDA-MB-435 BCa cells in mouse models [198]	
LIFR	miR-9 [125]; miR-629–3 [202]	• Functions in the Hippo-Yap pathway to suppress metastasis [201]	• Downregulated in breast tumors and inversely correlates with metastasis [125]
KDM1A	miR-137 [513], miR-329–3p [514], miR-708–5p [515]	• Lysine-specific demethylase 1A (LSD1, gene *KDM1A)* is a histone demethylase for H3K4me2/1 or H3K9me2/1, p53, DMNT1, E2F1, HIF-1α, and STAT3 [203]	• upregulated in breast tumors vs normal epithelial breast tissue [516]
MTBP	None listed in miRTarBase	• MDM2 Binding Protein (aka MDM2BP) is involved in cell cycle arrest • Locates in nucleus, interacts with MYC as a transcriptional cofactor [208]	• Overexpression was associated with reduced BCa OS [208] • Amplified in 19% of breast tumors and highest in TNBC [209]
MAP2K4	miR-27a-3p, miR-92a-3p	• Plays a role in MAPK-PI3K crosstalk signaling and is associated with drug resistance in several cancers [210] • Overexpression of MAP2K4 in BCa cells increased proliferation, migration, and invasion *in vivo* and *in vitro* [213].	• Inactivating mutations in ~7% of metastatic breast tumors and is considered a ‘driver gene’ [517] [518] • Mutated in brain metastases in HER2+/ERBB2+ BCa [519] • Important in resistance to buparlisib, a pan-PI3K inhibitor [210] • Mutation found in one metastatic lesion from a BCa patient who developed AI-resistance [520]
NDRG1	miR-769–3p [216]; miR-182 in prostate cancer cells [521]; miR-449a in endometrial cancer cells [522]	• MYCN (N-Myc) downstream regulated gene (NDRG1) is a direct target of HIFlα and XBP1 and is associated with ERα- BCa [214]	• High NDRG1 expression is associated with twofold higher risk of disease recurrence 5 years after diagnosis [214]
NME1 (Nm23, NM23-H1)	None in miRTarBase miR-645 in osteosarcoma cells [523]	• Gene expression reduced by methylation in BCa cells and tumors [524,525] • Important in non-homologous end joining for DNA repair [526] • Interacts directly with ERα [527] • Extracellular secretion and is found in extracellular vesicles [528] • Binds a cleaved form of the MUC1 transmembrane receptor (MUC1*) as a homodimer and stimulates the growth of human embryonic stem cells [529]	• Higher IHC staining in breast tumors correlated with longer metastasis-free survival in both nodepositive and node-negative groups of patients [530] • Lower Nm23 staining was associated with lower metastasis-free survival, independent of tumor size, grade, or histological grade [530]
GPR68 (OGR1)	None in miRTarBase; miR-18a-3p in Leydig cells [531]	• A proton-sensing GPCR • No studies related to BCa metastasis were found	• High expression in pancreatic cancer-associated fibroblasts and pancreatic

Metastasis suppressor	miRNA regulation	Role	Breast cancer
			adenocarcinoma tumors (PAC) [532]
RRM1 (Rho-GDI beta)	miR-101–3p in pancreatic cancer [533]	• Ribonucleotide Reductase Catalytic Subunit M - component of the ribonucleotide reductase (RNR) enzyme complex is essential for the *de novo* synthesis of deoxyribonucleotides (dNTPs) precursors for DNA synthesis [534].	• Higher in BCa tumors vs. adjacent normal breast tissue; however there was no association with RFS or OS [535] • Copy number changes are detected in primary BCa tumors but are not associated with altered clinical outcome [536] • Copy number variations predicted gemcitabine response [537]
AKAP12 (AKAP 250 or Gravin)	miR-186–5p [538]; miR-103 in HCC [539]	• A-Kinase Anchoring Protein 12-binds the regulatory subunit of PKA is a scaffolding protein that interacts with cyclins and F-actin downregulated in many cancers [540]	• *AKAP12* transcript is downregulated in human BCa tumors and low expression is associated with lower RFS [541].
CST6	None in miRTarBase	• Cystatin E/M (CST6) functions as an endogenous inhibitor of lysosomal cysteine proteases to protect cells against uncontrolled proteolysis and regulates cathepsins B and L [542] • Silenced by DNA hypermethylation in TNBC tumors [543]	• CST promoter methylation was associated with reduced DFS and OS in BCa patients [542] • promoter methylation was observed in 3/29 (10.3%) of breast tissues from mammoplasties, 11/31 (35.5%) patients with early BCa and 16/32 (50.0%) patients with metastasis; however there was no correlation with methylation in CTCs [544] • Upregulated in TNBC compared to normal and correlated with reduced DFS [545]
TIMP1 and *TIMP2*	*TIMP1*: miR-519a-3p, miR-181a-5p, miR-1293, miR-17–5p, miR-337–3p *TIMP2*: miR-519d-3p, miR-519c-3p, miR-200c-3p, miR-106–5p, miR-17–5p, miR-429	• tissue inhibitors of metalloproteinases (TIMPs) regulate ECM by activating MMPs • produced by mesenchymal stem cells are anti-metastatic in *in vitro* assays using MDA-MB-231 TNBC cells [546]	• Expression was comparable between malignant and benign tumors [547]
TIMP3	miR-181a-5p, miR-181b [548], miR-21–5p [549], miR-222–3p [550]	• TIMP3 inhibits the activity of MMP-1, −2, −3, −9, and −13 [547]	• Downregulated by methylation in breast tumors [551]
TIMP4	miR-200b-3p in prostate ca cells [552]	• TIMP4 inhibits MMP-2, −9, −7 [547] • TIMP4 stimulates BCa cellular invasion, migration, and VEGFA expression and secretion *in vitro* [553]	• No difference in TIMP4 expression in breast tumors vs. normal breast tissue [553]

Table 3.
Regulation of EMT-related genes by miRNAs in breast cancer and metastasis.

Genes involved in EMT are from those listed in dbEMT 2.0 [236] or are from the indicated references. We have included only some of the 265 "dual role" (oncogenic and tumor suppressive) and oncogenic EMR-related genes. Those miRNA gene targets not cited by reference number were identified as validated targets in miRTarBase [387].

EMT-related gene	miRNA regulation in BCa	Role and regulation	Breast cancer (BCa)
EPHA2	miR-200a [241]	• oncogenic cell-surface receptor tyrosine kinase • located at sites of cell-cell contact that is regulated by phosphorylation-unliganded EPHA2 is phosphorylated by AKT which results in enhanced pro-oncogenic signaling [239] • increased by TGFβ [554], not WNT-β-catenin/TCF-4 signaling [555]	• Overexpressed in aggressive forms of BCa, including the HER2+, and correlates with poor prognosis [240].
ETS2	miR-320 [556] miR-320b [557]	• Oncogenic TF • Increased by TGFβ in MDA-MB-231 cells [558]	• Increased protein expression in breast carcinomas vs. fibroadenomas or normal breast tissue [242]. • Higher nuclear phospho-ETS2 in AI-resistant lung metastasis (n =3) vs. matched primary breast tumor [245].
EZH2	miR-92b [559]; miR-26a [560]; miR-25, miR-214, miR-30d, miR-101 [187]	• EZH2 is a methyltransferase in the PRC2 complex that epigenetically silences gene transcription [246]. • It acts as a tumor suppressor or an oncogene [561]. • Increased by mutant p53 in TNBC [384]	• EZH2 increased in histologically normal breast epithelium with higher risk of developing cancer [562]. • High EZH2 gene expression correlates with lowered DFS in BCa patients [563]. • High EZH2 IHC staining is associated with high NOTCH1 (NICD1) staining and increased CSCs in human BCa tissues [249].
FOXO1	miR-27a, miR-96, and miR-182 [252]; miR-9, miR-153, miR-183, and miR-186 [564]; miR-5188 [253]	• FOXO1 is phosphorylated by AKT and inactivated in BCa [565].	• FOXO1 is a tumor suppressor whose expression is lower in breast tumors than normal breast tissue [252].
RHOA	miR-155 [388]; miR-146a [458]; miR-490–3p [566]; miR-101 [567]; miR-150 [119]; miR-381 [568]	• GTP binding protein that activates cytoskeletal reorganization and activates BCa cell invasion [255]. • Activated by TGFβ signaling [569]	• RHOA is upregulated in breast tumors [570].
SKP2	None for BCa, but miRNA-330–5p in pancreatic cancer [571]; miR-30d-5p in lung cancer [263]; miR-508–5p in gastric cancer [572]	• oncogene • Upregulated in TAM-R MCF-7 cells [573] • Repressed by FOXP3 in mouse mammary gland and tumors [574]	• High expression is associated with increased risk of local and distant recurrence in > 1,000 radiation therapy-treated BCa patients [262].

EMT-related gene	miRNA regulation in BCa	Role and regulation	Breast cancer (BCa)
CCN3	miR-30c [575]	• Small (30–40 kDa) secreted cysteine-rich protein that promotes the formation of osteolytic BCa metastases by modulating the bone microenvironment to favor osteoclast differentiation [576]. • Increased by TGFβ [577]	• CCN3 transcript expression was lower in high grade breast tumors [578], but higher in ER+ breast tumors of patients who relapsed on TAM therapy [579].
KLF4	miR-10b-5p [114] [269];, miR-29a/b/c [580]; miR-7 [581];	• TF with oncogenic and tumor suppressor activities. • KLF4 is a pluripotency factor that increases CSC [267].	• Low KLF4 transcript expression was correlated with BCa development and predicted lower overall survival and TAM-resistance in ERα+ primary tumors [582].
KLF5	miR-590–5p [272]	• Krüppel-like factor 5 (KLF5) is a zinc finger-containing TF regulated by Hippo, WNT, Notch, Ras, and TGFβ signaling pathways [12701]	• KLF5 IHC correlates with HER2+ and with shorter DFS and OS [583] • High KLF5 staining correlated with AR+ and reduced DFS [584]
GREM1	miR-27a in rat bone marrow mesenchymal stem cells [585]	• Gremlin 1 (GREM1) is a bone morphogenetic protein (BMP)-antagonist that is produced by cancer associated fibroblasts (CAFs) and increases CSC [586] • miR-27a is higher in breast tumors vs. normal breast [415], a result that would be expected to reduce GREM1 protein. • miR-27a is included in extracellular vesicles secreted by BCa cells and BCa patient serum and targets other genes in BCa (reviewed in [11])	• upregulated in breast tumors by gene amplification and is associated with metastasis and lower DFS in ER-BCa patients [587].
STAT3	miR-519d [276]; miR-124 in TNBC [588]	• TF activated by phosphorylation downstream of cytokine and growth factor signaling	• Nuclear pSTAT3 staining is increased in breast tumors and provides a survival advantage [277]
SALL4	miR-33b [589]	• Represses *CDH1* and increases *BMI1, CCND1*, and *CCND2* [280]	• *SALL4* is upregulated in human breast tumors and correlates with reduced OS [280] • miR-33b is downregulated in human breast tumors [589]
ILK	miR-625 in gastric cancer [590]; miR-145 in bladder cancer [591]	• integrin-linked kinase (ILK) is a serine/threonine kinase that interacts with β1-integrin to promote survival, migration and EMT [592] • non-canonical TGFβ signaling [593] • HIF-lα [594]	• ILK and CD44 doublepositive BCa tumor cells were located in regions with high levels of collagen that are considered to be CSC microenvironments [594]
GLI1	miR-361–3p in retinoblastoma [595]	• A member of the Kruppel family of zinc-finger TFs that is activated by Hedgehog (HH) signaling [283].	• GLI1 IHC staining is increased in breast tumors and positively associated with histological grade [597]

EMT-related gene	miRNA regulation in BCa	Role and regulation	Breast cancer (BCa)
		• Directly interacts with STAT3 and stimulates CSC [284] • Upregulated by TGFβ and Hedgehog signaling and downregulated by Notch signaling [596]	• expression inversely correlated with DFS, notably in Luminal A tumors [598]. • GLI1/tGLI1 activation and STAT3 activation gene signatures are co-enriched in TNBC and HER2-enriched breast tumors, but not in luminal breast tumors [284].
SIRT1	miR-22 [599]; miR-200a [600]; miR-34a [601]; miR-211–5p[602]	• Has both pro- and anti-EMT activities depending on the breast model studied. • Post-transcriptional activation by MYC [603] • Activated by AMPK [604] • Induced by E2 and GPER1-selective ligand G-1 via rapid EGFR/ERK1/2 signaling and the stimulation of c-Fos (*FOS*) expression which is recruited to the AP-1 site located within the SIRT1 promoter sequence [605].	• *SIRT1* overexpression was not correlated with the overall survival in BCa [606]. • Downregulated in aggressive breast tumors [290] • Downregulated in TNBC vs normal breast tissue • [291]
CCN2 (previously CTGF, connective tissue growth factor)	miR-124–3p, miR-18a-5p, miR-145–5p	• CCN2/CTGF is a secreted growth factor that is increased ~ 2-fold by TGFβ signaling in fibroblasts where it simulates angiogenesis, but it inhibits the migration and invasion of ovarian and CRC cancer cells [294] • CCN2/CTGF interacts with cytokines, growth factors, integrins and receptors for TGFβ and BMP [607] • Overexpression of CCN2 in MDA-MB-231 TNBC cells stimulated autophagy and inhibited xenograft tumor growth [294]	• CTGF (along with VEGFA) secreted by Hs578T, BT474, MDA-MB-231, HCC1954, HCC1419, and HCC202 BCa cells in exosomes induced a “secretome” in co-cultured Hs578Bst fibroblasts that stimulated migration of the fibroblasts [608]
PRKCE	miR-1–3p, miR-31–5p, miR-107, miR-146–5p	• PRKCE encodes protein kinase C epsilon (PKCξ) that is involved in inhibition of apoptosis, EMT, migration, anoikis resistance, and sternness in cancer [609]	• Overexpression is associated with BCa metastasis [610]
TP63	miR-196a2* [304]; miR-203–3p [611]	• Tumor protein 63 (TP63, also called p63) is a member of the p53 TF family with cell-specific oncogenic and tumor suppressor activities [301] • There are 6 protein isoforms due to differential promotors and alternative splicing [302] • TAp63 provides pro-apoptotic and senescence- inducing properties, whereas ΔNp63 isoforms stimulate cell survival [303] • miR-196a2* is upregulated by E2-stimulated ERα-ERK transcriptional activation in BCa cells [304]	• Overexpressed in highly aggressive ER- basal-like breast tumors [612] • ΔNp63 associated with metaplastic and medullary TNBC tumors, and with a basal phenotype, whereas TAp63 associated with AR, BRCA1/2 wild-type status and PTEN positivity and with improved OS [303]

EMT-related gene	miRNA regulation in BCa	Role and regulation	Breast cancer (BCa)
SUZ12	miR-200abc [447]; miR-200b [613]; miR-103/7 and miR15b/16 families [172]	• Core scaffolding subunit of the PRC complex [614] • Represses CDH1 and is required to CSC growth [613] • inhibited by transcriptional repressor GATA binding 1 (*TRPS1*) which acts as a tumor suppressor by binding to the SUZ12 promoter and preventing expression [615]	•
CDKN1B	miR-203 [309]; miR-455–5p [616]	• codes for p27 (p27Kip1), a tumor suppressor	• High breast tumor p27 correlates with a good prognosis [617] • Low p27 in breast tumors is associated with lower OS [618]
WT1	miR-193a in BCa [313];	• *WT1* (Wilms' tumor 1) gene encodes a zinc finger TF and RNA-binding protein that has both oncogenic and tumor suppressor activities in various cancers [310]	• Higher levels in ER- higher stage breast tumors, but lower levels in infiltrating tumors [619] • Higher WT1 mRNA associate with lower DFS [620] [621] • Vascular WT1 in tumor sections decreased as histopathological grade increased and was associated with poor prognosis [622]. • WT1 was higher in ERα-positive *vs* ERα-negative cancers [622].
HDAC1	miR-34a in BCa [623]	• Histone *deacetylase* involved in epigenetic silencing of transcription in a corepressor complex	• Higher HDAC1 mRNA was reported in ERα+/PR+, HER2-, LN negative, small, low grade breast tumors and was associated higher OS and DFS [624]
RUNX1	miR-378 in BCa cells [625]; miR-139–5p in glioma cells [626]	• RUNX1 is a TF that is a tumor suppressor in part by inhibiting ERα transcriptional activity [627]	• Lower expression in breast tumors and progressively decreases in association with metastasis and poor clinical outcome [628]
SREBP1	miR-18a-5p in BCa [629]	• Sterol regulatory element-binding protein 1 (SREBP1) is a TF regulating the transcription of genes controlling lipid homeostasis [630] • Associated with AI resistance by increasing KRT80 causing cytoskeletal rearrangements associated with poor survival [631]	• Overexpressed and associated with reduced DFS and OS [632]
NME1		• NME1 is one of a family of 10 nucleoside diphosphate kinases with various functions in transcription, DNA repair, and genomic stability [633]	• Expression was associated with ERα in breast tumors and increased metastasis-free survival [635]

EMT-related gene	miRNA regulation in BCa	Role and regulation	Breast cancer (BCa)
		• Metastasis suppressor gene [634]	
CDKN1A	miR-106b in human mammary epithelial cells (HMECs) [636]	• Cyclin Dependent Kinase Inhibitor 1, known as P21, $p21^{Waf1/Cip1}$ WAF, and CIP1 acts as a cell cycle inhibitor when in the nucleus or as an apoptosis inhibitor when localized in the cytoplasm. • Inducted by p53, it has both tumor suppressor and oncogene activity (by suppression of apoptosis) in BCa [637]	• Low in breast tumors with no prognostic value [638] • Cytoplasmic $p21^{Waf1/Cip}$ was associated with decreased OS and shorter DFS [639]
PPARG	miR-27b in neuroblastoma cells [640]; miR-130a-3p in cholangiocarcinoma [641]	• Peroxisome Proliferator Activated Receptor Gamma (PPARγ) is a nuclear receptor activated by endogenous metabolites of arachidonic acid (HODEs) that regulates gene transcription - primarily in skeletal muscle, liver, and adipocytes were it increases fatty acid oxidation [642] • Treatment of BCa cells with troglitazone, a PPARγ agonist, inhibited cell growth and increased markers of differentiation [643,172] • PPARγ agonists, thiazolidinediones, inhibited aromatase expression and activity and reduced estrogen synthesis in human breast adipose stromal cells [644] • Agonist-activated PPARγ induced proteosomal degradation of ER and cyclin D1 proteins in MCF-7 BCa cells [645]	• *PPARG* mRNA is lower in breast tumors vs. normal tissues [646]
CDH1	miR-9–5p [124], miR-199a-5p [318], miR-544a [319], miR-888–5p [320], and miR-421 [337] in BCa; miR-92a-3p [647]	• E-Cadherin is an epithelial cell-cell adhesion glycoprotein whose downregulation if a hallmark of EMT [648] • *CDH1* transcription is stimulated by EP300, FOXA1/2, and RUNX1 [316] • *CDH1* transcription is repressed by ZEB1 [317]	• Reduced E-cadherin correlated with shorter OS in node-negative patients [649] • Reduced or absent E-cadherin (by IHC) in breast tumors significantly increased the risk of all-cause mortality [650]
VIM	miR-124 [325] and miR-17–3p [326] in HCC cells; miR-378g [327]; miR-138 in renal carcinoma [651]	• Vimentin is a type III intermediate filament protein in the cytoskeleton • Increased VIM is a marker of EMT [322,323] and promotes cell migration [324]	• Increased VIM was detected in high grade breast carcinomas [652] • Increased in TNBC vs luminal breast tumors [653]
SPARC	miR-29a-3p and miR-29c-3p [108].	• Secreted Protein Acidic And Cysteine Rich (SPARC, also called osteonectin) is a secreted cell adhesion molecule correlated with metastatic behavior in BCa, with “expression generally restricted to aggressive lung-metastatic populations “[654]	• low SPARC protein was associated with worse DFS [655]

EMT-related gene	miRNA regulation in BCa	Role and regulation	Breast cancer (BCa)
E2F1	miR-20a [479]; miR-149 [656]; miR-17–5p [657]; miR-124 [658]; miR-205 [659,660]; miR-149–3p [656]	• E2F1 is a TF involved in the cyclin/cyclin-dependent kinase/retinoblastoma pathway that regulates transcription> 1,000 genes involved in cell proliferation, differentiation and apoptosis [661] • MYC upregulates E2F1 that stimulates transcription of the miR-106b-25 cluster, its host gene *MCM7*, and miR-20a in the miR-17–92 cluster [485] • E2F1 increases miR-15a [662].	• *E2F1* mRNA expression correlated strongly with the expression of other proliferation markers, *e.g.*, BIRC5, and low values were mainly found in ERα-positive and ERBB2-negative tumors [663].
YAP1	miR-10a-5p in thyroid cancer [664]; miR-15a and miR-16–1 in gastric cancer [665]	• Yes-associated protein (YAP), a transcriptional regulator regulated by cell shape and polarity that is deregulated in various cancers and has a mechanotransducer properties [666] • ZEB1 interacts directly with YAP to activate YAP target gene transcription in MDA-MB-231 TNBC cells and clinical data identified a ‘common ZEB1/Y AP target gene set’ that predicts poor RFS, OS, and metastatic risk [667]	• Increased YAP1 correlates with lower OS [668]
RASSF1	(miR-181b-5p in small cell lung cancer (SCC) was not verified by RASSF1–3’UTR luciferase assay [669])	• The RASSF1 gene encodes two major transcripts, RASSF1A and RASSF1C, that are tumor suppressors [670] • RASSF1 is a regulator of the Hippo tumor suppressor pathway to YAP1 [671] • RASSF1 localizes to the nuclear envelope, interacts with RAN and XPO6 (Exportin) and is required by nucleocytoplasmic actin transport to the cytoplasm from the nucleus [672].	• Located at 3p21.3 that undergoes allele loss and hyper methylation in breast tumors [670]
TGFB1	miR-675 [331]; miR-181a-5p [673]; miR-133b [364]; miR-142–3p in granulosa cells [674]	• Transforming Growth Factor Beta 1 (TGFβ1) binds TGFβ receptor type II (TpRII) receptor that heterodimerizes with TGβR2 (*TGFBR2*) to activate SMAD family TFs to regulate target gene transcription [328]	• TGFβ1 staining was inversely correlated with OS in BCa [675]
TP73	miR-193a-5p in prostate cancer [676]	• TP73 is also called P53-Related Protein (P73) and is a TF related to PTP53 and TP63 all of which control cell proliferation, differentiation, and apoptosis [677]. • TP73 is rarely mutated and has over 24 isoforms • TAp73 is considered a pro-apoptotic tumor suppressor protein whereas ΔNp73, produced by hypermethylation of the P1 promoter in the gene, acts as an anti-apoptotic	• P73 overexpression was associated with LN metastasis, vascular invasion, and high tumor grade [679]. • ΔNp73 isoform is frequently expressed in DCIS in association with high histological grade and lower DFS and OS [678]

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		oncoprotein as a dominant negative for TAp73 and TP53 [678]	
ECT2	miR-223–3p in BCa cells [680]	• Epithelial cell transforming sequence 2 (ECT2) is a guanine nucleotide exchange factor that plays a role in mitosis by recognizing PARylated α-tubulin during mitosis, thus regulating the completion of cytokinesis [681] • ECT2 stimulates invasion and migration of MDA-MB-468 TNBC cells [680]	• Increased in breast tumors relative to normal and related to tumor grade and staging, but not ER/PR, and predicts poor OS [682]
TCF3	miR-506–3p in neural stem cells [683]	• TCF3 (also known as TCF7L1) is a member of the TCF/LEF TF family that regulates and stem cell identity acting primarily as a transcriptional repressor [684]	• High expression in poorly differentiated, basal-like breast tumors [684]
SPRY2	miR-27a/b [336]; miR-128a [685]; miR-21 in gliomas [686] miR-23a and miR-24–2 [336]	• Sprouty (SPRY2) is a negative regulator in the EGF and FGF signaling pathways and is a tumor suppressor • In TNBC, increased EGF induced the expression of c-MYC, which increased the expression of mature miR-23a, miR-24–2, and miR-27a that decreased the expression of SPRY2; and promoted cell migration and invasion through activation of p44/42 MAPK [336].	• mRNA of both *SPRY2* and *SPRY1* is downregulated in breast tumors [687] • Low expression of SPRY2 mRNA was associated with increased pathological grade, high HER2, and was a significant independent prognostic factor of poor RFS and OS [688].
NOTCH1	miR-34a-5p [343]; miR-30a [344]; miR-139–5p [345]; miR-3178 [346] miR-10b [689] and miR-200b [690] in nasopharyngeal carcinoma cells	• NOTCH signaling promotes the self-renewal of CSC in various cancers and participates in tumor-stroma and tumor-endothelium interactions in CSC niches in primary and metastatic tumors [338,339] • CAFs secrete CCL2 that upregulates NOTCH1 and stimulates the stem cell-specific, sphere-forming phenotype in BCa cells and CSC selfrenewal [691]	• High NOTCH1 correlates with lower OS [340]
CAV1	miR-203–3p [611]; miR-124-3p in bladder cancer cells [692]	• Caveolin 1 is a scaffold protein in caveolae in the plasma membrane and is involved in cell signaling - it is considered a tumor suppressor in BCa [693]	• Lack of stromal CAV1 staining was associated with poor prognosis [694] • Stromal CAV1 staining was associated with ERa, tumor size, histological grade, and LN involvement and lack of CAV1 was associated with shorter DFS and OS [695]
WNT5A	miR-374a [696]	• Wingless-type MMTV integration site family member 5An (WNT5A) is a non-canonical secreted signaling WNT that is directly regulated by TGFβ's activation of SMAD binding to the WNT5A gene promoter in mammary epithelial cells [697]	• Increased WNT5A mRNA in breast tumors [699] • Lower WNT5A mRNA in breast tumors than normal breast tissues and low WNT5A correlated with lower OS [700]

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		• WNT5A is an autocrine and paracrine factor that binds heparin sulfate proteoglycans on the plasma membrane and non-canonical receptors: RYK, ROR1/2, and FZD4 [698]. • WNT5A and acts as a morphogen mammary gland development [698] • WNT5A represses cell migration and invasion by a number of pathways including increasing TGRFR1 to increase SMAD2 activation, increasing cAMP-PKA to activate CREB, by inhibiting ERK1/2 signaling [698]	• Lack of WNT5A protein staining correlated with tumor stage and lower OS [701] • Lack of WNT5A correlated with LN metastasis and poor RFS in TNBC [702]
VEGFA	miR-20a [703]; miR-20b[703]; miR-205 [704]; miR-185 [705]; miR-126 [706]; miR-140–5p [707]	• VEGFA (also referred to as VEGF) is an angiogenic factor that promotes tumor progression and is upregulated by HIF-1α [708]. • miR-20a which is downregulated by HIF-1α, resulting in increased VEGFA [703]. • VEGFA increases SOX2 expression, inducing SNAI2, EMT, increased migration and invasion of MDA-MB-231 and SUM149PT cells in vitro and represses lung metastasis of xenografted MD-AMB-231 cells in mice [709]	• VEGFA expression correlates with mutant p53 and lower RFS and OS in ER+ breast tumors [710] • VEGFA is higher in TNBC vs non-TNBC tumors [711] • Upregulated by tumor and metastasis suppressor RKIP in BCa cells [712] • Reduced in BCa tissues [712] • promotes breast CSC self-renewal and metastasis by downregulating SOX2-mediated expression of miR-452, that suppresses metastasis by downregulating *SNAI2* [709]
YWHAG	miR-181b-3p [713]	YWHAG is 14-3-3γ protein that mediates cell signaling and promotes BCa cell motility [714]	• High 14-3-3γ is associated with reduced OS [715] • Higher in metastatic BCa lines *vs.* MCF-7 and T47D luminal A cell lines [713]
TWIST1	miR-580 [716]; miR-300, miR-539, and miR-543 [717]; miR-720 [718]; miR-33b [282]; miR-151–3p [719]; miR-34a [343]; miR-20a [720]; miR-490–3p which is sponged by lncRNA *TP730 AS1* [721]	• Twist Family BHLH Transcription Factor 1 that upregulates the transcription of EMT markers • TWIST1 increased tumor cell dissemination, subsequent downregulation of TWIST1 enhanced metastatic colonization [722] • TWIST1 stimulates miR-424 and MET programming in later stages of metastasis by regulating the EMT-MET axis [723]	• High *TWIST1* mRNA was associated with shorter DFS and OS in ERα+/LN negative patients [724] • Immunostaining revealed increased TWIST1 protein in LN positive breast tumors [725].
SNAI1	miR-203 [726]; miR-129–5p [727]; miR-182 [138]	• SNAI1 (Snail Family Transcriptional Repressor 1) is referred to as Snail (SNAIL) and is a C2H2-zinc finger TF [373]. • represses *CLDN1* (Claudin1) transcription [728]	• *SNAI1* mRNA expression was reduced corresponding with prognostic indices and tumor grade [725].

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		• SNAIL interacts with H3K9 methyltransferase G9a and DNMT1 to silence *CDH1* and *FBP1* (fructose 1,6-bisphosphatase, a rate limiting enzyme in gluconeogenesis) in basal-like BCa cells [729]	
SNAI2	miR-30a [730]; miR-497 [731]; miR-124 [732]; miR-452 [709]	• Snail Family Transcriptional Repressor 2 (Slug or SLUG) is a C2H2-zinc finser TF that is a repressor by binding to E-boxes sequences [373]. • represses *CDH1* and *CLDN1* transcription [728] • SNAI2 transcription is inhibited by ERα overexpression in MDA-MB-468 cells and ERa ChIPs to the SNAI2 promoter with corepressor NCOR (*NCOR1*) and HDAC1 [733] • *SNAI2* was upregulated in endocrine-resistant BCa cell lines relative to parental MCF-7 cells [375]	• Immunostaining revealed increased SNAI2 (SLUG) protein in LN positive breast tumors and an association with lower OS [725]. • High SLUG staining was correlated with histological grade LN metastasis, TNM stage, and with decreased DFS and OS [734]. • Patients with ERα+ primary tumors with high SNAI2 (SLUG) staining showed lower PFS on endocrine therapy [375] • Metastatic tumors from patients treated with endocrine therapy showing high SNAI2 (SLUG) staining had lower PFS [375]
MUC1	miR-125b [735]; miR-145 [360]; miR-145 is sponged by LINC-ROR that is upregulated in TNBC cells and tumors [736]; miR-1226 [737]; miR-1226–3p is sponged by lncRNA MIR210HG [738].	• Mucin 1 (*MUC1*) is translated as a single polypeptide that undergoes autocleavage into two subunits that in turn form a stable heterodimer in the PM: MUC1-N (N terminus that is heavily glycosylated on the extracellular domain) and MUC1-C (Terminus) that is intracellular, in the nucleus, and in mitochondria [352] • MUC1-C interacts with TFs and stimulates EMT and CSC [350,739,359,358]	• Overexpressed in breast tumors vs normal breast [350] • MUC1 gene is amplified in ~ 40% of breast tumors and MUC1 is overexpressed in 90% of breast tumors [350]
ZEB1	miR-141–3p [163,164]; miR-200a [241]; miR-200 family including miR-141 and miR-429 [455,376] [740]; miR-205 [164]; miR-652–3p [741]; miR-101 [567]; miR-455–3p [380]	• Zinc Finger E-box-binding homeobox 1 • EMT-inducer downstream of TGFβ, WNT-β- catenin, and RAS-MAPK signaling pathways [165]. • ZEB1 promotes EMT by suppressing *CDH1* transcription [742] • ZEB1 upregulates pro-inflammatory cytokine *IL6* and *IL8* transcription in MDA-MB-231-D (bone metastatic) cells [743]	• ZEB1 is expressed in the stromal compartment of breast carcinomas [744] • Increased in epithelial cells in breast tumors [745] • ZEB1 expression in TNBC tumors was associated with lower DFS [746]
ZEB2	141–3p [163,164]; miR-200a [241]; miR-200 family-including miR-141 and miR-429 [163] [455,740] [376]; miR-155–5p [747]; miR-101 [567]; miR-124 [748];	• Zinc Finger E-box-binding homeobox 2 • ZEB2 promotes EMT by suppressing *CDH1* transcription [376] • TFAP2A stimulates *ZEB2* transcription [750]	• Upregulated in BCa tissues [127] • Higher in the serum of BCa patients than healthy women [147].

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	miR-30a-5p and miR-30a-3p [749]	• TET1, a demethylase upregulated in BCa, binds the *ZEB2* promoter and increases ZEB2 expression [751]	