



Review article epithelial to mesenchymal transition-associated microRNAs in breast cancer

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Abstract

Despite major advances, breast cancer (BC) is the most commonly diagnosed carcinoma and remains a deadly disease among women worldwide. Many researchers point toward an important role of an epithelial to mesenchymal transition (EMT) in BC development and promoting metastasis. Here, will be discussed that how functional changes of transcription factors, signaling pathways, and microRNAs (miRNA) in BC promote EMT. A thorough understanding the EMT biology can be important to determine reversing the process and design treatment approaches. There are frequent debates as to whether EMT is really relevant to BC in vivo, in which due to the intrinsic heterogeneity and tumor microenvironment. Nevertheless, given the importance of EMT in cancer progression and metastasis, the implementation of therapies against cancer-associated EMT will continue to help us develop and test potential treatments.

Keywords Epithelial-mesenchymal transition. MicroRNAs. Breast cancer. Metastasis. cancer therapy

Introduction

Breast cancer (BC) is the most prevalent malignancy among

women worldwide, and its incidence is 11.7% among all types of cancers. BC is very heterogeneous and based on the presence or absence of the hormone receptors epithelial-mesenchymal transition including progesterone receptor (PR), estrogen receptor (ER), and ERBB2 receptor or human epidermal growth factor receptor type 2 (HER2), BC is classified into three clinical subtypes: HER2 positive (HER2+), hormone-receptor (HR)-positive (HR+; ER+, PR+/- and HER2-), and triple-negative (TN; ER-, PR- and HER2-) [1]. The treatment strategy for this cancer is selected based on different factors such as morphology, size and grade of tumor, metastases, and the expression of ER, PR, and HER2 [2]. Metastasis is the main cause of breast cancer-related mortality, which is modulated by different factors such as epithelial to mesenchymal transition (EMT) [3]. Thus, understanding the molecular mechanisms of metastasis and EMT in this cancer is critical.

Metastatic cascade can be recognized as an inefficient and deadly process that is highly complex. The importance of metastatic cascade has been under numerous investigations, in the hope of decreasing metastatic progression and prolonging survival. The first step in cancer metastasis is the migration of epithelial cancer cells away from the primary tumors and penetrate the circulation blood. Invasion-metastasis cascade is an extremely versatile process that is

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regulated at several levels, whereby tumor cell adhesion is eliminated and cell motility is enhanced. The key process underlying tumor cell individualization and achievement of migratory and invasive capacities frequently occurs within the framework of EMT [4].

MicroRNAs (miRNAs) are a class of non-coding single-stranded RNAs (ssRNAs), which are small (approximately 18–24 nucleotides) and evolutionarily conserved. MiRNAs play important roles in regulating gene expression post-transcriptionally, which functions through repressing target mRNA translation or increasing the degradation of mRNA. Emerging evidence has demonstrated that deregulation of miRNAs is correlated with differentiation, apoptosis, metastasis, and invasion in various types of cancers. MiRNA microarray analysis has reported that multiple miRNAs contribute to tumor growth, chemoresistance, and metastasis in breast cancer. Accumulating evidence has demonstrated that miRNAs are correlated with BC. MiRNAs function as oncogenes (onco-miRNAs) and tumor suppressors.

In the past few years, many miRNAs have been identified to regulate multiple steps of the EMT process [5]. Given these attributes, EMT-related miRNAs are known to play a crucial role during tumorigenesis, and can be considered as potential biomarkers or therapeutic targets for BC. This review will summarize the existing literature regarding the

contribution of EMT during metastasis with the main focus on miRNA regulation in BC.

Overview of EMT

During the EMT process, molecular reprogramming and phenotypic alteration occur, and polarized immotile epithelial cells change to motile mesenchymal cells. This fundamental cellular process contributes to tumor-initiating potential, invasion, metastasis, and chemoresistance. In EMT the expression of several proteins decrease, which are responsible for enhancing cell-cell contacts such as E-cadherin and γ -catenin. The expression of mesenchymal markers also increases such as N-cadherin, vimentin, and fibronectin [6].

Metastasis, the process by which tumor cells migrated from the original site to other parts of the body, causes roughly 90% of carcinoma-related deaths. An early essential step of the metastatic cascade is a phenotypic switch termed EMT. EMT is a basic developmental program wherein epithelial cells (ECs) undergo many transcriptional and morphological transformations and acquire mesenchymal characteristics, that includes reinforced migratory capability, increased apoptosis, and elevated extracellular matrix (ECM) production (Fig. 1) [7, 8].

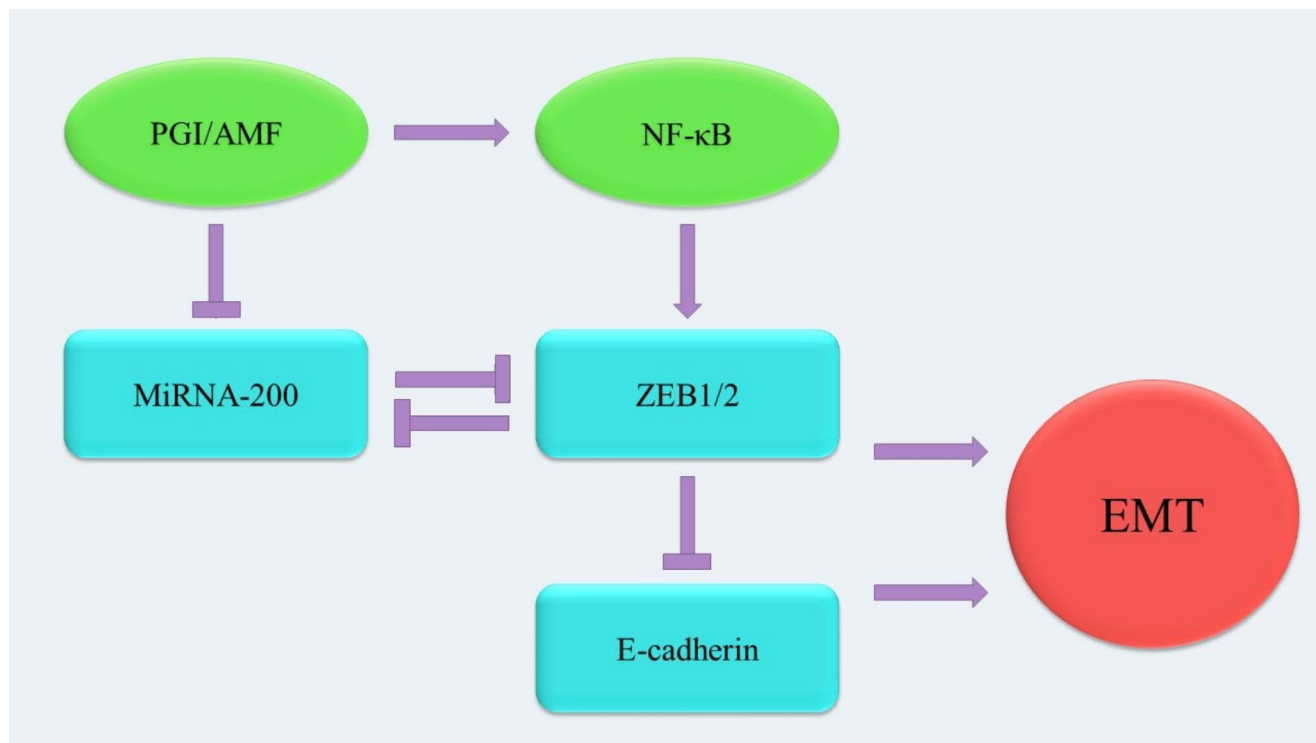


Fig. 1 A schematic illustrating epithelial to mesenchymal transition (EMT). Tumor cells are separated from the primary tumor, migrating through the blood vessels to another organ (metastasis). They get lodged in various organs by a process termed mesenchymal to epithelial transition (MET)

EMT signaling pathways and core regulators

EMT is regulated by several signaling pathways and growth factors according to the cellular contexts. Epidermal growth factor (EGF) and transforming growth factor (TGF) pathway have been widely investigated and shown that they contributed to angiogenesis progression [9]. Other mechanisms are also identified to drive EMT in BC including hepatocyte growth factor (HGF), fibroblast growth factor (FGF) [10, 11], insulin-like growth factor (IGF) platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), Stem cell factor (SCF)/c-kit signaling pathway, bone morphogenetic proteins (BMPs), autocrine motility factor (AMF), Wnt/ β -catenin/LEF-1, hedgehog proteins, nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), Notch, interleukin-like EMT inducer (ILEI), stress including hypoxia, inflammatory cytokine IL-6, leptin, cyclooxygenase-2/prostaglandin E2 (COX-2/PGE2), and ECM proteins [12]. Given that stimulation majority of signal transduction pathways can reinforce EMT and invasion processes. Following the multiple EMT-inducing signals and their downstream signaling effectors, the expression of EMT-activating transcriptional factors (EMT-TFs) is upregulated to coordinate this process. The major EMT-TFs include the Snail (Snail1, Snail2, Snail3) families of zinc finger transcription factors, TWIST (TWIST1 and TWIST2) basic helix-loop-helix protein (bHLH) family members, and also zinc finger E-box binding homeobox 1/2 (ZEB 1/2) [13, 14]. In the EMT process, downregulation of E-cadherin, which is an essential event in invasive/metastatic potential, is closely associated with loss of cell-cell adhesion junctions and gain of ability in motility and metastasis [15, 16]. The coordinated activity of diverse EMT-TFs can lead to reducing E-cadherin gene expression.

All of directly or indirectly repressors involved in tumor metastasis and EMT through a signaling network comprising signal transducer and activator of transcription 3 (STAT3), PI3K-AKT-mTOR signaling pathways, Ras/mitogen-activated protein kinase (MAPK) pathway, Wnt/ β -catenin pathway, and NF- κ B pathway, along with the final result of the reduction of E-cadherin and induction of metastatic proteins, like vimentin, fibronectin, N-cadherin, matrix metalloproteinase, etc. Also, changes in E-cadherin expression level are the result of a series of epigenetic modifications, for example, hypermethylation in the promoter region leads to the reduction of E-cadherin, associated with EMT phenotype in BC [17].

Cell junctions, cell adhesion, and the extracellular matrix

Ectopic expression of EMT-TFs leads to repression of genes encoding junction proteins, whereby ECs lose apical-basal polarity and cell junctions including adherens junctions, desmosomes, and tight junctions [8]. Since cellular adhesion is involved in cell signaling, differentiation, growth, inflammation, as well survival, so, alteration of these molecules affects multiple downstream pathways and might enhance cancer metastasis and EMT [18]. For instance, following the downregulation of E-cadherin expression, EMT up-regulates N-cadherin, which reduces the adhesion strengths and enhances motile and invasive capabilities [19, 20]. Likewise, upregulation of another EMT marker vimentin, as a significant regulator of cell motility, was associated with an increase in the receptor tyrosine kinase Axl which enhances breast epithelial cell metastatogenic capacity [21]. Additionally, several cell surface proteins and nonepithelial cadherin that are essential for migration and invasiveness are increased. Another study showed that the integrity of occludin and the tight junction is involved in the cancer progression when it was shown that the loss of occludin expression was significantly related to in the development of tumors [22]. The regulation of mesenchymal migration modes facilitates the formation and extension of new membrane protrusions and mesenchymal cell migration. Increased cellular protrusion and secretion of matrix metalloproteinases (MMPs) finally facilitate degradation of ECM, migration, and invasive cell behavior of cancer cells [23]. The crosstalk complexities between different downstream effectors displayed that developmental EMT is a process that in addition to involvement in cell adhesion and cytoskeleton organization, provides a range of many expression profiles of markers. Selection of these molecular markers and related activity changes in different signals increase the process of EMT.

EMT-related miRNAs

MiRNAs post-transcriptionally control tumor suppressor genes and oncogenes through targeting the complementary sequences of the 3'untranslated region (3'UTRs) of specific mRNAs, often resulting in gene silencing [24, 25]. Firstly, miRNAs are expressed as larger primary miRNAs (or pri-miR), which are processed in the nucleus by the Drosha-DGCR8 complex to liberate the precursor-miRNA (or pre-miR) structure. The pre-miRNA is subsequently transported to the cytoplasm during a process mediated via exportin-5 (EXP-5). MiRNA duplexes (approximately 22-nt) are excised from imperfectly pre-miRNA by Dicer.

A single strand of miRNA is loaded in the RNA-induced silencing complex, to bind to complementary target mRNA and trigger repression of corresponding protein expression, although the underlying mechanism is not yet been fully understood [26]. Hence, alterations of balance between mRNA–miRNA interactions may result in changes in the physiological status of the tissues and initiate pathological conditions [27].

Accumulating evidence has demonstrated that dysregulation of miRNAs is involved in human disease pathogenesis. Studies have also corroborated that miRNAs are highly correlated with tumor progression including BC [28, 29].

Almost 50% of human miRNA genes are frequently located on cancer-associated genomic regions (CAGRs) or fragile sites. Numerous miRNAs are known to regulate several well-known cancer-associated genes, and act as oncogene or tumor suppressor miRNAs [24].

Additionally, several miRNAs have been implicated in direct regulation of the EMT process [30]. Multiple miRNAs have been identified to regulate EMT. The regulatory miRNA mechanisms are very complex and their function is extremely under the influence of cellular functions. Clearly, this heterogeneity in studies makes a comparison of outcomes difficult. Furthermore, RNA studies are still poorly understood and several obstacles were identified in the interpretation of studies analyzing. Concerning EMT, miR-200 family, and miR-205, as key regulators of EMT, are able to maintain epithelial differentiation [31]. By contrast, MiR-21 involves in TGF- β -induced EMT and was one of the earliest detected cancer-promoting ‘OncomiRs’ [32]. Examples of miRNAs that impinge on the EMT-TFs regulation in another cancer cell is described in Fig. 2. Recently, various feedback loops among miRNAs and core EMT-TFs have been outlined in vivo or in vitro EMT-based studies. A study by Slabáková et al. showed that miR-34a is involved in different feedbacks including EMT regulators Snail, ZEB1, and AXL [33].

EMT-related miRNAs in BC

Breast carcinoma is a heterogeneous malignant disease, involving a diversity modification of gene expression and structure. Shahabi et al. in 2021 reported that let-7d and miR-185 suppressed EMT by targeting Rab25 expression in BC and supposed to be a new opportunity for this cancer [34]. Upregulation of miR-129-5p remarkably can enhance E-cadherin and inhibit the expression of vimentin and N-cadherin in MCF-7/doxorubicin-treated cells [35, 36]. MiR-129-5p decreased IC₅₀ of doxorubicin, paclitaxel, and vincristine in these cells. In MCF-7 cells, miR-129-5p expression level decreased by SOX4 and EZH2,

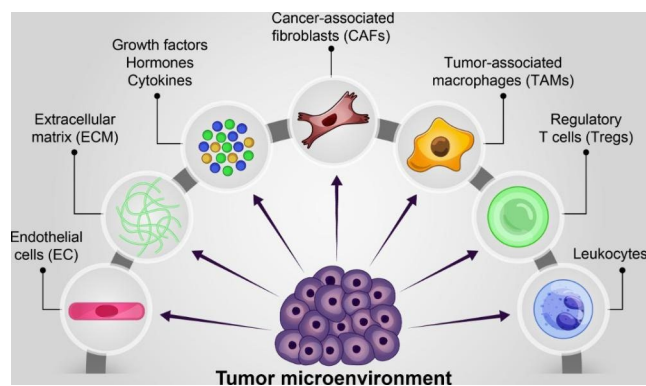


Fig. 2 MiR-200 plays a role in modulating the epithelial to mesenchymal transition (EMT) in breast cancer (BC) by interfering with phosphoglucose isomerase/autocrine motility factor (PGI/AMF), as an activator of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B). Loss of PGI/AMF expression decreases the activity of NF- κ B. Moreover, the expression of PGI/AMF correlates with zinc finger E-box binding homeobox 1/2 (ZEB 1/2) activity and finally EMT

that function as an epigenetic modification-silencing gene and a master control gene of EMT, respectively [37]. ZEB1 and ZNF217, which were suppressed by miR-200c, were recognized as a transcriptional activator of TGF- β and can promote the trastuzumab sensitivity and decrease migration and invasion in BC. Reportedly, ZEB1 can suppress miR-200c, therefore, ZNF217 might contribute to miR-200c inhibition through TGF- β /ZEB1 signaling [38].

Several other reports have described that altered expression of miR-10b, -206, -335, -373, and -520c promoted the late stages of malignant BC via impacting in tumor cell EMT, migration, invasion, angiogenesis, etc. [39]. A recent

Table 1 MicroRNAs (miRNAs) involved in the regulation of EMT process in BC

MiRNAs	Pathway	Mechanism of function	References
miR-9	E-cadherin	OncomiR	[86]
miR-10b	TWIST	OncomiR	[87]
miR-15a	BMI1	Tumor suppressor	[88]
miR-30a	vimentin	Tumor suppressor	[89]
miR-34	SNAIL, SLUG and ZEB1	Tumor suppressor	[90, 91]
miR-129-5p	TWIST1-Snail	Tumor suppressor	[92]
miR-135	Wnt/ β -catenin	Tumor suppressor	[93]
miR-136	E-cadherin	Tumor suppressor	[94]
miR-138	Vimentin	Tumor suppressor	[66]
miR-150-5p	E-cadherin	OncomiR	[64]
miR-153	ZEB2	Tumor suppressor	[95]
miR-190	TGF- β	Tumor suppressor	[65]
miR-300	Twist	Tumor suppressor	[96]
miR-424	TWIST1/2	Tumor suppressor	[97]
miR-497	Slug	Tumor suppressor	[98]
miR-590-5p	Wnt- β -catenin	Tumor suppressor	[99]
miR-720	TWIST1	Tumor suppressor	[100]

study in 2020 assessed the association of miR-93 with the EMT process and vasculogenic mimicry in triple-negative breast cancer (TNBC). Their results showed that knockdown of miR93 leads to an increase in the expression levels of Ecadherin and occludin as EMT-related genes and decreases the expression levels of vimentin and Ncadherin. Furthermore, the microtubuleforming potency of cells decreased after miR-93 knockdown [40]. Moreover, a recent study reported that up-regulation of miR-33b leads to inhibiting EMT, invasion, and metastasis through the alternation of E-cadherin, β -catenin, and vimentin expression levels [41].

Several examples of EMT-associated miRNAs will be explained in Table 1.

MiRNAs, EMT-related TFs, and signaling pathways in BC.

Many miRNAs can directly or indirectly target EMT-TFs in BC. Several examples of these regulatory networks are

described below. Based on the study of Ahmad et al. [42], miR-200 members (miR-200a/b/c) could involve in the regulation of EMT in BC by interfering with phosphoglucose isomerase/autocrine motility factor (PGI/AMF), as an activator of NF- κ B signaling. Loss of PGI/AMF expression reduced the activity of NF- κ B signaling (about 50%) and its downstream genes MMP-2 and uPAR in MDA-MB-231 and BT549 cells. In addition, the expression of PGI/AMF correlates with ZEB1/2 activity. MiR-200 members are required to inhibit ZEB1/2 by negative regulation of PGI/AMF (Fig. 2). In BC, increased miR-103/107 levels are related to metastasis potential and EMT. They affect the in vitro directional cell migration and invasive ability via indirectly decreasing miR-200 expression and also facilitate a metastatic cascade of otherwise non-metastatic BC cell lines under in vivo conditions [43]. Another study in 2020 reported that miR-4472 promoted EMT and metastasis in

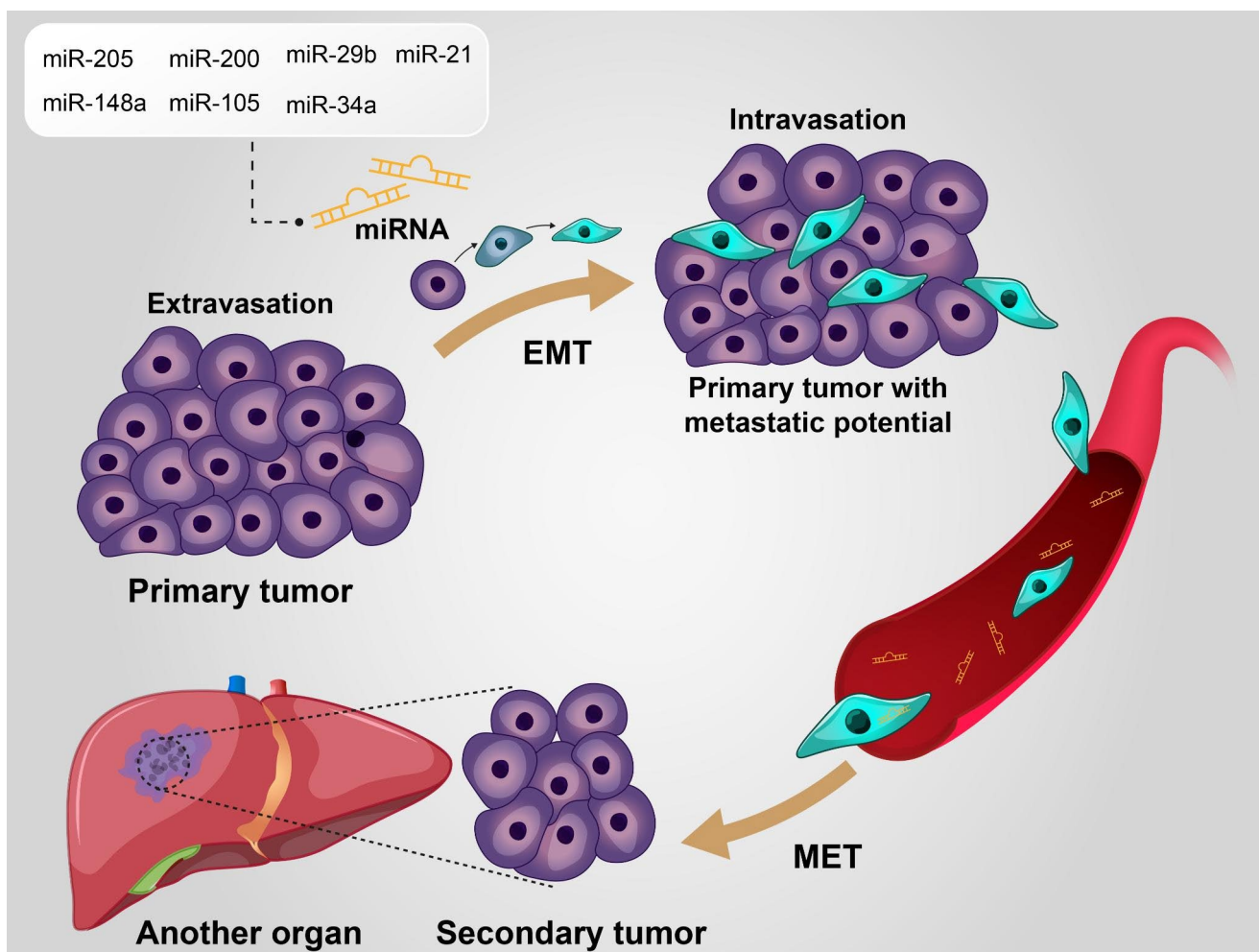


Fig. 3 Epithelial to mesenchymal transition (EMT), which can be modulated by microRNAs (miRNAs), comprises cancer-associated fibroblasts (CAFs), tumor-associated macrophages (TAMs), leukocytes, endothelial cells, regulatory T cells (Tregs), growth factors, cytokines, hormones, extracellular matrix (ECM), etc., tumor microenvironment (TME) represents a key factor for tumor heterogeneity maintenance, tumor initiation, progression, metastasis, and therapeutic resistance, and miRNA can provide a supportive environment surrounding the tumor

malignant BC through downregulation of repulsive guidance molecule A (*RGMA*) as an EMT suppressor [44]. Moreover, a recent study in 2021, reported that increased miR-614 expression and repression of TAPT1 and Mirol1 can regulate the EMT in BC [45]. Bo lei et al. reported an important role of miR-615-3p in the progression of EMT in BC via the TGF- β signaling pathway [46]. Based on Bracken's group finding, an EMT network inclusive of the negative feedback loops have been identified among pro-mesenchymal TFs (driven by Snail, ZEB, Wnt, and members of the Notch family) and epithelial-enforcing miRNAs (members of the miR-200, -203 and 34 families). These reciprocal repressions not only can reinforce the activation of the EMT program but also control the balance of epithelial versus mesenchymal phenotype of the cells [47].

In metastatic BC cells, EMT-TF TWIST could activate transcription of the miR-10b gene and induce its expression, and thereby preventing translation of its target (homeobox D10 mRNA), which was inversely related to pro-metastatic gene, RHOC [48].

On the other hand, as shown by Nairismägi et al. [49], miR-145a-5p, miR-151-5p as well as a combination of miR-145a-5p plus miR-151-5p and miR-151-5p plus miR-337-3p remarkably suppressed the translation of TWIST1. Among the different miRNA functions in cancer, identifying their multiple interactions with oncogenes and cancer signaling pathways could lead to exploring new therapeutic opportunities.

A large number of studies signified that overexpression of the epidermal growth factor receptor (EGFR) impinging on EMT and BC development [50]. Several miRNAs have been known to associate with the EGFR pathway as repressors which are mentioned in Table 1.

Crosstalk between miRNAs and microenvironmental factors

The tumor microenvironment (TME) plays a pivotal role in forming cancer or non-cancer cell phenotypes. It significantly contributes to cancer initiation, development, metastasis, therapeutic response, and clinical outcome [51]. TME comprises different types of stromal cells such as cancer-associated fibroblasts (CAFs), tumor-associated macrophages (TAMs), leukocytes, endothelial cells, regulatory T cells (Tregs), and immune cells in addition to extracellular components including growth factors, cytokines, hormones, ECM, etc., which are within the tumor or in the surrounding of the tumor and nourished by a vascular network and the extracellular matrix [52]. Cytokines, hormones, and growth factors can transmit signals between cancer cells and the

TME, which lead to the transformation through EMT and metastasis [53, 54] (Fig. 3).

Accumulating evidence has also demonstrated that a plethora of EMT-promoting microenvironmental factors consists of pro-inflammatory cytokines, hypoxia conditions, and ECM components. It has been well noticed that miRNAs can be affected by EMT-related cytokines [55]. These findings were supported by the study of Keklikoglou et al. [56], who reported that NF- κ B mediated inflammation and EMT process due to reduction in miR-520/373 family. Moreover, a regulatory loop between miR-448/NF- κ B was described in MCF-7 BC cells [57]. Hypoxia and/or HIF-1 orchestrates metastasis and EMT phenotype via the coordinated regulation of diverse EMT-TFs (e.g., TWIST and Snail) [58]. A study by Azimi et al. [59] reported that the existence of a reactive oxygen species (ROS)/EMT axis in which hypoxia-induced ROS mediate N-cadherin and SERPINE1 expression in BC cells. Numerous studies also exhibited that alterations of CpG are associated with dysregulation of miRNAs expression in cancers such as BC [60]. Overall, the cross-regulation among EMT-TF/miRNA and oncogenes/miRNA was briefly described. Nevertheless, despite the interaction loops between the expression pattern of miRNAs and EMT regulators, it is usually unclear whether miRNA expression alteration leads to EMT, or it is the EMT pathway that causes dysregulation of miRNA.

MiRNAs and cell architecture components in BC

Various miRNAs are described to control EMT-TFs and cellular architecture components including BC Fils-Aime et al. [61] discovered that the downregulation of tumor suppressor miR-584 is a prerequisite for the TGF- β -induce cell migration of BC cells. They recognized that TGF- β reduces the expression of miR-584, and leads to rearrangement of the actin cytoskeleton, and migration of BC. MiR-23b, the main regulator of cytoskeletal remodeling, modulates cell architecture and reinforces in vivo invasion of tumor cells during BC progression. Overexpression of miR-23b abolished EMT phenotype and increased the E-cadherin level [62]. MiR-9 was also one of the upregulated miRNAs in BC tissues and cancer cells. MiR-9 has been shown to be able to inhibit E-cadherin, and thereby elevates BC cell motility and invasion capacity. Transcriptional repression of E-cadherin by miR-9, leads to the activation of the Wnt/ β -catenin pathway, which can increase the level of gene encoding VEGF and angiogenesis [63]. MiR-150-5p is believed to be an oncogene miRNA and shown to be upregulated in all BC cell lines. Loss of miR-150-5p expression impeded the abilities of cell migration and invasion by suppressing

the level of mesenchymal markers (i.e. N-cadherin, vimentin, and β -catenin) [64]. MiR-190 is downregulated in BC clinical specimens and correlates with better survival in BC patients. It is directly controlled by ZEB1 and makes a negative feedback loop with TGF- β /SMAD2 signaling in human BC. Forced the expression of miR-190 also reversed the TGF- β -mediated EMT progression, and BC metastasis via SMAD2 inhibition both in vitro and in vivo [65].

MiR-138 is another miRNA, that is downregulated in BC tissues compared to adjacent normal tissue. By comparing expressing miR-138 in MCF-7 and MDA-MB-231 cell lines, miR-138 has been signified to be able to increase and decrease vimentin and E-cadherin expression levels, respectively. By functioning as a feedback loop, miR-138 affects the EMT phenotype, and thereby modulates tumorigenesis, lymph node metastasis in BC cells [66]. All these findings validate the ability of miRNAs to regulate EMT in tumorigenesis, through the targeting of cell architecture components. It is worth noting that some miRNAs targeted multiple EMT/MET components in BC. For example, ectopic expression of miR-221/222 family significantly increases EMT in luminal cells by negatively targeting Notch3 and E-cadherin in luminal cells, whereas the miR-221/222 repression promoted MET in basal-like BC cells [67].

The potential value of EMT-related miRNAs in BC treatment

Functional genomics research has enabled pathway-based therapeutic strategies for cancer management. Despite significant progress in finding signaling networks in tumor cells, effective treatment choices are scarce. The discovery that a miRNA could be involved in the different cancer pathways, makes them highly promising therapeutic candidates in cancer [68].

Prior studies offered that high expression of miRs –24 [69], –125 [70] and –214 [71] were correlated with low survival. In contrast, the expression level of miR –206 and –145 [72], –155 [73] and –375 was positively related to a better prognosis. Given the relevance of miRNAs and EMT in the development of BC, two emerging questions are how miRNAs control EMT cascade, and another important question is whether miRNA-based therapeutic approaches in BC can be reliable treatment options in oncology.

EMT-related miRNAs, and therapy resistance

Several studies in this regard have focused on the association between dysregulation expression of miRNAs in EMT

regulation and treatment failure of BC. For instance, in human BC cells, epigenetic silencing of miR-200 members is related to drug-resistant phenotypes and EMT features. More precisely, miR-200-mediated upregulation of E-cadherin was directly related to repression of ZEB1 expression as well as indirectly association in the enhancement of acetylation of histone H3 at the promoter of E-cadherin in both mesenchymal MDA-MB-231 and BT-549 BC cells [74]. In another study, miR-375 re-expression has been reported to be linked with restored tamoxifen sensitivity and inhibited the EMT phenotype in TamR BC cells [75]. In addition, several miRNAs have been contributed to the cytokine-mediated BC chemoresistance due to the activation of the EMT phenotype. MiR-30c regulates drug resistance of BC by negatively regulation EMT-related cytokines including vimentin, twinfilin 1, stress fiber F-actin, interleukin-11 (IL-11), and IL-6 [76]. Moreover, in 2020 Hong Li et al. evaluate the effect of miR1297 on BC cell EMT and proliferation and its molecular mechanisms related to fatty acid 2-hydroxylase (FA2H). FA2H is a hydroxy fatty acid enzyme, which can increase the sensitivity of cancer cells to chemotherapy drugs. In this study, researchers proposed miR-1297/FA2H as a novel potential therapeutic agent [77]. As mentioned before, lots of miRNAs such as miR-137, miR-34a, miR-142-3p, miR-129, miR-205, and miR-99a play essential roles on CSCs (cancer stem cells) maintenance and so they can serve as novel tools for therapeutic purposes via modulation of breast CSCs [78]. Wang et al. in 2020 reported that miR-1976 downregulated in TNBC and promoted EMT and CSCs maintenance. They also proposed that this downregulation is associated with a low survival rate in BC patients [79]. These studies undoubtedly provide essential data about the association between the acquisition of EMT and maintenance of stem-like characteristics in BC patients. These studies undoubtedly provide essential data about the association between EMT and stem-like phenotype in BC patients. However, as reviewed in the current manuscript, the majority of studies are cell-based studies, whereas there is only limited evidence of reporting on in vivo experiments.

TGF- β suppression, miR-200c, and silencing ZEB1 or ZNF217 can inhibit metastasis and trastuzumab resistance in BC. Thus, the interaction between miR-200c/ZEB1 and miR-200c/ZNF217/TGF- β /ZEB1 can inhibit the metastasis and trastuzumab resistance of cancer cells, suggesting that EMT might be involved in the molecular induction of the malignant behaviors of breast cancers [80]. Because of the inhibitory characteristic of EMT, miR-708-3p is also recognized as a tumor-suppressor miRNA in BC. Moreover, miR-708-3p can be proposed as a proper option for overcoming chemoresistance and metastasis in BC [81]. The miR-106b-25 cluster comprises miR-25, miR-93, and miR-106b,

which target a transcriptional stimulator of E-cadherin such as EP300 and up-regulated in doxorubicin-resistant. With this cluster, a single miRNA upregulation may lead to that target cells achieving the EMT phenotype, besides proliferative capability in doxorubicin therapy [82]. It seems EMT may be significantly associated with poor prognosis and enhanced chemoresistance in BC, whereas miRNAs can modulate EMT. Therefore, miRNAs can be suggested as a useful therapeutic approach for overcoming chemoresistance in BC.

Challenge and limitation

Suppression of EMT is a crucial therapeutic strategy, which may have a serious effect on disease outcomes. As reviewed by Malek et al. [83], there are 3 different strategies to inhibit the EMT process via (a) EMT extracellular inducers, (b) EMT-related TFs, and (c) the EMT downstream effectors. Different studies have noted that miRNAs have an established role in regulating EMT through directly or indirectly targeting families of EMT-TFs or affecting the integrity of the epithelial architecture during EMT development. Other studies have also stated a close relation between dysregulated miRNA and cancer progression. Therapeutic strategies include up-regulation or downregulation of specific miRNAs since dysregulation of miRNA expression has been observed in several cancers. miRNA-based therapy approach effectively employs synthetic antisense oligonucleotides (also known as anti-miRNAs) to block OncomiR, or synthetic miRNA mimics to reactivate tumor-suppressive miRNAs. However, due to major challenges like off-target multiple gene regulation, obstacles of *in vivo* miRNA delivery, and pharmacokinetics, clinical research on miRNA-based therapeutic strategies for cancer patients is still in the early stage. EMT suppressing or reversing can effectively cause a significant adverse event in favor of MET as well tumor colonization at metastatic sites through circulating cancer cells [84]. Additionally, molecular heterogeneity of cancer and plasticity of EMT phenotype indicates the need for a multimodal treatment strategy that is not only focused on one EMT-target gene. For instance, the combination of chemotherapy and anti-miRs and or miRs replacement strategies were widely studied both *in-vivo* and *in-vitro* experiments. Roscigno et al. have displayed that inhibition of miR-24 using transfection of an anti-miR-24 oligonucleotide, might be a potentially effective approach for combating resistance to cisplatin and survival in BC cells that harbored EMT phenotype [69]. Furthermore, Plantamura et al. reported that miR-205 expression level is significantly correlated with aggressiveness of BC and it is decreasing from a less aggressive subtype to a more aggressive one.

They also propose that this affects drug response and patient survival [85]. Overall, further research about EMT-regulating miRNAs in various cancer models is needed to more translate present knowledge to the clinical context.

Future directions

Currently, cancer treatments based on miRNAs have attracted more attention because in this approach the genes, which are not been manipulated previously, can be targeted. Moreover, miRNAs are remarkably flexible for regulating a wide range of genes. However, due to challenges in the stability and delivery of miRNAs, a longer time is required for getting better results. Development in biological science, biochemistry, and nanotechnology can develop the available knowledge on miRNA-based therapies. A combination of miRNAs and alongside medicines such as small molecules or antibodies may provide superior outcomes for cancer patients. Using novel biotechnology techniques for working on miRNAs, scientists may present promising approaches for RNA-based therapeutics to overcome cancer.

Conclusions

EMT can enhance the migratory potential and invasiveness of BC cells, however, the interpretation of regulatory networks in which miRNAs control the EMT process is still not fully understood. Moreover, the function of many miRNAs and pathways is still unknown. Although the miRNA-mediated EMT process has been known as a promising target to treat cancer, they still have many issues hindering their reliability of the clinical application. Conversely, a better understanding of regulatory mechanisms of miRNAs, new therapeutic approaches targeting miRNAs must be identified, which will establish a more effective means for treating BC patients particularly in combination with chemo or radiation therapies.

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