Breast cancer invasion by microRNAs aid

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Review

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Abstract: In 2018, there were an estimated 8.6 million new cases of cancer in women and 4.2 million deaths from cancer worldwide. In addition, 20% of women who are diagnosed with breast cancer will go on to develop metastases. Therefore, there is an urgent need to discover new molecular markers for the diagnosis and prognostic prediction of metastatic illness and to create novel treatment agents. MicroRNAs (miRNAs) have been studied extensively in breast cancer and have been shown to induce numerous alterations in the expression of genes involved in carcinogenesis. In this review, we compile recent information on breast cancer-specific miRNA expression profiles and their role in regulating invasive processes, in conjunction with alterations in cytoskeletal structure, cell-cell adhesion junctions, cancer cell-extracellular matrix interactions, tumor microenvironments, epithelial-to-mesenchymal transitions, and cancer cell stem abilities. Finally, we discussed the role of miRNA isoforms and exosome-mediated miRNA transfer in cancer invasiveness, and we focused on how epigenetic regulation affects individual miRNAs and how those miRNAs interact with other regulatory genes. While more work is needed to fully understand the role of miRNAs in cancer, the findings presented here help advance the treatment of metastatic disease.

Keywords: Female cancer; breast cancer; invasiveness; metastasis; microRNA (miRNA) target genes; epigenetic control

1. Introduction

As a prologue, the International Agency for Research on Cancer's GLOBOCAN 2018 estimates suggest over 8.6 million new cases of female cancer and 4.2 million related deaths. Breast, cervix uteri, mainly endometrial corpus uteri, ovary, vulvar, and vaginal cancers had respective rates of occurrence of 24.2%, 6.6%, 4.4%, 3.4%, 0.5%, and 0.2%, and death rates of 15%, 7.4%, 2.1%, 4.4%, 0.5%, and 0.2% [1]. The following may be deduced by comparing the prevalence and distribution of various cancers. While about one-fifth of breast cancer patients (BC) develop metastatic illness, upon first diagnosis around 6% had distant metastases in the bone, liver, lung, and non-axillary lymph nodes and fewer in the brain [2-4]. However, 13% of cervical cancer (CC) patients were diagnosed as having advanced disease, and the survival statistics for those with metastases that spread via the haematogenous and lymphogenous systems are distinct. Lymph nodes in the peritoneum are a potential entry point for CC metastasis to other organs, including the lung, liver, bone, and brain [5]. About 75% of patients with ovarian cancer (OC) had cancer cell spread in the peritoneal cavity at the time of diagnosis [6], making it the second most lethal of all gynecological cancers. Most of these tumors were primary and epithelial in nature [7], but 10-20% were found to be metastases from other cancers that had spread to the ovary. The high incidence of the less aggressive endometrioid type [8] contributes to the high five-year overall survival in patients without metastasis, particularly when endometrial cancer (EC) is identified at an early stage when the malignant alterations are still confined to the uterus. Early metastasis to the cervix, vagina, and myometrium from non-endometrioid cancers is prevalent, and lung metastases from more distant sites are also common. Rare ECs are endometrial metastases from other malignancies or melanomas, such as those of the breast, ovary, lung, stomach, or intestines [9]. Because metastases are often resistant to standard treatment, only palliative therapeutic options exist, making metastatic illness an extremely significant medical concern. Metastasis development is also known as the invasion-metastasis cascade and it entails a complicated process defined in separate phases. The cancer cells intravasate locally through surrounding extracellular matrix and stromal cell layers and reach the lumina of neighboring lymph

and blood arteries, where they survive and are carried through the circulatory system escaping physical damage and host immune response. The cancer cells cling to the vessel walls and subsequently extravasate into the parenchyma of a distant organ, where the ones that make it may multiply into macro-metastases. Both malignant and nonmalignant cells in the TM experience genetic and epigenetic alterations throughout these processes [12]. Less than 0.01% of cancer cells in the systemic circulation become macroscopic metastases [13], making metastatic spread look exceedingly inefficient. Early dissemination of semi competent metastatic cancer cells from a primary tumor, accumulating diverse molecular changes at distant body sites, rather than late dissemination of fully malignant cells, is supported by expanding understanding of the molecular characteristics and interactions of cancer and non-malignant cells[12,14,15]. There is evidence that these metastasized cancer cells may lie latent for a considerable amount of time, perhaps years [16]. The interaction of cancer cells with microenvironmental components, blood supply constraints, or an active immune system may influence the beginning of proliferating dormant cancer cells [10]. For patients with metastatic seeding, a better understanding of the mechanisms leading to successful colonization of cancer cells should contribute to the development of more effective therapy [17]. For patients with early cancer lesions, an understanding of the mechanisms allowing the physical relocation of cancer cells from primary tumors is likely to be helpful for preventing metastasis.

2. Biogenesis of microRNAs:

It was found about two decades ago that epigenetic control of gene expression is mediated by small, non-coding RNA molecules called microRNAs (miRNAs) that are around 22 nucleotides in length. The majority of miRNAs are sequence-specific regulators of important biological processes such differentiation, development, and cell proliferation [18], and they are substantially conserved across mammalian species. As of the most recent miRTarbase update (9/2017; http://mirtarbase.mbc.nctu.edu. tw/php/statistics.php), we know that there are 2,599 human miRNA molecules and 15,064 target genes. Western blotting, luciferase assays, microarrays, and next-generation sequencing have been used to experimentally verify 5831, 7676, 12,886 and 359,298 of the 380,639 miRNA-target interactions, respectively [19]. According to the most recent version of the Database of Differentially Expressed miRNAs in Human Cancers (v2.0; http://www.picb.ac.cn/ dbDEMC/statistics.html) [20], more than twice as many up- and down-regulated miRNAs in BC as in any gynecological cancer have been identified. However, a more comprehensive cancer-specific miRNA database updated in February 2009 found 507, 188, 66, and Based on these findings, we aimed to summarize what is currently known about the abnormal miRNA expression profiles that are linked to several invasive processes throughout the progression of breast cancer. The miRNA sequences, which are often found in introns but sometimes in exons, may either share a promoter with the host gene or, if positioned in inter-genic regions, can have their own promoter and be transcriptionally controlled in isolation. Furthermore, miRNAs are present on all human chromosomes except Y [22], and they may be found either as independent units or in tandem in bi- or poly-cistronic clusters. Most major miRNA tr consist of several hundred nucleotides, including a 50 prime cap and a 30 poly(A) tail, and are transcribed by RNA polymerase II in the nucleus [23]. Drosha ribonuclease III (DROSHA) and its cofactor, the double-stranded RNA-binding protein DiGeorge syndrome critical region 8 (DGCR8), cleave this precursor during micro-processing. The resulting pre-miRNAs have hairpin loop structures and are 60–70 nucleotides in length [24]. The pre-miRNAs are then actively exported from the nucleus to the cytoplasm by exportin-5 (XPO5)/Ran guanosine triphosphate (GTP) transporter [25,26], and the pre-miRNA is subsequently cleaved near the terminal loop by ribonuclease III DICER1 complexed with transactivation-responsive RNA-binding protein (TRBP,TARBP2)or protein activator of interferon-induced protein kinase (PACT,PRKRA). This yields roughly 22 nucleotide-long miRNA duplexes [27,28]. Stable-pairing passenger strands are often degraded, whereas guide strands are typically unstable at position 50 (miRNA) [29]. Using miRNA complementarity in a region that is just 2-8 nucleotides long, miRNA-induced silencing complex (miRISC) attaches to the 30 UTR of the mRNA target. The ribonuclease argonaute 2 (AGO2) then degrades the guide miRNA strand. Partial complementation causes reduced expression by mRNA removal or translation impairment owing to blocking the initiation site for the RNA-polymerase [30,31]. Near-perfect matching causes mRNA breakdown due to steric hindrance. However, a number of previously published research suggest that

miRNA binding to other areas in target mRNA aids in the preservation of mRNA translation. This indirect approach is mediated by miRNA interactions with AU-rich regions in the 30 UTR region or by the binding sequences of regulatory ribonucleoproteins, both of which are found in target mRNAs. As a result of these interactions, repressor protein complexes were recruited, which relieved translational repression of mRNAs [32,33]. Direct binding of specific miRNAs to the 50 UTRs of target mRNAs has been shown to initiate transcription in the human fetal kidney and Wilms' cancers [34]. Another research showed that miRNAs may initiate gene expression by focusing on promoter regions [35]. Furthermore, numerous isoforms of miRNAs (isomiRNAs) that arise from a miRNA locus may now be detected using next generation sequencing (NSG) technology. The miRNAs' stability, subcellular localization, and target selection may all be altered by post-transcriptional modifications, including incorrect cleavage during pre-miRNA processing, which can yield isomiRNAs. By altering target recognition, these physiological isomiRNAs serve several purposes in miRNA synthesis [36–38]. In most cases, a single miRNA may control many biological processes by affecting the expression of multiple mRNA targets. In normal cells, numerous regulators oversee each stage of miRNA biogenesis, from transcription to the generation of mature miRNA. Excellent evidence for this was found in animal cell cultures. Disruptions in these regulatory systems and in the miRNA pool have been linked to a wide range of human illnesses [39].

3. The role of microRNAs in cancer was first documented in chronic lymphocytic leukemia, which shows that miRNA expression is correlated with the development of human malignancies. MiR-15a/16a cluster on chromosome 13q14 was commonly deleted in these individuals, suggesting that these miRNAs function as tumor suppressors [40]. Cancer-associated miRNAs are often split into two groups. In general, oncogenic miRNAs (oncomiRs) from the first group are substantially expressed. They play a significant role in keeping the tumor phenotype stable and contribute to tumor growth. Tumor suppressive microRNAs (miRsupps), which are typically down-regulated in numerous malignancies, impede carcinogenesis by regulating cell proliferation, death, immune-cell formation, and other cancer-associated processes. For this reason, a single miRNA may play either an oncogenic or tumor suppressive function in distinct malignancies, earning them the name "context-dependent miRNAs." Examples of miRNAs with dual functions described by several authors include miR-17 (tumor suppressive in BC and oncogenic in B-cell lymphomas), miR-26 (tumor suppressive in hepatocellular carcinomas and oncogenic in gliomas and metastatic lung cancers)anscripts (pri-miRNAs) and miR-29 (tumor suppressive in lung tumors, cell lymphomas, and acute myeloid leukemias and oncogenic in B-cell chronic lymphocytic leukemia and BC) [41,42]. MiRNAs have been demonstrated to have an important role in the metastasis of cancer cells in recent studies. Invasiveness, migration, and the acquisition of a poor prognostic phenotype are all in this category. MetastamiRs are a class of microRNAs that have been shown to be up-regulated and down-regulated in a variety of neoplasias, including BC [43,44]. While previous research showed that the miRNA pool was generally down-regulated in multiple human cancers compared to miRNAs in normal tissues [45,46], more recent studies found that miRNA expression profiles varied among tumor types. This variation could be used to identify the specific cancer or tissue of origin. Different function patterns, evolutionary rate, gene expression, chromosomal distribution, molecule size, free energy, transcription factors, and targets were discovered in the first comprehensive bioinformatic study of human oncomiRs and miRsupps. This suggests that in human malignancies, oncomiRs cleave target mRNAs more often than miRsupps. Furthermore, in contrast to miRsupp sequences, which were often found in deleted chromosomal areas [47], oncomiR-encoding sequences were mostly prevalent in amplified chromosomal regions. The expression of numerous classic oncomiRs in patient plasma samples has declined with BC progression, although these "pioneer" data reinforce evidence that oncomiRs in cancer patients are normally up-regulated and miRsupps deleted or down-regulated. Based on these findings, it is impossible to categorize specific miRNAs as oncogenic or tumor suppressor [48, 50]. In order to better distinguish between various cell types, particularly cancer cells, modern molecular techniques have led to the use of miRNA microarrays and NSG. In addition, the identification of several miRNA iso forms linked with cancer provides further evidence that these isomiRNAs play a significant role in miRNA-mRNA regulatory networks and that changed isoRNA expression profiles contribute to the development of cancer [37,51,52].

4. MicroRNA (miRNA) synthesis is dysregulated in many human malignancies, leading to widespread alterations in miRNA expression levels. MiRNA pool imbalance results from the up- or down-regulation of components of the miRNA-processing machinery. Many solid tumors have altered global miRNA expression profiles due to up-regulation of genes encoding key DROSHA, DGCR8, and DICER1 components [53,54]. These changes contribute to the fundamental characteristics of cancer development, including enhanced cell proliferation, migration, and invasion. Decreased miRNA levels have been linked to invasion, metastasis, and poor patient survival [54-56], and studies have demonstrated that down-regulation of the DROSHA and DICER1 genes and their subsequent protein production occurs in many different cancers. Impairment of miRNA biogenesis is affected by both genetic and epigenetic abnormalities in miRNA regulatory factors. Mutations in DROSHA, DGCR8, XPO5, and DICER1 have been found in Wilms tumors (childhood kidney cancer) at both the somatic and germline levels [57,58]. Additional DICER1 mutations were identified in non-epithelial OC and pleuro-pulmonary blastoma (pediatric lung tumor) [59,60]. Tumors of the endometrium, colon, and stomach that exhibited microsatellite instability also included heterozygous XPO5-inactivating mutations [61], which impaired the export of pre-miRNA from the nucleus to the cytoplasm. Two DROSHA polymorphisms and one DGCR8 polymorphism were shown to have significant roles in human carcinogenesis for both laryngeal carcinoma and BC in a recent meta-analysis [62]. In BC patients, the reduced mRNA expression of DROSHA and/or DICER1 has been detected in 15% to 75.5%, and these levels were significantly related with high grade malignancies and a high Ki-67- stimulated cell proliferation index[63,64]. According to other studies, individuals with metastatic disease tended to have lower DICER1 mRNA levels, and this trend was shown to be significantly related with hormone receptor status and the luminal A subtype [65]. During the progression of ductal carcinoma in situ (DCIS), another research demonstrated that DICER1 protein expression in breast tissues gradually decreased, with the greatest decrease occurring in metastatic malignant cells. Lower rates of disease-free survival were related with a loss of DICER1 protein, and tumors with higher grades and a lack of hormone receptor and BRCA1 DNA repair-associated (BRCA1) protein expression were more aggressive [66]. When comparing triple negative breast cancer (TNBC) and normal adjacent tissue, researchers found decreased DICER1 mRNA expression and increased DROSHA levels, but no differences in DROSHA expression between lymph node metastases (LNM) and primary tumors, but significant increases in DICER1 expression[67,68]. Accumulation of primary miRNA transcripts and inadequate miRNA maturation may be triggered by upregulating DROSHA and downregulating DICER1. This can contribute to cancer development. One polymorphism in each of the DGCR8 and DROSHA genes has been established in a group of Chinese and African women, and these are significantly associated with BC risk [69,70]. However, no pathogenic mutations or epigenetic changes in the encoded genes of the two crucial DROSHA and DICER1 enzymes involved in miRNA regulation have been identified in breast tumors. One missense mutation and a high or high/middle methylation index in the XPO5 gene were also discovered in blood DNA samples, and they were related with an increased and a decreased risk of BC, respectively, in a case-control study of BC [71]. 14 genes involved in miRNA biogenesis have been found to include three extra polymorphisms. These are located in the genes AGO1, AGO2, and DEAD-box helicase 5 (p68, DDX5) [72]. This provides more evidence that genetic variations in genes affecting miRNA production may be particularly helpful in assessing the risk of developing BC. Furthermore, up-regulation of miR-103/107 and miR-191/425 clusters targeting the DICER1 gene influenced BC miRNA processing dysregulation and increased proliferation, invasion, and metastasis in BC tumor cells. Last but not least, it was shown that miR-103/107 helped kick off the epithelial-to-mesenchymal transition (EMT) by suppressing miR-200 [73,74].

5. MicroRNA Dysregulation in Invasive Breast Cancer The fundamental step needed for BC cell dissemination to secondary organs is cancer cell invasion, and this may be mediated by identified cell contact mechanisms such as EMT, collective invasion, and macrophage-cancer cell feedback loops. These entail various interactions between tumor cells and stromal cell sub-populations and occur via soluble factor signaling, direct cell-cell adhesion, and extracellular matrix (ECM) re-modeling [75]. BC progression, cancer relapse, metastasis, and poor prognosis are all dependent on self-renewal, differentiation, tumorigenesis, and chemoresistance, all of which have been demonstrated to be capabilities of the specific heterogeneous sub-populations of invasive cancer cells (BCSCs) that have now been characterized [76]. Several factors, including aberrant miRNA synthesis, cause these cells to be ahead of their normal

counterparts when it comes to initiating the numerous alterations in gene expression involved in invasion-associated pathways.

5.1. MicroRNAs and Cell Adhesion Multiple cytoskeletal regulatory proteins, cell-cell adhesion molecules, and extracellular matrix (ECM) proteins work together to keep cell-cell and cell-ECM adhesions stable, which is crucial for maintaining proper cellular and organismal homeostasis [77]. Detachment and metastasis in cancer are facilitated by the dysregulation of adhesion-associated molecules, which is typically influenced by aberrantly produced miRNAs[78].

In Mojdeh Mahmoudian and colleagues' study, it was discovered that certain microRNAs showed increased expression in BC tumor compared to the adjacent tissues. Specifically, hsa-miR-25-3p, -29a-5p, -105-3p, and -181b1-5p were upregulated, while hsa-miR-335-5p and -339-5p were downregulated. The upregulation or downregulation of these candidate microRNAs was found to be associated with TNM stages, except for hsa-miR-339-5p. Additionally, with the exception of hsa-miR-105-3p, each candidate microRNA correlated with HER-2 status. Furthermore, the analysis of ROC curves revealed that the combination of these six microRNAs could potentially serve as a biomarker to differentiate between tumor and non-tumor breast tissue samples.

5.1.1. Actin polymerization and depolymerization in the highly dynamic cytoskeleton causes substantial changes in cell activity that are function-specific. The small GTPase (s GTPase) family known as Ras homologues (Rho) controls these functions [79]. Multiple microRNAs (miRNAs) with a Rho superfamily member target have been found in BC cells. Some microRNAs, like miR-155, directly suppress the expression of RhoA protein [80], while others, like miR-10b, initiate invasion indirectly by suppressing homeobox D10 (HoxD10) and up-regulating the pro-metastatic RhoC gene (via the Twist family basic helix-loop-helix transcription factor, TWIST) [81]. Another member of the Rho superfamily, cell division cycle 42 (CDC42), a small GTPase, and C-X-C motif chemokine receptor 4 (CXCR4) were down-regulated by miR-224 [82], which facilitated cell invasion. Important effector that binds with RhoGTPases during cytoskeletal re-organization is encoded by the oncogene p21 activated kinase 1 (PAK1), which itself encodes the serine/threonine p21-activating kinase PAK1. Down-regulation of miR-494 has been linked to increased PAK1 protein expression in BC samples, and the encoding gene for PAK1 has been shown to be a direct target of miR-494. This may explain the clonogenicity, migration, and invasion of BC cell lines found in other studies [83]. In addition, it is well acknowledged that the gene that codes for the cytoskeletal protein tropomyosin 1 (TPM1) acts as a tumor suppressor. miR-21 controls this directly [84]. microRNA (miR)-661 destabilized tight junctions by aiming at the gene encoding two proteins. The phospholipid transferase STAR-related lipid transfer domain protein includes 10 (STARD10) is involved in epithelial cell polarity, whereas the nectin cell adhesion molecule-1 (Nectin-1) controls cell-cell junctions and cytoskeletal architecture. Additionally, by down-regulating epithelial markers, miR-661 up-regulation in SNAI1-induced EMT cells facilitates cell invasion. It has been observed that the reduction of STARD10 expression correlates negatively with markers of EMT-related, basal-like subtypes in breast cancer samples [85]. MicroRNAs (miRs) 200a and 206 have been identified as regulators of the connexin 43 (CX43) adhesion molecule, which has been shown to promote intracellular communication [86] and to influence cytoskeletal modification and cell migration. Two separate investigations have shown an association between higher CX43 mRNA and protein levels and enhanced cell proliferation, migration, and invasion when miR-200a or miR-206 levels were reduced. CX43 mRNA expression was also greater in both lung and hepatic metastases from BC compared to the main tumor [87,88]. Members of the WAVE actin cytoskeleton re-modelling family, including Wiskott-Aldrich syndrome protein family member 3 (WAVE3, WASF3), were substantially expressed in BC, particularly at more advanced stages. Levels of miR-200 cluster members and miR-31 were reduced in BC cell lines after they were used to silence the wave3 gene, and cytoskeletal changes in the tumor tissues correlated with an invasive phenotype [89,90]. In addition to its moderating effect, WAVE3h has a new role in NF-kappa B (NF-B) signaling by regulating the formation of invadopodia and assisting in ECM breakdown [91, 92]. Junctional adhesion molecule-A (JAM-A) is a transmembrane cell-cell junction protein involved in tight

junctions and influencing the cytoskeletal organization via its connection with the actin-bundling protein facsin [92]. Over-expression of miR-145 inhibited JAM-A gene targeting, leading to reduced cell motility and invasiveness in various BC lines [93]. In contrast, active BC cell movement was seen after JAM-A suppression by up-regulated miR-495 [95], suggesting that down-regulationofmiR-145 expression in BC might permit JAM-A gene sufficient expression to promote cancer cell motility.

5.1.2. The principal defenders of tissue integrity are cell-cell adhesion junctions, and cell-cell adhesion receptors allow the beginning of several signals transduction pathways [77]. The transmembrane glycoprotein E-cadherin, encoded by the Cadherin 1 (CDH1) gene, is essential for the formation of adherens junctions between adjacent epithelial cells [96,97]. Its cytoplasmic tail interacts with many intracellular proteins to mediate the association between E-cadherin and the actin cytoskeleton. E-cadherin inactivation is thought to be a critical step in the invasion-metastasis cascade in many epithelial malignancies, including BC, and E-cadherin immuno labeling has been beneficial in distinguishing breast lobular lesions from ductal lesions in cases with inconclusive histology findings [98].

Several somatic mutations in CDH1, as well as loss of heterozygosity (most often seen in invasive lobular breast cancer) and promoter methylation [99-101], were discovered to directly block the CDH1 gene. This miRNA was shown to be up-regulated in aggressive and metastatic cancers [102]. While miR-9 expression was lower in malignant tumors than in benign ones, it was higher in malignant tumors than in benign ones, albeit still lower than in normal tissues. These findings reveal the dynamic nature of miR-9 during tumor growth [103], revealing its various roles. Furthermore, CDH1 silencing indirectly controlled other miRNAs by focusing on numerous key transcription factors that aid in cancer cell EMT. This link is discussed in later Section 5.3. The CUB domain-containing protein 1 (CDCP1) transmembrane glycoprotein has been defined in BC cell lines as a regulator of cell adhesion and motility [104]. This protein contributes to the disruption of adherens junctions and is found broadly expressed in human epithelial malignancies and related with advanced stages and poor patient survival. Down-regulation of the targeted miR-198 may increase CDCP1 gene expression [105,106].

MicroRNAs and Cell-Extracellular Matrix Interactions 5.1.3 Detachment of cancer cells also requires weakening of cell-ECM connections. Bidirectional signaling across the cell membrane is mediated by integrin / heterodimers, the major receptors of ECM proteins found on the surface of cancer cells. Deregulation of integrins permits regulation of cell proliferation, differentiation, survival, adhesion, and motility, all of which contribute to cancer's invasiveness and metastasis [107]. Targeting several subunit partners of 1 (2, 5, and V) and 3 integrins, miR-31 provides strong evidence for its role as a major regulator of integrins [108]. In addition, a number of research have looked at how miRNA may control certain integrins. In BC cells, targeting by miR-373 reduced integrin 2 (ITGA2) mRNA, which in turn reduced cell-cell contacts, depolymerized F-actin fibers, and facilitated cell motility. Additionally, miR-373 expression was shown to be significantly higher in BC, especially in patients with LNM, compared to surrounding non-malignant tissues [109], while ITGA2 protein levels were found to be significantly lower in BC, particularly in patients with LNM. Over-expression of miR-142-3p, on the other hand, was shown in an additional in vitro investigation to influence many genes involved in cytoskeletal structure and cell motility, including Wiskott-Aldrich Syndrome Like (WASL) and ITGAV, which suppress BC cell invasiveness [110]. Furthermore, one of the 1 family integrins (31) indirectly affected BC invasion by activating the Rac1/PAK1 pathway signaling, mitogen-activated protein kinase (MAPK), c-Jun NH2-terminal kinase (JNK), and PAK1[111]. HoXD10-dependent miR-7 was demonstrated to specifically target two kinases, PAK1 and focal adhesion kinase (FAK), and the down-regulation of this miRNA, together with the up-regulation of PAK1 and FAK protein, was linked with a more invasive phenotype. The miR-7 reduction was also more pronounced in individuals with metastatic BC [112,113]. In addition, miR221/222 were shown to be the primary regulators of BC cell proliferation and invasion through targeting STAT5A, ADAM17, and integrin 4 (ITGB4) genes. ITGB4 encodes an adhesion molecule that interacts with laminin receptors. Although the scientists could not confirm an inverse link between miR-221/222 and ITGB4 expression, it was noted that patients with poorly differentiated G3 tumors expressed ITGB4 on the protein level, and that miR-221/222 was down-regulated in luminal BC. The ADAM multi domain proteins, which have two main disintegrin and metalloprotease domains, are involved in proteolysis and cell adhesion

and are largely found on the cell membrane. Proteolytically active ADAMs participate in ECM re-modeling by shedding changeable substrates, such as adhesion ligands, growth factors and their receptors and different cytokines. Alterations in the expression of adenosine deaminases (ADAMs), especially ADAM9, 10, 12, 15, and 17, were linked to cancer development and progression [115]. There, miR-33a, miR-126, and miR-154 were identified as regulators of ADAM9 transcription. The levels of these miRNAs gradually decreased throughout carcinogenesis from early stage non-metastatic and LNM-positive breast cancers compared to normal breast tissues [116-118]. In contrast, ADAM8 controls many miRNAs, miR-720 among them. Extracellular signal-regulated kinase (ERK) signaling cascade activation by the disintegrin and cysteine-rich regions of this protein causes aggressive behaviors in TNBC cells. In addition, high-expression ADAM8 was associated with elevated miR-720 levels in the serum of TNBC patients [119]. Even though ADAM proteins without metalloproteinase domains are inactive as proteases, they may nevertheless interact with integrins via their disintegrin domains. Alterations in these proteins contribute to cancer's ability to spread throughout the body [120]. The tumor suppressor ADAM23 is epigenetically inactivated in patients with breast cancer (BC) due to promoter methylation [101,121,122]. Although the miRNA that controls the expression of ADAM23 has not yet been found, we have shown that it likely plays a role in the metastasis of mesenchymal circulating tumor cells in a recent publication [123].

Cancer Microenvironment and MicroRNAs 5.2 Changes in the micro-environment, which includes stromal cells such fibroblasts, endothelial cells, adipocytes, and immune cells, as well as ECM components, have been demonstrated to play an important role in cancer development [124]. Intercellular interaction within the TM may be regulated by stromal miRNAs that are abnormally expressed [125]. Invasion and metastasis are aided by the various cytokines and chemokines produced by cancer-associated fibroblasts (CAFs). Furthermore, it was recently revealed that tumor cell intravasation may be facilitated by increasing vascular permeability thanks to the interaction between fibroblast-derived C-X-C motif chemokine ligand 12 (CXCL12, SDF1) and endothelial cells [126]. MiR-126 and miR-126* directly target the CXCL12 gene, which in turn reduces the production of the CC-motif chemokine ligand 2 (CCl2) by cancer cells. MiR-126 and miR-126* were shown to reduce mesenchymal stem cell and inflammatory monocyte recruitment in the tumor stroma environment, therefore inhibiting breast cancer spread in a mouse xenograft model [127]. Tumor development, angiogenesis, metastasis, and survival are all facilitated by the chemokine CXCL12, which is generated by stromal fibroblasts and interacts largely to the highly expressed CXCR4 receptor on the surfaces of cancer cells [128]. The CXCR4 protein was shown to be significantly suppressed by miR-494 alone, and its expression was found to be down-regulated in BC cells, according to a separate research. Through the CXCR4-dependent Wnt/-catenin signaling pathway, this miRNA also had a role in suppressing BC formation [129]. In addition, miR-320 was shown to be a downstream regulator of the phosphatase and tensin homologue (PTEN) gene in stromal fibroblasts in both animal models and BC patient samples. Breast tissue endothelial and epithelial cells have different mRNA expression profiles according to the PTEN gene. In addition, miR-320 down-regulation in BC and the up-regulation of its direct ETSproto-oncogene2 (ETS2) target were critical in the loss of PTEN which increased tumor invasiveness and angiogenesis via micro-environmental modification [130]. Additional research showed that miR-200 cluster members (miR-200a, miR-200b, miR-200c, and miR-141) in the stroma directly enabled the re-programming of normal fibroblasts into CAF. By reducing their expression, these miRNAs promoted ECM re-modeling, invasion, and metastasis of BC cells by targeting genes involved in cell growth and differentiation, such as friend leukemia integration 1 (FLI1) and transcription factor 12 (TCF12) [131]. The expression of fundamental extracellular matrix (ECM) proteins such collagens, laminins, and fibronectin was also altered by aberrantly produced miRNAs. These were shown to function as ligands for integrin extracellular domains in several cancer types[77,78]. Down-regulation of miR-539 targeting and up-regulation of flamminin subunit alpha 4 (LAMA4) mRNA and protein expression in TNBC have been reported [132]. Finally, miR-335 expression targeting the extracellular matrix (ECM) component tenascin-C encoding gene (TNC) was discovered to be correlated with metastatic suppression.

Other structural ECM proteins including glycosaminoglycans, proteoglycans, and matricellular proteins [124], and the loss of miR-335 was observed in BC patients with poor prognosis [133]. Furthermore, various ECM re-modeling enzymes directly influenced ECM function and biomechanical features that facilitated the separation of cancer cells from primary tumors. Matrix metalloproteinases were overexpressed, which led to collagen proteolysis in the

basement membrane [124]. Matrix metalloproteinase 14 (MMP14), found on the surfaces of BC cells, was shown to be active in collective migration [134], and both the up-regulation of MMP14 and the down-regulation of the targeting of miR-181a-5p were more pronounced in the invasive front of breast tumors than in adjacent normal tissue [135]. Conversely, miR-21 up-regulation, which was mostly seen in patients with LNM in conjunction with a reduction in tissue inhibitor of metalloproteinases 3 (TIMP3) protein, increased ECM disintegration and cancer cell invasion [136]. Urokinase plasminogen activator (uPA) was discovered to activate many pro-matrix metalloproteinases (MMPs) to induce disintegration of extracellular matrix (ECM) and basement membranes [137]. The function of miR-193b in BC invasiveness was shown in the up-regulation of uPA expression in metastatic BC and the negative correlation between miR-193b and uPA protein expression [138]. However, BC cells that substantially produced uPA in combination with the reduced expression of DROSHA and DGCR8 had lower levels of mature miR-193a, miR-193b, and miR-181a, but not their main targeted miRNA transcripts [139]. This demonstrates the effect of defective miRNA synthesis on uPA up-regulation. Down-regulation of miR-29b in GATA3-expressing luminal breast cancers led to metastatic development and a mesenchymal phenotype in cancer cells, suggesting a complex role for the transcription factor GATA3 in micro-environmental re-modeling and metastasis inhibition. MiR-29b was hypothesized to suppress metastasis by targeting pro-metastatic regulator genes involved in differentiation and epithelial plasticity [140]. These genes included vascular endothelial growth factor A (VEGFA), angiopoietin-like 4 (ANGPTL4), platelet-derived growth factor (PDGF), lysyl oxidase (LOX), and matrix metalloproteinase 9.

5.3. Many physiological processes, such as embryo implantation, embryogenesis, and organ development, include the epithelial-mesenchymal transition (EMT) and its reversal, mesenchymal-epithelial transition (MET). These systems are involved in the pathological processes of tissue regeneration, organ fibrosis, the development of cancer, and the spread of cancer metastases. While undergoing EMT, epithelial cancer cells lose their polarity, cell-cell connections, and cell-basement membrane interactions, and instead take on the properties of a mesenchymal cell, including increased migratory ability, invasiveness, and resistance to apoptosis [141]. TGF-, Notch receptor and Wnt/-catenin signaling pathways, as well as growth factors that bind tyrosine kinase receptors, are only a few examples of the extracellular signals and transcription factors that may launch the EMT program [142,143]. Enhanced TGF- levels were detected in the plasma and invasive fronts of tumors in BC patients, and these linked with the presence of LNM [144,145]. TGF- is a multi-functional cytokine that is a prominent inducer of EMT. TGF-1-induced EMT has recently been reported, and it has been demonstrated to facilitate BC cell migration via chemotaxis in lymphatic vessels[146]. In addition, other investigators observed that TGF-1 directly regulates the expression of miR-10 and miR-23a, and that increased expression of these two miRNAs is linked to aggressive BC. Wnt/-catenin signaling was triggered thanks to miR-23a's ability to specifically target and inhibit the CDH1 gene. Both miR-10b and miR-23a were shown to have a role in TGF-1-induced EMT and tumor metastasis in BC cell lines and patient tissues (refs. 147,148). In addition, it was shown that EMT and metastasis in metastatic BC cells were driven by hyperactivated Wnt/-catenin signaling. Accompanying the ectopic overexpression of miR-374a in these cells was the downregulation of its direct targets, the negative regulators of Wnt/-catenin signaling WNT inhibitory factor 1 (WIF1), PTEN, and WNT family member 5A (WNT5A). Patients with breast cancer who had spread to other parts of the body had miR-374a levels that were much higher than normal [149]. The CDH1 gene encodes E-cadherin, the major cell-cell adhesion protein, and its blockage is the hallmark of EMT induction [150]. Important regulators of EMT were identified, including the transcription factors snail family transcriptional repressor 1 (SNAIL1), SNAIL2/SLUG, zinc finger E-box binding homeobox 1 (ZEB1), ZEB2 and TWIST1 (encoded by the SNAI1, SNAI2, ZEB1, ZEB2 and TWIST1 genes, respectively). These inhibit E-cadherin production by interacting with E-box regions in the CDH1 gene's promoter[151]. However, several microRNAs control not just E-cadherin but also EMT inducers. MiR-200 is part of a cluster that has been linked to EMT regulation. Five members make up this family, with three situated in an intergenic region of chromosome 1 (miR-200b, miR-200a, and miR-429) and two on chromosome 12 (miR-200c and miR-141) in an intron of a non-coding RNA. Additional authors examined miR-200 expression in 70 TNBC breast tumors and discovered that HER2-positive, primarily metaplastic malignancies had lower expression of the miR-200 cluster compared to ER-positive tumors. In metaplastic breast cancer and in vitro models of spontaneous EMT, all five members of the miR-200 cluster were shown to be downregulated, together with increased expression of the EMT-transcriptional inducers SNAI1, SNAI2, ZEB1, and ZEB2, and hypermethylation of

the miR-200c/141 region [152]. Several research have looked at the function of certain members of the miR-200 cluster in EMT. There, the Kindlin family proteins were originally categorized as integrin-regulating molecules. They involved in a wide variety of biological activities, ranging from cell adhesion and migration [153] to the regulation of gene expression. Direct targeting and silencing of its encoding gene, fermitinfamilymember2 (FERMT2), by miR-200b inhibited EMT and metastasis [154]. Expression of Kindlin-2 was correlated with the BC metastatic phenotype in human and mouse BC cells. Studies have shown that miR-200b/429 acts to suppress ZEB1 expression, and that tumor protein p53 binding protein 1 (TP53BP1, 53BP1) is a new negative regulator of EMT. In vitro tests failed to reveal direct interaction between 53BP1 and either miR-200 or miR-429 [155], despite the fact that 53BP1 expression positively associated with both miR-200 and miR-429 expression and negatively correlated with ZEB1 gene expression in 18 BC samples. Actin interacting proteins TKS5, SH3PXD2A, and myosin light chain kinase (MYLK) were recently discovered to be new targets of miR-200c. The scientists demonstrated that tumor cell invasion was regulated by a feedback loop involving ZEB1 and miR-200c. Co-expression of ZEB1 with TKS5 and MYLK genes, as well as down-regulated targeting by miR-200c [156], was linked to the simultaneous activation of EMT and invadopodia development in BC cell lines and patient samples. It was also shown that miR-30a, which directly targets ZEB2 expression, is induced in TNBC patients by p53 by binding to the MIR30A promoter. In addition, p53 deficiency, LNM, and poor prognosis were revealed to be associated with low miR-30a expression in BC. According to the results of this investigation, miR-200c expression may be influenced by tumor aggressiveness via the p53/miR-30a/ZEB2 axis [157]. Another key EMT related cluster, DLK1-DIO3, was discovered to include seven tumorsuppressing miRNAs (miR-300, -382, -494, -495, -539, -543, and -544) situated on chromosome 14. These miRNAs were down-regulated in EMT BC cells and in invasive ductal BC samples, and they target the encoding genes of recognized EMT activators such as TWIST1, ZEB1/2, and B lymphoma Mo-MLV insertion region 1 homologue (BMI1). MiR-300, miR-539, and miR-543 were shown to specifically target the TWIST1 gene in in vitro tests, whereas miR-300, miR-494, miR-495, and miR-544 were shown to suppress BMI1 expression. The ZEB1gene's repression by miR-494 and miR-539 was later discovered. Increased expression of certain members of the miR-200 cluster was also found to be significantly correlated with the up-regulation of miR-300, miR-494, miR-539, and miR-543 [158], which may have been caused by the inhibition of TWIST1, which was thought to be a miR-200 repressor because of its binding to the promoter region of this cluster. The other major EMT inducers are also controlled by miRNAs outside of the above-mentioned clusters. In p53 loss-of-function cancer cell lines, including BC, miR-34 levels were reduced, which is a direct regulator of SNAIL1, leading to SNAIL1 protein-dependent activation of EMT. These data showed that p53, miR-34, and SNAIL1 all work together as part of the EMT program [159]. Downregulation of miR-124 and upregulation of the targeted SNAI2 gene expression in BC cell lines and patients was also found by other studies [160]. The expression of miR-203 and miR-200 cluster members was found to decrease over time during SNAI1-induced EMT in a separate BC in vitro study [161]. Furthermore, miR-203 inhibited endogenous SNAI1, forming a double-negative miR-203/SNAI1 feedback loop, which, like the well-studied miR200/ZEB1 feedback loop, may serve as an EMT-inducing core network. Down-regulation of miR-205 was linked to a metastatic phenotype [162], and a miRNA microarray analysis indicated that DCIS, invasive, and metastatic BC samples all had significantly different miRNA expression profiles than normal tissues. It has been revealed that miR-205 directly targets genes encoding EMT-initiating transcription factors ZEB1 and ZEB2 [163]. The SNAIL2/SLUG transcription factor and miR-221 in BC cell lines were shown to have a direct correlation by other studies. Restricting cell migration was linked to suppressing SNAIL2, which in turn was shown to maintain miR-221 expression, and vice versa [[164]]. E-cadherin was downregulated because miR-221 aimed for the CDH1 open reading frame. Here, we show a unique method whereby SNAIL2-promoted miR-221 overexpression inhibits E-cadherin post-transcriptionally [165]. Increasing expression of miR-221 and miR-222 was shown to promote a basal-like BC subtype by down-regulating epithelial genes and up-regulating mesenchymal-specific genes that aided in invasiveness and boosted cancer cell motility. Also, miR-221/222 repressed ZEB2 transcription, which in turn lowered E-cadherin expression in a roundabout way [166]. This was accomplished by targeting the transcriptional repressor gata binding 1 encoding gene (TRPS1). Less attention has been paid to the role of miRNAs in regulating TWIST1 expression in BC than to the primary EMT-associated transcription factors. Down-regulation of miR-720 was linked to the prevalence of lymph node metastases [167], since this miRNA targeted the TWIST1 gene. In addition, down-regulation of miR-506 was detected in BC tissues [168], and it was projected to target additional EMT-participating genes. The over-expression of miR-506

led to the suppression of TGF-β-induced EMT and inhibited cell adhesion, invasion, and migration via the down-regulation of the mesenchymal genes such as SNAI2, vimentin (VIM), and the CD151 molecule (raph blood group) (CD151). Furthermore, NF-B bound to the upstream promoter region of miR-506, reducing its transcription [169]. Metastatic breast cancer (BC) cell lines and tissues exhibited down-regulation of the EMT inhibitor miR-153. MiR-153, when normally expressed, inhibited the migration and invasion of BC cells by directly targeting the metadherin (MTDH) gene, an inductor of EMT [170]. In addition, miR-375 activated the TGF- signaling network and induced EMT by targeting the gene encoding the short stature homeobox 2 (SHOX2) transcription factor. The scientists investigated microarray data for BC gene expression from the Gene Expression Omnibus database and discovered that the loss of miR-375 expressionandthegainofSHOX2expressionwasassociatedwithpoorsurvivalinBCpatients;andthis shows the significance of SHOX2 in BC progression [171].

5.4. Cancer stemness and microRNAs The activation of EMT is a key step in the spread of cancer cells and the creation of BCSCs, a small fraction of cancer cells with stem cell-like traits [172,173]. Specifically, BCSCs release TGF- and express miRNAs that regulate self-renewal and differentiation-related genes and signaling pathways [174,175]. These actions drive EMT. Multiple miRNAs contribute to controlling the balance between self-renewal and differentiation, a key feature of BCSCs. The downregulation of the miR-200, miR-183, and let-7 clusters and the upregulation of miR-221 [176-180] are, nonetheless, crucial for the stemness preservation of human BCSCs. The above-mentioned characteristics of BCSCs are promoted by down-regulation of the miR-200 cluster, which in turn increases expression of polycomb repressor complex proteins like BMI1 and suppressor of zeste 12 homologue (SUZ12) [176,181]. Maintaining the BCSC phenotype and controlling BC metastasis depend on SUZ12's ability to regulate the expression of E-cadherin and the miR-200/SUZ12/E-cadherin axis. By suppressing SUZ12 and preventing the regulation of E-cadherin, overexpression of miR-200b controls tumor development and invasiveness [181]. The interactions between miR-200 cluster members and transcriptional factors such as ZEB1 and ZEB2 can also inhibit the transcription of the entire miR-200 cluster [182,183], and specific protein 1 (Sp1) and p53 binding has been shown to lead to the activation of miR-200b/200a/429, miR-200c, and miR-183 transcription [184,185]. In addition, the miR-200 cluster, miR-22, and ZEB1/ZEB2 interaction plays a crucial role in regulating stemness and EMT. By directly targeting genes that code for members of the ten eleven translocation (TET) family of methylcytosine dioxygenases, miR-22 is able to limit the expression of the miR-200 cluster and so exercise its metastatic potential. Patients whose miR-22 levels are too high also tend to have their TET-miR-200 cluster axis silenced, which has been linked to poor clinical outcomes [186]. Authors have shown that miR let-7 expression is lower in BCSCs compared to non-stem cancer cells in primary tumors and cancer cell lines [178], and this miR influences critical BCSC properties such as self-renewal, multipotent differentiation, and the potential to produce tumors. Protein expression of Harvey rat sarcoma virus oncogene homologue (H-RAS) and high mobility group AT-hook 2 (HMGA2), both of which are recognized let-7 targets, is suppressed in response to elevated let-7 levels [187,188]. DNA-binding proteins encoded by these genes have been linked to stem cell self-renewal and pluripotency as well as their involvement in mesenchymal cell differentiation and tumor development. Moreover, whereas H-RAS silencing in a BCSC-enriched cell line decreased self-renewal with minimal effect on differentiation, HMGA2 silencing promoted differentiation but not self-renewal [178]. Similarly, keeping miR-30 expression low and increasing the expression of its direct gene target, ubiquitin-conjugating enzyme 9 (UBC9), kept BCSCs' capacity for self-renewal intact. Ubc9 is important for the sumoylation of several proteins associated to the self-renewal process [189]. Three of the most important transcription factors are the octamer-binding transcription factor 4 (OCT4), the Sry-related high-mobility box 2 (SOX2), and the homeobox transcription factor (NANOG). These master regulators of stem cell pluripotency are in charge of keeping ESCs in an undifferentiated condition. Auto-regulation of gene expression via the binding of these three proteins to their own promoters and the promoters of the genes encoding the other two factors improves gene stability and aids in the maintenance of the pluripotent state [190]. In addition, throughout the process of ESC production [190], they undergo direct epigenetic regulation by the binding of ESC-specific miRNAs to their promoter regions [191] and through the gradual removal of DNA and H3K9 methylation [192] at the post-transcriptional level. As was previously noted, miR-221 overexpression aids in the preservation of stem cells in BC. Targeting and inhibiting the DNMT3B gene allows this miRNA to function as an oncomiR, altering the DNA methylation of several genes' promoter areas. This includes the NANOG and OCT3/4 promoter regions. Both miR-590-5p and miR-140 operated as

tumor suppressors and suppressed stemness by targeting the SOX2 gene, whereas their levels were shown to be lower in BCSCs compared to differentiated cells[180]. The number of BCSC therefore dropped [193,194].

6. Aberrant expression of many genes, leading to their inefficient function, is a common feature of tumor tissues, and this is often due to epigenetic regulation of microRNA production. The accumulation of genetic abnormalities and epigenetic processes, such as aberrant hyper- and hypo-methylation of DNA and changes in histone modifications after the re-modeling of the chromatinstructure, may generate changes in expression profiles in cancers[195]. MiRNAs may function as oncogenes, tumor suppressors, modulators of metastasis, and regulators of cancer cell stemness, as indicated above. The methylation of promoter miRNA by its own transcriptional units or those of host genes where the miRNA sequences are situated is a common source of miRNA expression dysregulation in cancer [196,197]. Numerous studies have looked at the role of epigenetic inactivation in the regulation of BC-associated miRNAs with tumor-suppressor activity, including those that mediate the suppression of cell proliferation and EMT [198]. Several miRNA genes that play a role in the invasive processes discussed before were also found to have their promoters methylated. Despite the presence of CpG islands in both the transcription start areas of miR-200b/200a/429 and miR-200c/141 [152,199], DNA methylation silencing was only seen in miR-200c/141. MiRNA epigenetic regulation is crucial during EMT processes, as shown by the correlation between miR-200c/141 methylation and upregulated SNAI1, SNAI2, ZEB1, and ZEB2 target genes in invasive BC [152]. Similar hyper-methylation of upstream promoter regions upon activation of the EMT programme, largely within the TWIST1 protein signaling network, concurrently inactivated seven miRNAs (miR-300, -382, -494, -495, 539, 543, and 544) clustered in the DLK1-DIO3 area [158]. Furthermore, miR-203 was revealed to be a regulator of the EMT-associated SNAI1 gene [161], while another investigation indicated that miR-203 targeted SNAI2 [200]. Furthermore, miR-203 was shown to be epigenetically silenced in BC cells that had already spread, and this loss of miR-203 expression led to EMT processes and the formation of cancer stem cells [200,201]. The more intricate epigenetic control of miR-205 also triggered EMT. The expression of miR-205 was modified because the DNA methyltransferase-mediated DNA methylation of the MIR205 host gene promoter was suppressed by the chromatin-modifying polycomb group ring finger 2 (Mel-18, PCGF2) protein. As a result, miR-205 was less likely to target ZEB1 and ZEB2 during active transcription. Metastatic BC cell lines were more aggressive in their invasion and migration when Mel-18 was knocked out [163]. An opposing effect on miR-205 production came from Erb-B2 receptor tyrosine kinase 2 (ErbB2) signaling which down-regulated miR-205 via the Ras/Raf/MEK/ERKpathway,andthisinfluencedDNAmethyltransferaseactivityandconsequentlyled to the hyper-methylation of the MIR205 host gene [202]. Another research discovered that miR-34c was down-regulated in breast tumor starting cells that exhibited stem cell traits such as the ability to self-renew, undergo EMT, and migrate. This miRNA's production was inhibited by decreased Sp1 DNA binding activity due to hyper-methylation of a single CpG site in its promoter region [203]. Sections 5.1.1 and 5.1.3 detailed how miR-31 expression was linked to integrin modulation and therefore cytoskeletal re-modeling and cell-ECM interactions. Recently, the scientists showed that promoter hyper-methylation in the LOC554202 miR-31 host gene is crucial in BC invasiveness. This phenomenon was mostly seen in highly aggressive TNBC basal subtype cell lines [204]. Similarly, miR-126/miR-126* was down-regulated by promoter methylation of its EGF-like domain multiple 7 (EGFL7) host gene in cancer cells. Insufficient miR-126/miR-126* levels impeded recruitment of mesenchymal stem cells and inflammatory monocytes in the TM, which aided BC metastasis [127]. In addition to its frequent silencing in human BC due to genetic deletion, miR-335 has also been shown to be silenced by promoter hyper-methylation in metastatic derivatives derived from malignant cell populations of multiple different BC patients [205]. Different Writers a link between DNMT3B protein over-expression and miR-124a-3 hyper-methylation was discovered when researchers examined the methylation profiles of three genomic loci of miR-124a in fresh frozen BC samples in more detail. There was a correlation between LNM and a high mitotic score in cancer tissues and the simultaneous methylation of the miR-124a-1, miR-124a-2, and miR-124a-3 loci [206]. A major deregulator of DNA methylation in BC, miR-221 is also involved in a wide variety of other epigenetic processes. As of yet, this miRNA has only been identified in relation with BC stemness [180], but it has been demonstrated to directly target the primary de novo methyltransferase DNMT3B-encoding gene, which might contribute to substantial alterations in DNA methylation profiles. Histone methylation dysregulation is linked to a variety of epigenetic changes

that increase the invasive potential of BC. Important epigenetic regulator lysine-specific demethylase 1 (LSD1) is specifically targeted by miR-708 in BC cell lines. LSD1 demethylates mono- and dimethylated lysine 4 and lysine 9 in histone 3. The effects ofmiR-708 inhibition on cell proliferation and invasion were attenuated by overexpressing LSD1[207]. Researchers also demonstrated that the polycomb repressor complex 2 (PRC2) generated trimethylation of lysine 27 in histone 3 (H3K27) controlled miR-708 suppression in metastatic breast cancer. In addition, over-expression of neuronatin, which controls ion channels, was made possible by the steady reduction of the miR-708-targeted neuronatin (NNAT) gene during breast metastatic growth. Metastasis and cell migration are both triggered by elevated calcium levels within the cell [208]. Table 1 summarizes the expression variations, kinds of epigenetic regulation, target genes, and involvement in invasion-metastasis cascade stages of miRNAs related with certain invasive processes and cancer cell stemness in BC. Figure 1 categorizes the up- and down-regulated miRNAs according to the several mechanisms involved in BC invasion.

A major deregulator of DNA methylation in BC, miR-221 is also involved in a wide variety of other epigenetic processes. This miRNA was demonstrated to directly target the primary de novo methyltransferase DNMT3B-encoding gene, which might cause to large alterations in DNA methylation patterns, however this has only yet been reported in conjunction with BC stemness [180]. Histone methylation dysregulation is linked to a variety of epigenetic changes that increase the invasive potential of BC. Important epigenetic regulator lysine-specific demethylase 1 (LSD1) is directly targeted by miR-708 in BC cell lines. LSD1 demethylates mono- and dimethylated lysine 4 and lysine 9 in histone 3. Overexpression of LSD1 might reverse the effects of miR-708 suppression on cell proliferation and invasion [207]. The polycomb repressor complex 2 (PRC2) was shown to control miR-708 repression in metastatic BC via the trimethylation of histone 3 (H3K27) at lysine 27. In addition, over-expression of neuronatin, which controls ion channels, was made possible by the steady reduction of the miR-708-targeted neuronatin (NNAT) gene during breast metastatic growth. Metastasis and cell migration are both triggered by elevated calcium levels within the cell [208]. Table 1 summarizes the expression variations, kinds of epigenetic regulation, target genes, and involvement in invasion-metastasis cascade stages of miRNAs related with distinct invasive processes and cancer cell stemness in BC. Figure 1 categorizes the up- and down-regulated miRNAs according to the several mechanisms involved in BC invasion.

7. Multifunctional microRNAs in Invasive Processes It is commonly acknowledged that individual miRNAs may control several genes engaged in different biological systems. Thus, several of the aforementioned miRNAs serve multiple roles in the invasive processes. Multiple actions have been shown for miR-200, DLK1-DIO3, and miR221/222 clusters in normal cells (Figure 2A-C). Specific processes linked to BC invasiveness and stemness are initiated, as previously summarized, when the expression of these miRNAs is down-regulated or up-regulated, respectively.

Defects in cytoskeletal structure, TM, EMT modification, and cancer stemness were linked to down-regulation of members of the miR-200 cluster. Specifically, this down-regulation promoted the expression of the cytoskeletal re-modeling gene WAVE3, the ECM-altering genes FLI1 and TCF12, the EMT genes SNAI1, SNAI2, ZEB1, and ZEB2, and the regulators of stem cell self-renewal and pluripotency, BMI1 and SUZ12 [89,131,152,176,181]. Single members of the miR-200 cluster, such as miR-200a, also contributed to the cytoskeletal alterations by elevating CX43 expression, while miR-200b and miR-200c encouraged EMT start by independently up-regulating FERMT2, ZEB1, TKS5, and MYLK genes, respectively [87,154,156]. Loss of miR-494 led to cytoskeletal and micro-environmental re-organization by influencing expression of the PAK1 oncogene and the CXCR4 chemokine receptor [83,129], whereas down-regulation of miRNAs from the DLK1-DIO3 cluster mostly affected EMT discussed in Section 5.3 [158]. Increased expression of the laminin subunit LAMA4 gene was responsible for the TM alterations observed [132], since miR-539 was down-regulated. On the other hand, elevated miR-495 triggered the cytoskeletal adjustments via downregulating the

junctional adhesion protein JAM-A [95]. By downregulating adhesion and proteolytic molecules (Section 5.1.3. [114]), miR-221/222 impacted the cell-ECM interaction; conversely, by upregulating their expression, they facilitated EMT induction via direct or indirect suppression of the CDH1 gene. By inhibiting DNMT3B, the re-expression of cancer stemness genes NANOG and OCT 3/4 was made possible [165,166,180]. Multiple miRNAs played roles in the regulation of multiple invasion-related processes. Down-regulation of other miRNAs, including as miR-30a, miR-31, andmiR-34c, influenced many processes, whereas up-regulation of miR-21 affected cytoskeletal and TM re-organization [84,136]. Furthermore, miR-30a and miR-34c promoted EMT and stemness; miR-31 modified cytoskeletal and cell-ECM interactions; and miR-126 and miR-126/126* affected cell-ECM interactions and TM, separately [90,108,117,127,157,159,189,203]. Increased serum miR-720 expression in ADAM8-expressing TNBC patients and its down-regulation in primary BC combined with other decreases in metastatic tumors associated with its inability to target the TWIST1 EMT gene [119,167] provided insight into the multiple roles miR-720 plays in breast tumorigenesis. TWIST1 acted as an inducer or repressor of the miR-10b and miR-200 cluster, SNAIL2 stimulated miR-221 up-regulation, and the proteolytically active ADAM8 activated miR-720 expression [81,119,158,165]. These miRNAs are all involved in regulating the invasiveness of breast cancer cells.

8. While the activities of miRNAs expressed in breast cancer cells and stromal cells were described previously, exosome-mediated transfer of miRNAs to other cells allows them to exert their full effect during the invasive process [209]. All cells actively release exosomes, which are defined as nanovesicles of endocytic origin. Many biological processes, such as cell-cell communication and cancer cell invasion, rely on the exchange of proteins, messenger RNAs, and microRNAs. In addition, recent findings suggest that exosomes produced from tumor cells play a critical role in cancer development, invasion, and dissemination [210]. Certain microRNAs (miRNAs) were discovered to be significantly elevated in plasma exosomes of BC patients compared to plasma exosomes of healthy controls when produced from human BC cell lines [211]. Higher levels of miR-373 were also found in more aggressive TNBC in a serum level investigation of identified exosomal miRNAs in BC subtypes [212]. Exosomes released by metastatic BC cells and conveying miR-10b have been demonstrated in cell line models to stimulate invasive characteristics in non-malignant breast cells. The downregulation of HOXD10 and KLF4, two of miR-10b's target genes, provided evidence for the role of miR-10b in normal cells [213].

Furthermore, the latest work has demonstrated that elevated miR-21, miR-378e and miR-143 levels in exosomes derived from CAFs relative to normal fibroblasts might contribute to the establishment of aggressive BC cell phenotype [214]. In addition, miR-9 released by tumor cells may be transferred by exosomes to the recipient normal fibroblasts, resulting in enhanced cell motility, as observed by other investigators. miR-9 is abundantly expressed in numerous BC cell lines. CAFs derived from TNBC patients were shown to have an increased level of miR-9 compared to normal fibroblasts [215]. Specifically, miR-9, miR-10b, miR-21, and miR-373 have all been shown to have a role in the invasiveness of BC via various mechanisms. Furthermore, macrophage-secreted exosomes (macrophagessecreted exosomes) may carry oncogenic miRNAs into BC cells [216], promoting BC invasiveness from tumor-associated macrophages. BC generated exosomes cells have also been shown to have the independent capacity to convert pre-miRNAs into mature miRNAs. Using a DICER-dependent mechanism, exosomes derived from BC patient cells and sera promote normal epithelial cells to tumor formation [217]. These exosomes include pre-miRNAs, with DICER, AGO2, and TRBP proteins.

9. Clinical Potential of microRNAs Numerous investigationsin to the association of miRNAs and cancer has been performed over the past two decades, and key findings were achieved for miRNA synthesis and cancer-specific modifications in miRNA expression in tumor tissues. Some progress has been made in miRNA-based cancer treatment [218], and the miRNAs found in the bloodstream have been identified as potential biomarkers. Profiling of miRNAs has improved accurate classification of many forms of cancer [45,219], and several studies have sought to use aberrant

miRNA expression profiles to detect clinical states of cancer or subtypes. For instance, early-stage BC miRNAs have been identified, and two separate investigations have defined different combinations of miRNAs for discriminating ER, progesterone receptor (PR), or HER2 status [219,220]. Excellent reviews can be found at [42,221,222], which highlight the efforts of many authors to use the gradually identified aberrant expression profiles of miRsupps and oncomiRs to develop new diagnostic, prognostic, or predictive biomarkers. The assessment of possible miRNA-based indicators may be influenced by the findings of various studies showing dynamic changes during breast carcinogenesis and the dual functions of several miRNAs as oncogenes and tumor suppressors [48, 50]. In addition, recent research has focused on dissecting the relationships between miRNAs and important oncogenes, tumor suppressors, and regulatory genes. Research into the connection between cancer invasiveness and miRNA isoforms associated with the disease and exosome-mediated miRNA transfer to other cells has attracted a lot of attention in recent years. All of these findings add up to a more intricate network, which might be valuable for novel approaches to customized therapy. RNA-based treatment has also made great strides. some tens of tiny interfering miRNAs with tumor suppressive effects and oncogenic antisense oligonucleotides have been investigated to produce novel anticancer treatments, and some miRNAs have presently being studied in phase I or II clinical studies. AntimiRs 103/107, 122, and 155 have been tested and developed for treatment of diabetes, hepatitis C, and cutaneous T-cell lymphoma, respectively [223]. Mimics of miR-16, miR-29, and miR-34 have been used to target mesothelioma and non-small cell lung cancer, scleroderma, and multiple solid tumors. However, just 16% of all anti-cancer therapeutic drugs produced reach phase III trials, and only 10.4% of these are typically approved by the FDA [224]. Unfortunately, no RNA-targeted medications have yet been licensed by the FDA [225], and one-fourth have not been studied in human clinical trials.

10. Conclusions

The ever-expanding catalogue of human miRNAs gives rise to high hopes that further studies will shed light on the complexities of miRNA control of gene expression in both healthy and diseased states. Alterations in miRNA expression profiles are now widely believed to have a role in the etiology of several human illnesses, including cancer. A greater understanding of the molecular mechanisms underlying cancer cell detachment from the primary site, dissemination and propagation in secondary organs, and the miRNA regulation of relevant genes is urgently needed due to the high incidence of female malignancy-associated death, predominantly associated with BC, and the relatively high percentage of metastases. These findings will serve as a foundation upon which to build novel therapeutic compounds for the prevention and treatment of metastatic illness, as well as the identification of precise diagnostic and prognostic indicators. In this study, we compiled the most up-to-date information on the expression of miRNAs and the genes they regulate, focusing on their roles in breast cancer invasiveness and cancer cell stemness. We then focused on the epigenetic deregulation of particular miRNAs and their modified relationships with other regulatory genes. Many of the miRNAs we looked at have also been studied extensively in cell culture, animal models, and human clinical samples. The favorable development in metastasis researchisreflectedintheincreasingnumberofcell-freemiRNAexpressionstudiesofplasmasamples from cancer patients which were not included in our study. Further improvement in monitoring cancer recurrence and therapeutic efficacy is anticipated with the development of suitable techniques for miRNA quantification in circulating tumor cells. Finally, our established findings may effectively contribute to patient care and, eventually, lead to the extension of patients' lives, despite the varying detection techniques for the quantification of miRNA expression and the limitations imposed by analytic interpretation.

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