

Role and underlying mechanisms of miR-200 family in breast cancer (Review)

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Abstract. Breast cancer (BC) is the most common malignant tumor among women. Its significant heterogeneity and complex molecular mechanisms pose major clinical challenges, including limited therapeutic efficacy and drug resistance. Recently, microRNAs (miRs) have been recognized as key post-transcriptional regulators involved in tumorigenesis and tumor progression through multiple pathways. Among these, the miR-200 family (miR-200a, miR-200b, miR-200c, miR-429 and miR-141) has attracted considerable attention due to its pivotal role in BC. The present review systematically summarizes the genomic characteristics, expression regulation mechanisms and biological functions of the miR-200 family in BC. Special emphasis is given to their roles in epithelial-mesenchymal transition, cell proliferation, apoptosis, maintenance of stemness, and remodeling of the tumor microenvironment. Furthermore, members of the miR-200 family have potential as diagnostic and prognostic biomarkers and are closely linked to chemotherapy resistance. The present review aims to provide novel insights and a theoretical foundation for the diagnosis, treatment, and deeper investigation of BC by comprehensively examining the functional mechanisms of the miR-200.

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1. Introduction

Breast cancer (BC) is the most prevalent malignant tumor among women and the leading cause of cancer-related mortality. Although medical advancements have significantly improved clinical outcomes, incidence and mortality rates remain persistently high (1). This situation is mainly due to the complexity of BC, which involves dysregulation across multiple molecular networks, including accumulation of genetic mutations, abnormal epigenetic modifications, and alterations in the tumor microenvironment (TME) (2). Despite increased understanding of these molecular mechanisms, BC's inherent complexity and heterogeneity present substantial therapeutic challenges, particularly limited treatment efficacy and drug resistance (3). Therefore, deeper investigation of the molecular mechanisms underlying BC pathogenesis and identification of novel therapeutic targets constitute critical research priorities requiring immediate attention.

MicroRNAs (miRNAs or miRs) are a class of highly conserved, non-coding RNA molecules of ~22 nucleotides in length. They mediate mRNA degradation or translational repression by specifically binding to the 3' untranslated region (3' UTR) of target mRNAs, thus achieving fine-tuned regulation of gene expression at the post-transcriptional level (4). Extensive research indicates that dysregulated miRNA expression is closely linked to the initiation and progression of various malignant tumors. By modulating malignant cellular behaviors, such as proliferation, invasion, migration and drug resistance, miRNAs play a crucial role in cancer progression. For example, in BC, miR-182-3p can induce apoptosis of

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tumor cells by targeting TRF2, significantly inhibiting tumor growth (5); in lung cancer (LC), miR-193b-3p downregulates prion protein expression by targeting PRNP, thus diminishing the proliferation, migration and invasive capabilities of LC cells (6).

Notably, systematic investigations into miRNA families have emerged as novel approaches to elucidate core tumor regulatory networks. Compared with individual miRNAs, members of the same family often share sequence homology and functional synergy, thus forming more stable regulatory networks across various pathways, such as the miR-34 family (7) and the miR-200 family (8). Among these, the miR-200 family has received considerable attention due to its pivotal role in regulating key biological processes such as epithelial-mesenchymal transition (EMT). Dysregulation of this family correlates with tumor progression and poor prognosis in various cancers, including hepatocellular carcinoma (9), LC (10) and ovarian cancer (OC) (11). This pan-cancer functional conservation suggests that in-depth investigations of the miR-200 family may not only elucidate the pathogenesis of specific cancers but also uncover shared molecular mechanisms underlying malignant tumor development. From a preventive medicine perspective, identifying and validating these critical regulatory factors, which exhibit abnormalities at early stages of multiple cancers, holds significant value for developing universal early screening biomarkers and molecular intervention strategies targeting precancerous lesions. In BC, the miR-200 family influences disease progression by regulating multiple critical pathways, including cell proliferation, EMT, invasion, migration, cellular stemness and TME modulation. However, the precise mechanisms of action, synergistic or antagonistic relationships between family members, and dynamic changes across BC subtypes and stages remain incompletely reviewed. The present study aims to systematically review research progress concerning the miR-200 family in BC, examine its molecular regulatory mechanisms and biological functions, and evaluate its potential clinical utility as a diagnostic biomarker and prognostic indicator for BC. This endeavor seeks to provide novel theoretical foundations and therapeutic strategies for managing BC.

2. Overview of the miR-200 family

The miR-200 family consists of five members: miR-200a, miR-200b, miR-200c, miR-429 and miR-141. Based on their chromosomal locations, this family is divided into two gene clusters (Fig. 1A): The miR-200b/miR-200a/miR-429 cluster located at 1p36.33 (intergenic spacing: 665 bp between miR-200b and miR-200a, 1053 bp between miR-200a and miR-429) and the miR-141/miR-200c cluster at 12p13.31 (spacing: 331 bp). The miR-200 family is highly conserved across vertebrates, suggesting a critical regulatory function throughout evolution (12,13).

The biosynthesis of the miR-200 family follows the classical miRNA maturation pathway. Its expression is finely regulated by epigenetic modifications. In epithelial cells, activating histone modifications (H3K4me3 and H3Ac) are enriched at the promoters of miR-200 family members, maintaining their high expression levels; in mesenchymal cells,

these family members are specifically suppressed by distinct epigenetic mechanisms. The miR-200b/miR-200a/miR-429 cluster is suppressed by PRC2-mediated H3K27me3, while the miR-200c/miR-141 cluster is silenced through DNA methylation and H3K9me2 modifications (14,15). Although both clusters exhibit high expression levels in epithelial cells via H3K4me3 and H3Ac modifications, they show distinct epigenetic silencing patterns in mesenchymal cells. This phenomenon reveals the complex regulatory network of the miR-200 family during evolution and suggests its essential role in maintaining epithelial phenotype and inhibiting EMT. Furthermore, oxidative stress reportedly upregulates miR-200 family expression levels, though this response varies among subclusters. Expression of the miR-200c/miR-141 cluster is significantly enhanced, whereas the miR-200b/miR-200a/miR-429 cluster displays relatively modest upregulation (16). Additionally, maturation of the miR-200 family is regulated by multiple transcription factors. For example, p53 can directly bind to response elements RE1 and RE2 within the miR-200 promoter to activate transcription, thereby increasing its expression (17). The ZEB family also serves as a critical regulator. Specifically, ZEB1/2 bind to the conserved E-box element (CACCTG) in the promoter regions of miR-200 family members, inhibiting their transcription and expression. Conversely, miR-200 family members target the 3'UTR of ZEB1/2, reducing their expression. This reciprocal regulation establishes a double-negative feedback loop between ZEB1/2 and the miR-200 family (18,19).

Members of the miR-200 family exhibit high sequence homology and can be divided into two clusters based on nucleotide differences in their seed sequences: the miR-200b/200c/429 cluster (seed sequence: AAUACUG) and the miR-200a/141 cluster (seed sequence: AACACUG). The seed sequences of these clusters differ by only one nucleotide (Fig. 1B), suggesting substantial overlap in their target genes. To validate this hypothesis, potential target genes of miR-200 family members were systematically analyzed using bioinformatics approaches. Results revealed that the miRTarBase (<https://mirtarbase.cuhk.edu.cn/>) identified 24 shared target genes (Fig. 2A), miRDB (<https://mirdb.org/>) predicted 207 shared target genes (Fig. 2B) and miRWalk (<http://mirwalk.umm.uni-heidelberg.de/>) predicted 2,611 shared target genes (Fig. 2C).

3. Role of the miR-200 family in BC and its molecular mechanisms

Studies indicate that the miR-200 family regulates essential biological behaviors in BC cells, including proliferation, migration, invasion and apoptosis, through diverse molecular mechanisms. Currently identified regulatory mechanisms include (Fig. 3): (i) Members of the miR-200 family directly bind to the 3'UTR regions of downstream target genes, precisely modulating their expression by mediating mRNA degradation or translational inhibition (20-24). This direct targeting constitutes the fundamental mechanism behind their biological functions. (ii) Multiple long non-coding RNAs (lncRNAs) and circular RNAs act as 'molecular sponges' (25-28) (Fig. 4). These molecules competitively bind miR-200 family members via miR-200 response elements,

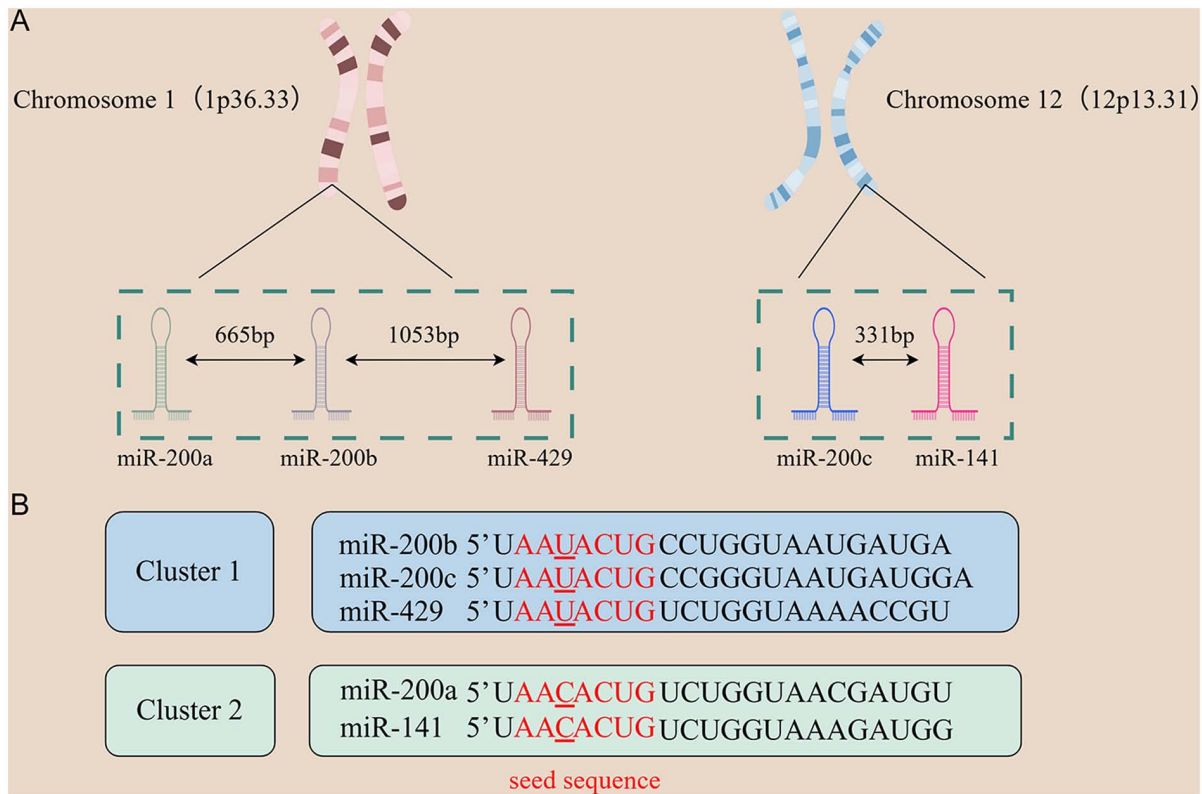


Figure 1. Chromosomal locations and sequence characteristics of the miR-200 family. (A) The miR-200 family is divided into two clusters based on chromosomal location. Cluster 1 (human chromosome 1) contains miR-200a, miR-200b, and miR-429, while cluster 2 (human chromosome 12) contains miR-200c and miR-141. (B) The miR-200 family is divided into two clusters based on seed sequences. Cluster 1 contains miR-200b, miR-200c, and miR-429, while Cluster 2 contains miR-200a and miR-141. The third nucleotide of the seed sequences in the two clusters differs (underlined in the figure). The figure was created by www.figdraw.com. miR, microRNA.

preventing miR-200 from interacting with its target mRNAs and thereby attenuating its inhibitory effects. Additionally, certain cytokines dynamically regulate miR-200 expression by interacting with its binding sites (29-32). (iii) The miR-200 family further modulates downstream signaling pathways, such as PI3K/AKT, MAPK/ERK and NF-κB, by regulating the expression of target genes, thereby systematically influencing tumor progression (33-39). Thus, the miR-200 family constructs a multi-tiered regulatory network in BC, spanning direct gene regulation to complex signaling pathway modulation, forming a precise molecular regulatory system. These findings not only enhance understanding of BC pathogenesis but also provide a theoretical foundation for developing targeted therapeutic strategies.

Invasion and migration. The primary threat to survival in patients with BC arises from the highly invasive and migratory characteristics of tumor cells. These malignant cells break through tissue barriers via multiple pathological pathways and molecular mechanisms, causing systemic dissemination and eventually forming lethal metastatic lesions in distant organs (40). Numerous studies have recently confirmed that differential expression of the miR-200 family between epithelial and mesenchymal cells positions it as a key molecular regulator of BC invasion and migration. Members of this family significantly influence BC cell invasion and migration through multi-pathway and multi-target regulatory networks (Table I), providing critical insights into the mechanisms underlying BC metastasis.

EMT. Under normal physiological conditions, epithelial cells maintain tissue integrity through tight junctions, adherens junctions and other cellular structures. These features provide strong adhesion and limit migratory capability. Mesenchymal cells, by contrast, show reduced cell-cell adhesion and reorganized cytoskeletal structures, resulting in increased motility and invasiveness. EMT refers to the transition from epithelial to mesenchymal phenotypes, characterized by the downregulation of epithelial markers (for example, E-cadherin) and the upregulation of mesenchymal markers (for example, N-cadherin and vimentin). This transformation allows tumor cells to gain migratory and invasive properties, significantly enhancing their metastatic potential (41). EMT is primarily mediated by core transcription factors, such as ZEB1, ZEB2, Snail and Twist, which repress epithelial gene expression by binding to E-box motifs in their promoter regions (42). Notably, a precise double-negative feedback loop exists between the miR-200 family and the ZEB family (ZEB1/ZEB2). On one hand, miR-200 family members directly target and suppress the expression of ZEB1 and ZEB2 (43-50), blocking EMT and inhibiting the invasive and migratory capacities of BC cells. Conversely, the ZEB family transcriptionally suppresses miR-200 family expression (51-53), thereby promoting EMT and increasing tumor metastatic potential. This reciprocal regulatory mechanism establishes a dynamic equilibrium that critically governs BC invasion and metastasis. Notably, this classical miR-200/ZEB feedback loop has also been identified as a

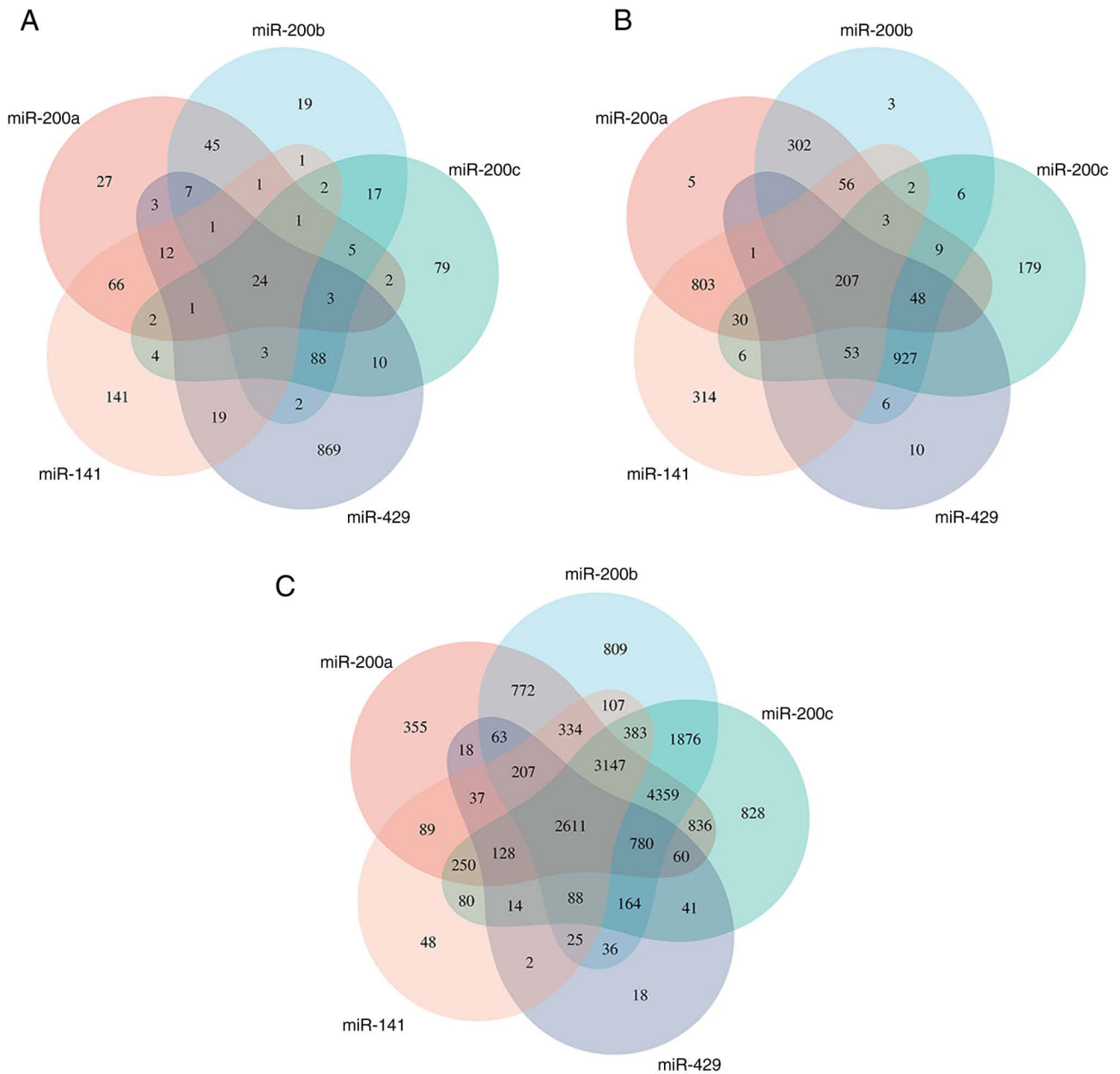


Figure 2. Target gene overlap among miR-200 family members. Common target genes for the five members of the miR-200 family were predicted using three widely used databases. (A) miRTarBase database (<https://mirtarbase.cuhk.edu.cn/>) predicted 24 common target genes. (B) miRDB database (<https://mirdb.org/>), predicted 207 common target genes. (C) miRWalk database (<http://mirwalk.umm.uni-heidelberg.de/>), predicted 2611 common target genes. miR, microRNA.

central mechanism driving invasion and metastasis in various epithelial tumors, including OC (54) and colorectal cancer (CRC) (55), highlighting its conserved role in maintaining epithelial phenotypes and suppressing malignant transformation. In addition to the ZEB family, miR-200 family members further regulate tumor metastasis by targeting other drivers of EMT. For instance, the lncRNA ATB acts as a molecular sponge to competitively bind miR-200c, thereby alleviating its inhibitory effect on Twist. This interaction promotes EMT and enhances the invasive and migratory capabilities of BC cells (25). SIRT1 induces the epigenetic silencing of E-cadherin in BC (56). Eades *et al* (20) demonstrated that miR-200a targets and suppresses SIRT1 expression, thereby inhibiting EMT and reducing tumor invasion.

In addition, the miR-200 family regulates tumor EMT through several other mechanisms, thereby influencing tumor invasion and migration. Studies indicate that ELK3 acts synergistically with ZEB1 to suppress E-cadherin expression (57). Kim *et al* (21) demonstrated that miR-200a specifically binds to the 3'UTR of ELK3 mRNA, significantly reducing ELK3 protein levels, restoring E-cadherin expression, and suppressing BC cell invasion and migration. Kim *et al* (22) further showed that miR-200a targets and downregulates IMP2 and IMP3 expression, thereby blocking EMT and inhibiting cell migration and invasion. Another study revealed that the p38 MAPK subtype p38 γ negatively regulates miR-200b expression by inhibiting its transcriptional activator GATA3. Conversely, miR-200b overexpression reduces

Table I. Role of the miR-200 family in BC and its target genes.

First author/s, year	miR-200 family members	Biological processes	Targets	Roles	(Refs.)
Ahmad <i>et al</i> , 2011; Gregory <i>et al</i> , 2008; Lorenzo-Martin <i>et al</i> , 2019; Lu <i>et al</i> , 2015; Roy <i>et al</i> , 2014; Ye <i>et al</i> , 2015; Zhang <i>et al</i> , 2019; ZOU <i>et al</i> , 2018; Choi <i>et al</i> , 2016	All members	Invasion and migration	ZEB1/2	Inhibit EMT, thereby suppressing invasion and migration	(43-50)
			-	Promotes the phosphorylation of FAK and AKT, thereby enhancing cell migration and invasion	(72)
Lim <i>et al</i> , 2013; Eades <i>et al</i> , 2011; Kim <i>et al</i> , 2020; Kim <i>et al</i> , 2018; Yu <i>et al</i> , 2013	miR-200a	Cell stemness Invasion and migration	- SIRT1, ELK3, IMP2/3	Suppressing stem cell properties Inhibit EMT, thereby suppressing invasion and migration	(14) (20-22)
			YAP1	Induce cells to resist anoikis, thereby promoting metastasis	(61)
Tsouko <i>et al</i> , 2015; Ming <i>et al</i> , 2015; Zeng <i>et al</i> , 2019; Yao <i>et al</i> , 2014; Wang <i>et al</i> , 2021			EPHA2, Cx43	Inhibit cell invasion and migration	(65,66)
		Proliferation and apoptosis	TFAM, MET, EGFR	Inhibit cell proliferation	(31,80)
			YAP1	Inhibit the cell cycle, thereby suppressing cell proliferation	(89)
Sossey <i>et al</i> , 2018; Xu <i>et al</i> , 2018; Hong <i>et al</i> , 2016; Li <i>et al</i> , 2014; Yuan <i>et al</i> , 2020; Humphries <i>et al</i> , 2014; Humphries <i>et al</i> , 2017; Zheng <i>et al</i> , 2017; Wang <i>et al</i> , 2021	miR-200b	Invasion and migration	Suz12, Kindlin-2 ERM	Inhibit EMT, thereby suppressing invasion and migration Disrupts cytoskeletal remodeling and inhibits invasion	(23,29) (68-70)
			Protein kinase C α , ARHGAP18, FUT4	Inhibit cell invasion and migration	(74,75,78)
		Proliferation and apoptosis	JAZF1	Promoting pyroptosis and apoptosis	(34)
Peng <i>et al</i> , 2023; Yao <i>et al</i> , 2015			DMD	Inhibit cell proliferation	(83)
			Sp1	Promote apoptosis and inhibit cell proliferation	(90)
Iliopoulos <i>et al</i> , 2010		Cell stemness	Suz12	Inhibit stem cell growth	(100)
Peng <i>et al</i> , 2021; Li <i>et al</i> , 2018; Howe <i>et al</i> , 2011	miR-200c	Invasion and migration	c-JUN, Twist TrkB	Inhibit EMT, thereby suppressing invasion and migration Restore anoikis, thereby inhibiting cell migration	(24,25) (62)
Sigloch <i>et al</i> , 2015; Song <i>et al</i> , 2015; Zhang <i>et al</i> , 2019; Lin <i>et al</i> , 2024		Proliferation and apoptosis TME	PAK KRAS, PDE7B -	Inhibit cell invasion and migration Inhibit cell proliferation Reprogramming CAF states to promote carcinogenesis	(76) (35,92) (95)

Table I. Continued.

First author/s, year	miR-200 family members	Biological processes	Targets	Roles	(Refs.)
Meng <i>et al.</i> , 2020			-	Upregulating PAI-2 promotes M2-type TAM polarization, thereby accelerating triple-negative BC metastasis	(96)
Raue <i>et al.</i> , 2022			-	Reduce macrophage recruitment to tumor sites	(97)
Tang <i>et al.</i> , 2019; Wu <i>et al.</i> , 2017 Zhang <i>et al.</i> , 2020	miR-429	Cell stemness Invasion and migration	Jagged1, ZEB1, Bmi1 CRKL, MMP9	Inhibit cell stemness Inhibiting bone metastasis in BC	(101,102) (71)
Zhang <i>et al.</i> , 2020; Bi <i>et al.</i> , 2021 Wang <i>et al.</i> , 2015 Li <i>et al.</i> , 2023		Proliferation and apoptosis	Fibronectin 1, SYNJ1 XIAP DLC1	Inhibit cell proliferation Promote apoptosis Promote tumor proliferation	(36,86) (85) (87)
Zhou <i>et al.</i> , 2021; Sun <i>et al.</i> , 2020; Li <i>et al.</i> , 2017 Xu <i>et al.</i> , 2023 Dong <i>et al.</i> , 2021	miR-141	Invasion and migration Proliferation and apoptosis	High-mobility group box 1, ANP32E, KLF12 Malat 1 RBMS3	Inhibit cell invasion and migration Inhibit cell proliferation Inhibit apoptosis and promote cell proliferation	(28,33,77) (37) (88)
Tang <i>et al.</i> , 2019		TME	TCF12	Inhibiting CAFs from secreting CXCL12 thereby suppresses BC progression	(32)
Zhou <i>et al.</i> , 2017	miR-200b/c	Invasion and migration	Git2	Inhibit MET to suppress the colonization of metastatic lesions	(26)
Ren <i>et al.</i> , 2019 Sun <i>et al.</i> , 2018		TME	MMP2/9 IKK β	Inhibit cell invasion Weakening the ability of CAFs to promote epithelial-mesenchymal transition and invasion in tumor cells	(27) (38)
Jin <i>et al.</i> , 2017	miR-200c/141	Invasion and Migration	-	Increased SerpinB2 promotes cell migration	(73)
Liu <i>et al.</i> , 2018		Cell stemness	HIPK1	Overexpression of miR-200c/141 promotes the formation of epithelial-like ALDH ⁺ BC stem cells, while its underexpression favors maintaining the characteristics of mesenchymal-like CD24 ⁺ CD44 ⁺ BC stem cells	(39)
Li <i>et al.</i> , 2017	miR-200b-5p/ 429-5p	Proliferation and apoptosis	LIMK1	Inhibit the cell cycle	(93)
Tang <i>et al.</i> , 2019	miR-200s	TME	DNMT3B	Inhibit CAF activation	(32)

BC, breast cancer; miR, microRNA; TME, tumor microenvironment; CAFs, cancer-associated fibroblasts.

Suz12 expression, reversing p38 γ -induced EMT process (29). Additionally, miR-200b suppresses EMT by directly inhibiting Kindlin-2 (23). Peng *et al.* (24) demonstrated that miR-200c blocks EMT and inhibits migration by directly targeting c-JUN. Tumor metastasis is a dynamic, reversible process. Tumor cells entering circulation must activate EMT

to enhance invasive capacity; however, during implantation in distant organs, they must revert to epithelial characteristics via mesenchymal-epithelial transition (MET) to establish metastatic colonies (58). Zhou *et al.* (26) found that in metastatic BC (MBC) lesions, the lncRNA H19 sequesters miR-200b/c, thereby relieving suppression of its target gene Git2. This

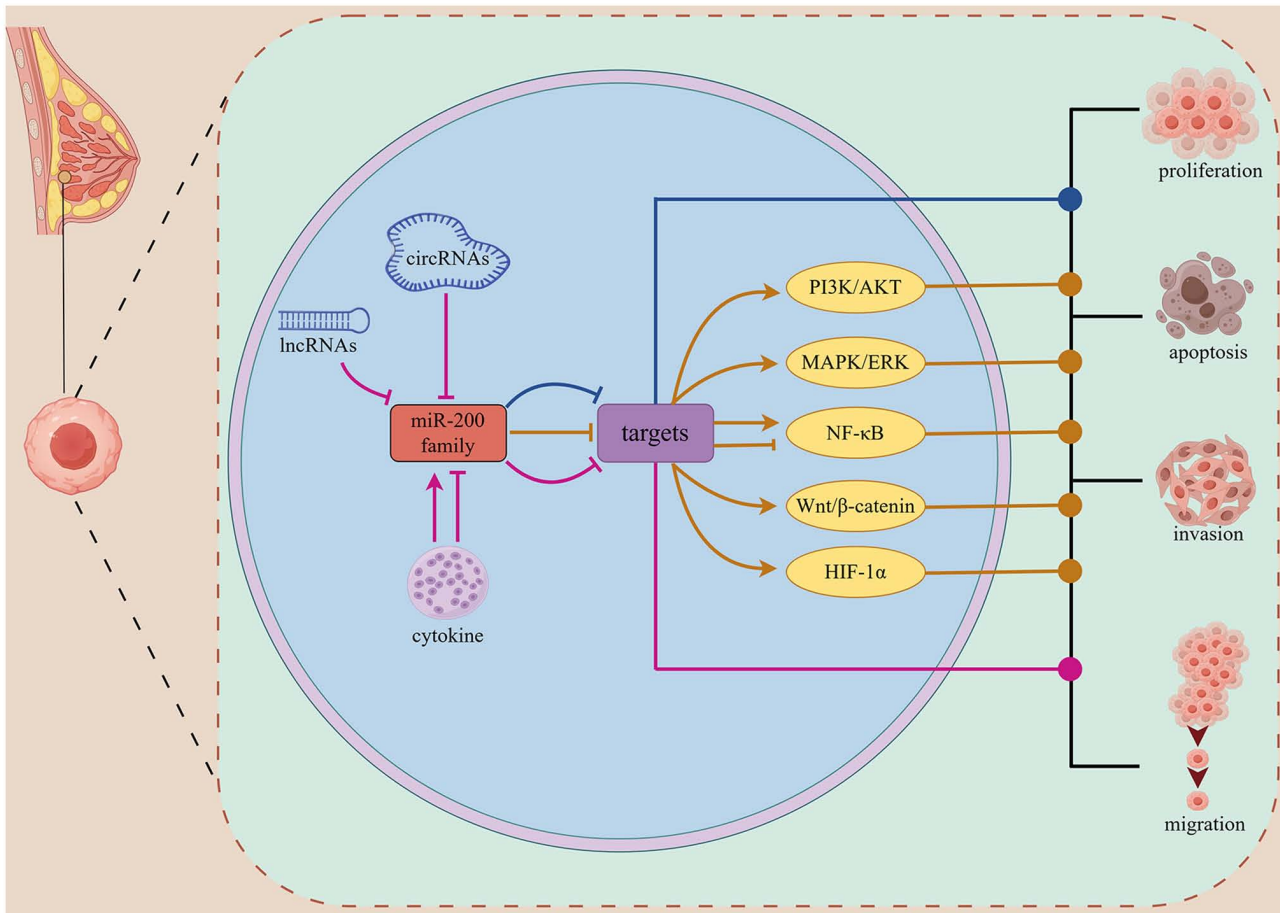


Figure 3. The molecular mechanisms by which the miR-200 family regulates malignant behavior in breast cancer cells. Blue pathway: the miR-200 family directly inhibits related target genes, regulating tumor proliferation, invasion, migration, and apoptosis. Pink pathway: lncRNAs, circRNAs, and cytokines regulate tumor progression by upregulating/downregulating miR-200 levels, thereby inhibiting/promoting target gene expression. Yellow pathway: the miR-200 family regulates tumor progression by modulating the expression of its target genes, thereby influencing the activation status of downstream signaling pathways. lncRNA, long non-coding RNA; circRNA, circular RNA; miR, microRNA; \dashv , inhibition; \rightarrow , promotion. The figure was created by www.figdraw.com.

results in Arf6 inactivation and maintains E-cadherin expression, thus inhibiting EMT and promoting MET, facilitating the colonization of metastatic sites (26). Collectively, these studies indicate that the miR-200 family influences EMT via a multi-level regulatory network, playing a pivotal role in BC metastasis.

Anoikis. Anoikis is a form of programmed cell death triggered when cells detach from the extracellular matrix or loss intercellular adhesion. It effectively limits the survival and migration of detached tumor cells. However, malignant tumor cells can acquire resistance to anoikis, promoting metastasis (59). The role of the miR-200 family in this process appears complex. It has been reported that the loss of YAP1 function can protect cells from anoikis (60). Yu *et al* (61) showed that miR-200a promotes metastasis by inhibiting YAP1, thereby inducing tumor cell resistance to anoikis. By contrast, Howe *et al* (62) reported that miR-200c restores apoptosis sensitivity by downregulating TrkB, thus suppressing cell migration. This functional discrepancy suggests that miR-200 family members may exhibit distinct roles depending on specific microenvironmental contexts. The underlying mechanisms require further exploration. Additionally, miR-200-mediated regulation of anoikis through the Orphanage pathway is not exclusive to BC. In endometrial carcinoma, miR-200 family

members (miR-141 and miR-200b/200c/429) directly suppress Sestrin proteins (SESN2 and SESN3), weakening resistance to anoikis following loss of anchorage. This observation suggests that the miR-200/Sestrin axis may also play a critical role in endometrial carcinoma metastasis (63).

Genes associated with invasion and migration. The miR-200 family also exerts its biological effects by regulating multiple genes involved in invasion and migration. Studies indicate that EPHA2 binds its ligand, Ephrin-A1, resulting in EPHA2 degradation and suppression of tumor invasion and migration. In the absence of Ephrin-A1, EPHA2 accumulates excessively, promoting invasion and migration (64). Tsouko *et al* (65) reported that Ephrin-A1 expression is nearly absent in triple-negative BC (TNBC), leading to elevated EPHA2 expression. miR-200a directly targets EPHA2, reducing its expression, thereby increasing AMPK activity and ultimately suppressing tumor cell invasion and migration (65). Additionally, miR-200a targets and downregulates connexin 43 (cx43) expression, thus inhibiting cellular metastasis (66). The ezrin-radixin-moesin (ERM) protein family is critical for maintaining cytoskeletal structure, facilitating cell movement, and contributing to BC invasion and migration (67). Studies have demonstrated that miR-200b downregulates ERM family proteins (Ezrin, Radixin and

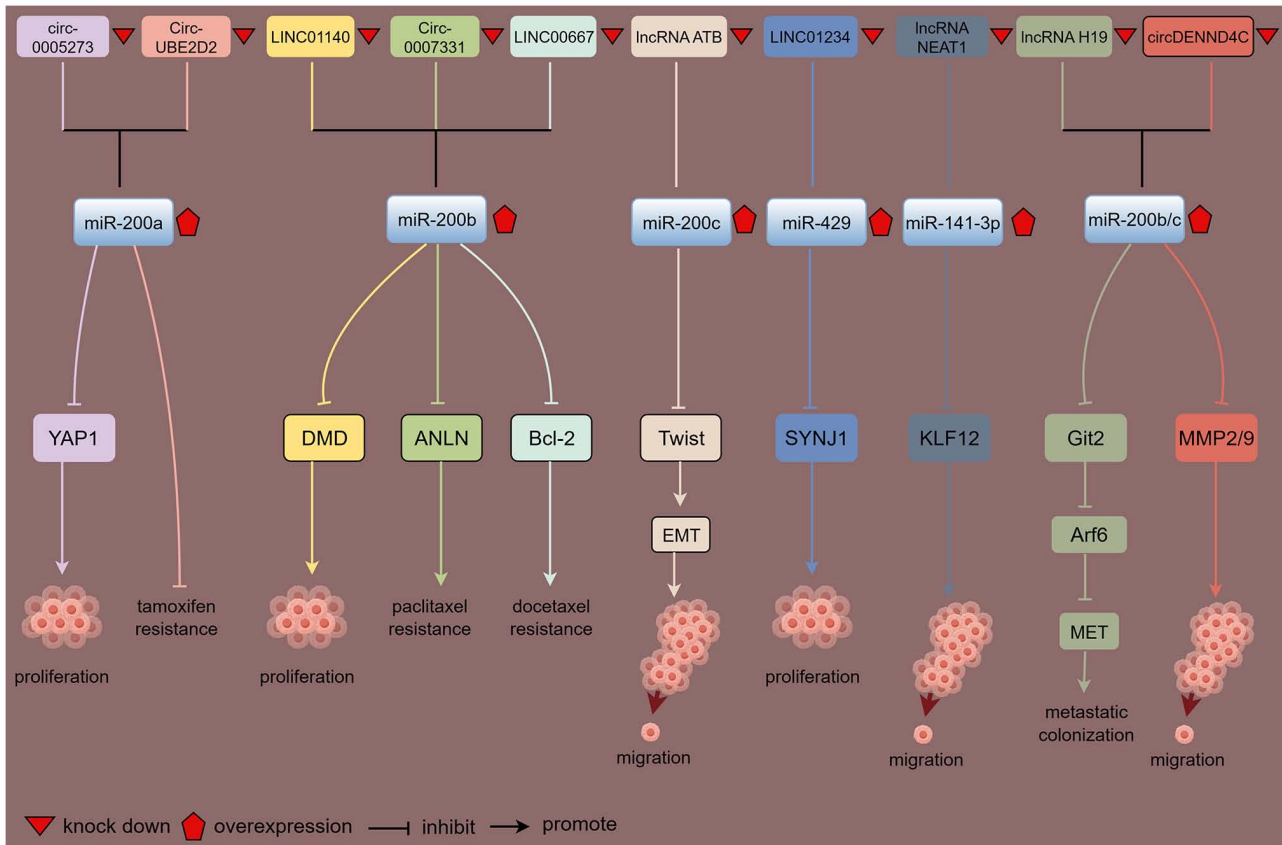


Figure 4. Network diagram of lncRNA/circRNA regulation of the miR-200 family. Downregulation of lncRNA/circRNA leads to miR-200 upregulation, which in turn targets downstream genes to regulate breast cancer progression. The figure was created by www.figdraw.com. lncRNA, long non-coding RNA; circRNA, circular RNA; miR, microRNA.

Moesin), disrupting cytoskeletal remodeling and inhibiting invasion (68-70). Additionally, Ren *et al* (27) showed that knockout of circDENND4C upregulates miR-200b/c, which suppresses glycolysis and MMP2/9 expression, consequently decreasing cell invasion. Other studies reported that miR-141-3p downregulates high-mobility group box 1 protein expression, suppressing hypoxia-induced HIF-1 α pathway activity and cell migration (33). miR-429 can reduce BC bone metastasis by targeting and downregulating CRKL and MMP9 expression (71). However, a comprehensive study on the miR-200 family reported conflicting results. Stable overexpression of the miR-200b/200a/429 or miR-141/200c clusters inhibited MDA-MB-231 cell proliferation but significantly enhanced migration and invasion. Compared with miR-200b/200a/429, the miR-141/200c cluster showed stronger suppression of cell proliferation and greater promotion of migration and invasion. Further analysis revealed that overexpressing either miR-200b/200a/429 or miR-141/200c increased phosphorylation of FAK and AKT, thus enhancing cell migration and invasion. Compared with miR-200b/200a/429-overexpressing cells, those expressing miR-141/200c secreted higher levels of vascular endothelial growth factor A and exhibited increased integrin- α V expression, further augmenting migration and invasion (72). Additionally, Jin *et al* (73) suggested that the miR-200c/141 cluster promotes BC metastasis by upregulating SerpinB2 (PAI-2); however, the precise molecular mechanisms involved require further clarification. These discrepancies highlight

the functional heterogeneity of the miR-200 family across different BC subtypes and TME.

Other mechanisms. Besides the aforementioned pathways, the miR-200 family can inhibit cell invasion and migration by targeting molecules such as protein kinase C α (74), ARHGAP18 (75), PKA subunits (PRKAR1A and PRKACB) (76), ANP32E (77) and FUT4 (78). Furthermore, lncRNA NEAT1 acts as a sponge for miR-141-3p. Upon interference with NEAT1 expression, miR-141-3p levels significantly increase, thereby reducing KLF12 expression, inhibiting cell invasion and migration, and decreasing chemotherapy resistance (28). Conversely, FOXP3, as an endogenous tumor suppressor, inhibits BC metastasis by promoting the expression of miR-200c and miR-141 (30). Liu *et al* (79) notably reported that BC cells specifically package miR-200c into exosomes through a Rab1A-mediated sorting mechanism. The cells then actively secrete these exosomes, thereby evading the tumor suppressive effects of miR-200c, promoting metastasis, and reshaping the immune microenvironment. This finding reveals a novel mechanism underlying BC metastasis and suggests new therapeutic opportunities (79).

In summary, the miR-200 family plays a complex and critical role in BC invasion and metastasis through multiple pathways, including the regulation of EMT, anoikis, and invasion- and migration-related genes. Although most studies support its tumor-suppressive role, some findings suggest pro-metastatic effects. These discrepancies indicate that future research should clarify its regulatory mechanisms across BC

subtypes and microenvironments. More broadly, pathways regulated by the miR-200 family, such as EMT and anoikis, represent core biological processes that enable cells to acquire migratory capabilities. Therefore, deepening the understanding of miR-200 family-regulated networks in cancer not only provides potential therapeutic targets for advanced metastatic disease but also suggests that monitoring these pathway activities in precancerous lesions or early-stage cancers may enable earlier intervention by predicting invasive potential.

Proliferation and apoptosis. The miR-200 family also plays an essential role in regulating BC cell proliferation and apoptosis. Its members influence tumor biological behaviors by targeting diverse signaling molecules (Table I). Current studies suggest that miR-200a, miR-200b and miR-200c predominantly function as tumor suppressors in BC by inhibiting cell proliferation and promoting apoptosis. Yao *et al* (80) demonstrated that miR-200a directly targets TFAM, inhibiting its protein expression and thereby consequently BC cell proliferation. Additionally, FEN1, a critical DNA metabolism regulator involved in DNA replication, damage repair, and telomere maintenance, is closely associated with tumor proliferation (81,82). Studies indicated that FEN1 forms a FEN1/proliferating cell nuclear antigen (PCNA)/DNA methyltransferase 3a (DNMT3a) complex with PCNA and DNMT3a, suppressing miR-200a expression via DNMT3a-mediated methylation. FEN1 knockout significantly upregulated miR-200a, which then targeted and downregulated hepatocyte growth factor (MET) and EGFR, thereby inhibiting the PI3K/AKT and MAPK/ERK signaling pathways and ultimately reducing BC cell proliferation (31). Chrysophanol activated the NF- κ B signaling pathway by upregulating miR-200b and downregulating JAZF1, inducing pyroptosis and apoptosis, thus significantly reducing BC cell viability (34). Additionally, LINC01140 promotes BC progression by competitively inhibiting miR-200b through sponge adsorption. Knockdown of LINC01140 increased miR-200b levels, reducing downstream DMD expression and suppressing cell proliferation (83). miR-200c inhibits tumor proliferation both *in vitro* and *in vivo* by directly targeting KRAS and subsequently suppressing the AKT and ERK signaling pathways (35). Notably, Jones *et al* (84) showed that miR-200c expression is downregulated in Claudin-low BC, a rare subtype of TNBC, and restoring its expression significantly inhibited tumor cell proliferation, colony formation and tumor growth *in vivo* (84).

It is noteworthy that miR-429 exhibits a dual role in BC. Zhang *et al* (36) reported that miR-429 suppresses cell proliferation by targeting fibronectin 1, thereby inhibiting the Wnt/ β -catenin signaling pathway. Other studies demonstrated that vitamin E δ -tocotrienol exerts anticancer effects both *in vitro* and *in vivo* by upregulating miR-429, suppressing its target gene XIAP, and inducing apoptosis (85). Additionally, Bi *et al* (86) showed that LINC01234 is highly expressed in TNBC, and its knockdown upregulates miR-429, decreases SYNJ1 expression, inhibits cell proliferation, and promotes apoptosis. By contrast, Li *et al* (87) found that miR-429 is overexpressed in the TNBC cell line MDA-MB-468 and promotes tumor proliferation by degrading the tumor suppressor factor DLC1. The regulatory role of miR-141 is also context dependent

in BC. Xu *et al* (37) reported that MALAT1 is overexpressed as an oncogene in TNBC and is further induced under hypoxic conditions. Overexpression of miR-141-3p suppresses the post-transcriptional MALAT1/HIF-1 α signaling pathway, thereby inhibiting autophagy initiation and cell proliferation (37). However, another study identified that miR-141-3p promotes proliferation and inhibits apoptosis by targeting and downregulating RBMS3 (88).

In addition, members of the miR-200 family influence BC cell proliferation and by regulating cell cycle progression. Dysregulation of the Hippo signaling pathway has been reported to promote proliferation and inhibit apoptosis, with YAP1 acting as a key downstream effector. Wang *et al* (89) demonstrated that miR-200a directly targets YAP1, induces G0/G1 cell cycle arrest, and reverses the pro-proliferative effects of circ-0005273. Furthermore, Yao *et al* (90) found that miR-200b targets Sp1, leading to G2/M phase arrest, a reduction in S-phase cells, inhibition of proliferation, and induction of apoptosis. Elevated intracellular cAMP levels are known to induce cell cycle arrest and apoptosis (91). Zhang *et al* (92) demonstrated that miR-200c downregulates PDE7B, increases intracellular cAMP levels, elevates the proportion of cells in the G1 phase, and suppresses cell proliferation. Moreover, Li *et al* (93) demonstrated that miR-200b-5p and miR-429-5p downregulate LIMK1 and its substrate CFL1, inhibit cyclin D1/CDK4/CDK6 and cyclin E1/CDK2, and ultimately impair cell cycle progression. Nevertheless, studies focusing on miR-200 family-mediated cell cycle regulation in BC remain limited. Whether this family regulates the cell cycle through additional molecular mechanisms to promote BC progression requires further investigation.

TME. It has been demonstrated that the TME, composed of cellular and non-cellular components, plays a pivotal regulatory role in BC progression (94). Among these components, the miR-200 family acts as an essential regulator, influencing TME remodeling through multiple targets and pathways (Table I). Sun *et al* (38) showed significantly reduced miR-200b/c expression in cancer-associated fibroblasts (CAFs), closely linked to their pro-tumorigenic properties. Restoration of miR-200b/c expression directly targets and decreases IKK β , inhibiting NF- κ B signaling. This process subsequently reduces expression and secretion of downstream effector PAI-1, diminishing the ability of CAFs to facilitate tumor cell EMT and invasion (38). Tang *et al* (32) revealed a TGF- β 1-miR-200-DNMT3B regulatory axis that promotes tumor progression: TGF- β 1 suppresses miR-200 (miR-200a/b/c and miR-141) expression in CAFs, alleviating their post-transcriptional inhibition of DNMT3B. Elevated DNMT3B promotes methylation of CpG islands in the miR-200 promoters, leading to stable epigenetic silencing. This self-sustaining positive feedback loop enables CAFs to maintain a persistently activated phenotype. Additionally, reduced miR-141 expression elevates its target gene TCF12, promoting CXCL12 secretion by CAFs. CXCL12 subsequently activates the c-Myc/Cyclin D1 pathway in tumor cells, enhancing BC progression (32). Conversely, Lin *et al* (95) reported that oxidative stress induces DNA demethylation of the miR-200c promoter in CAFs, significantly upregulating its expression. Highly expressed miR-200c reprograms CAFs toward a MET state via the miR-205-COMMD1-NF κ B-HIF

axis, inducing a senescent phenotype. These reprogrammed CAFs enhance cancer cell proliferation, apoptosis resistance and immune suppression through paracrine secretion of factors such as TGFB2, CCL5, PDGFA/B and lactate, ultimately promoting tumor progression (95).

In another crucial TME component, tumor-associated macrophages (TAMs), the miR-200 family similarly exerts significant regulatory effects. TAMs, abundant immune cells within the TME, can be classified based on activation status into antitumor M1 and pro-tumor M2 subtypes. Meng *et al* (96) demonstrated that miR-200c promotes M2-type TAM polarization by upregulating PAI-2, thereby accelerating TNBC metastasis; however, the detailed molecular mechanisms remain to be clarified. Raue *et al* (97) described another aspect of miR-200c function: Apoptotic tumor cells release miR-200c, which macrophages then internalize. Uptake of miR-200c suppresses migration-related gene expression in macrophages, reducing their recruitment to tumor sites (97). These findings illustrate the complex mechanisms by which the miR-200 family regulates BC progression by modulating various cellular components of the TME.

Cell stemness. A major cause of BC treatment failure is the persistence of cancer stem cells (CSCs). CSCs drive tumor initiation, progression and resistance to treatment. Due to their unique self-renewal capacity and multipotent differentiation potential, CSCs not only directly contribute to tumor progression and metastasis but also mediate chemotherapy resistance through various molecular mechanisms (98). Previous studies demonstrated that the miR-200 family, as key epigenetic regulators, plays a crucial role in controlling the stemness and phenotypic plasticity of BC stem cells (BCSCs) (Table I). For example, Hsu *et al* (99) found that inhibition of the miRNA processing enzyme Dicer significantly reduces miR-200b expression, whereas transfection with miR-200b mimics decreases the expression of stemness-associated transcription factors (Oct-4, Nanog, SOX-2 and KLF4), thus inhibiting CSC properties. Moreover, miR-200b suppresses mammary spheroid formation and maintenance by directly targeting Suz12, ultimately impairing CSC proliferation (100). Similarly, Tang *et al* (101) confirmed that miR-200c expression is generally reduced in BC cells and BCSCs. Overexpression of miR-200c directly targets and suppresses Jagged1, ZEB1 and Bmi1, thereby inhibiting tumor-sphere formation in HER2⁺ BC cells and decreasing the proportion of CD44⁺CD24⁻ cells. Importantly, miR-200c-mediated inhibition of stemness significantly restores sensitivity to trastuzumab, suppressing tumor growth and metastasis (101). Additional studies indicate that miR-200c inhibits BCSC proliferation and tumorigenicity by targeting BMI1 (102). Notably, BCSCs exist in two plastic states: epithelial-like (ALDH⁺) and mesenchymal-like (CD24⁻CD44⁺). These states interconvert and possess distinct biological behaviors: Epithelial-like BCSCs exhibit higher proliferation potential, whereas mesenchymal-like BCSCs show stronger migratory and invasive abilities (103). Liu *et al* (39) clarified the molecular basis of this phenomenon, demonstrating that miR-200c/141 inhibits HIPK1 expression by directly binding its 3'UTR. HIPK1 downregulation reduces phosphorylation at β -catenin Ser552, suppressing Wnt/ β -catenin signaling. This regulatory axis determines

BCSC state transitions: High miR-200c/141 expression promotes epithelial-like (ALDH⁺) BCSCs, while low expression favors mesenchymal-like (CD24⁻CD44⁺) BCSCs. These results provide a theoretical basis for novel therapeutic strategies targeting tumor growth and metastasis, suggesting the miR-200c/141-HIPK1- β -catenin axis as a potential therapeutic target (39). Additionally, Lim *et al* (14) reported that immortalized human mammary epithelial cells can spontaneously transition from a non-stem cell to a stem-like phenotype, which strongly correlates with the absence of miR-200 family expression. Restoration of miR-200 family expression reverses stem-like properties and promotes differentiation toward an epithelial phenotype, highlighting the crucial role of that the miR-200 family in stem cell and non-stem cell state transitions (14).

4. Biomarker

Currently, BC diagnosis, staging and prognosis primarily depend on tissue biopsy. However, this method is invasive, causes significant patient discomfort, and is difficult to repeat. Moreover, tissue biopsy has limited effectiveness in early diagnosis and dynamic monitoring, often delaying detection until advanced stages. Therefore, developing non-invasive, effective biomarkers is crucial for early screening and precise management of BC. Although CA125 and CA153 are widely used clinical markers for BC monitoring, they face substantial limitations, including low sensitivity, poor specificity and limited value in early diagnosis, prognosis assessment and treatment guidance (104,105). By contrast, miRNAs possess unique advantages such as high stability, ease of quantitative detection, and abundant presence in bodily fluids, enabling non-invasive and dynamic monitoring (106). Previous studies (107,108) demonstrate that specific miRNAs, particularly members of the miR-200 family, show promise as novel biomarkers for early BC detection, offering opportunities to overcome existing diagnostic limitations.

Diagnostic value. Numerous studies highlight the significant diagnostic and classification roles of the miR-200 family in BC (Table II). However, expression patterns vary across research contexts. Xu *et al* (107) quantified expression levels of all the miR-200 family members in 99 pairs of BC tissues and adjacent normal tissues using quantitative PCR (qPCR). They observed significant downregulation of all miR-200 members in cancer tissues and found that miR-200 could effectively distinguish patients with and without lymph node metastasis (107). These findings support the miR-200 family as potential diagnostic biomarkers for BC. Inflammatory BC (IBC) is a rare yet highly aggressive subtype often misdiagnosed due to the lack of reliable molecular biomarkers. Fahim *et al* (108) analyzed miRNA expression in primary tumors of patients with IBC and non-IBC using miRNA PCR arrays. They found significant downregulation of miR-200b-3p, miR-200c-3p and miR-203a-3p, with significant upregulation of miR-181b-5p in IBC. Receiver Operating Characteristic (ROC) curves demonstrated that each miRNA individually distinguished patients with IBC from patients with non-IBC. Notably, combining miR-181b-5p, miR-200b-3p and miR-200c-3p significantly improved diagnostic accuracy [area under the curve (AUC)=0.897],

Table II. Potential utility of miR-200 family in cancer diagnosis.

First author/s, year	miR-200 family members	Cases	Sample type	Testing technology	Expression	AUC	(Refs.)
Xu <i>et al</i> , 2016	All members	99 BC vs. 99 NC	Tissue	qPCR	Downward	-	(107)
Fahim <i>et al</i> , 2020	miR-200b-3p/200c-3p	17 IBC vs.18 non-IBC	Tissue	qPCR	Downward	0.713/0.743	(108)
Qiao <i>et al</i> , 2024	miR-200c	51 BC vs. 47 NC	Serum exosomal	qPCR	Downward	0.854	(109)
Khalil <i>et al</i> , 2024	miR-200a	46 MBC vs. 54 NMBC vs. 50 NC	Serum	qPCR	Highly expressed in BC, and MBC is higher than NMBC	Distinguishing between MBC and NMBC: 0.708	(110)
Papadaki <i>et al</i> , 2019	miR-200b	110 MBC vs. 133 Early BC	Plasma	qPCR	Upward	0.72	(111)
Braicu <i>et al</i> , 2018		48 BC vs. 28 NC	Plasma	qPCR	Upward	0.8772	(112)

miR, microRNA; BC, breast cancer; NC, normal control; IBC, inflammatory BC; MBC, metastatic BC; NMBC, non-metastatic BC; AUC, area under the curve; ROC, receiver operating characteristic; qPCR, quantitative PCR.

indicating potential molecular diagnostic markers for this challenging subtype (108). Qiao *et al* (109) reported significantly decreased expression of miR-200c in serum exosomes from patients with BC. ROC analysis indicated that miR-200c effectively discriminated patients with BC from healthy controls (AUC=0.854). Combining miR-200c with CEA, CA125 and CA153 increased diagnostic accuracy to an AUC of 0.914 (109). However, discrepancies exist regarding miR-200 expression patterns in circulation. Khalil *et al* (110) used qPCR to analyze blood samples from 54 patients with non-metastatic BC (NMBC), 46 patients with MBC and 50 healthy controls. They observed significant overexpression of miR-200a in the serum of patients with BC, with higher levels in MBC compared with patients with NMBC. Further analysis showed that miR-200a distinguished between MBC and NMBC, achieving an AUC of 0.708 (110). Similarly, Papadaki *et al* (111) found significantly higher plasma expression of miR-200b and miR-200c in patients with MBC compared with early-stage patients. The diagnostic AUC for miR-200b alone was 0.720, improving to 0.797 when combined with miR-21, miR-190 and miR-200c, suggesting that circulating miRNAs reflect distinct tumor biological characteristics (111). Additionally, Braicu *et al* (112) analyzed The Cancer Genome Atlas data and found significant overexpression of miR-200b was in TNBC and DPBC (ER⁺, PR⁺ and HER2⁻) compared with normal breast tissue, consistent with clinical plasma measurements. miR-200b effectively discriminated patients with BC from healthy controls, achieving an AUC of 0.8772. Notably, the present study independently validated miR-200b expression consistency between tumor tissues and plasma samples (21 TNBC, 47 DPBC and 19 normal samples), providing robust evidence supporting miR-200b as a reliable liquid biopsy biomarker (112).

Prognosis assessment value. The miR-200 family also exhibits significant prognostic value in BC (Table III). Yao *et al* (90) analyzed miR-200b expression levels in 278 paired BC and adjacent normal tissues by qPCR, showing significant downregulation in BC tissues. Further analysis indicated that low miR-200b expression was closely associated with aggressive clinicopathological features (advanced TNM stage, ER-negative status and HER-2-positive status) and predicted poorer clinical outcomes (90). Similarly, Ye *et al* (113) found reduced miR-200b expression in BC tissues. Patients with lower miR-200b levels exhibited significantly decreased overall survival (OS) and disease-free survival (DFS) compared with those with higher expression (113). A total of ~70% of BCs are estrogen receptor-positive (luminal subtype), and endocrine therapy remains one of the most effective adjuvant treatments. However, recurrence occurs in up to 40% of patients. Amorim *et al* (114) demonstrated that low expression of miR-200b-3p correlated with shorter endocrine resistance-free survival and DFS. Combining miR-200b-3p with miR-182-5p further improved prognostic accuracy (114). However, when examining circulating miRNAs, the clinical significance of miR-200 family expression patterns differs. Two studies by Fischer *et al* (115,116) revealed that high baseline plasma miR-200 expression in MBC correlated positively with circulating tumor cell (CTC) positivity and predicted shorter OS and progression-free survival (PFS). Moreover, high baseline miR-429 levels specifically indicated an increased risk of early recurrence. Notably, dynamic miR-200 expression changes during treatment also held prognostic importance: Effective therapy significantly reduced miR-200a/b/141 levels, which rebounded upon disease progression. Patients maintaining high miR-200

Table III. Potential utility of miR-200 family in cancer prognostic assessment.

First author/s, year	miR-200 family members	Sample type	Expression	Characteristics	(Refs.)
Yao <i>et al.</i> , 2015	miR-200b	Tissue	Downward	Low expression indicates greater invasiveness	(90)
Ye <i>et al.</i> , 2014		Tissue	Downward	Low expression is associated with shorter OS and DFS	(113)
Amorim <i>et al.</i> , 2019		Tissue	Downward	Low expression is associated with shorter ERFs and DFS	(114)
Fischer <i>et al.</i> , 2022; Fischer <i>et al.</i> , 2022	All members	Plasma	Upward	High expression is associated with shorter OS and PFS; the risk of recurrence is significantly increased by 3-5 times if miR-200a/b/141 remains highly expressed after treatment	(115,116)
Madhavan <i>et al.</i> , 2016		Plasma	Upward	High expression is associated with shorter OS and PFS	(117)
Shao <i>et al.</i> , 2019	miR-200a	Plasma	Upward	High expression is associated with chemotherapy resistance	(118)
Navarro-Manzano <i>et al.</i> , 2022	miR-200c-3p	Plasma	Upward	High expression is associated with shorter OS	(119)

miR, microRNA; OS, overall survival; DFS, disease-free survival; ERFs, endocrine resistance-free survival.

expression after treatment experienced a 3-5-fold increase in early recurrence risk. These findings suggest that miR-200 family members could serve as liquid biopsy biomarkers for clinical prognosis and treatment monitoring, particularly when combined with CTC detection for identifying high-risk patients (115,116). Similarly, Madhavan *et al.* (117) performed a multicohort study demonstrating that elevated plasma miR-200 levels correlated with poorer OS and PFS, surpassing the predictive power of CTC detection alone. Notably, high miR-200a/b/c expression predicted metastasis risk up to two years before clinical diagnosis (AUC=0.82), highlighting its potential as an early surveillance biomarker (117). MBC typically carries a poor prognosis and primarily relies on chemotherapy; however, drug resistance frequently leads to treatment failure and disease progression. Shao *et al.* (118) observed significantly higher plasma miR-200a levels were in patients with chemotherapy-resistant MBC compared with sensitive patients, with high expression correlating with advanced disease stage. ROC analysis confirmed the high accuracy (AUC=0.881) of plasma miR-200a in differentiating chemotherapy-resistant from sensitive cases, indicating its potential as a predictive biomarker for chemotherapy resistance in MBC (118). Navarro-Manzano *et al.* (119) measured plasma miR-200c-3p levels in 28 healthy women, 42 patients with MBC and 171 patients with locally advanced BC (LABC) using qPCR. They found significantly elevated miR-200c-3p levels in LABC and MBC groups compared with healthy controls, with high expression associated with reduced OS (119).

Discussion on miR-200 expression differences between tissues and circulation. Although the miR-200 family shows significant diagnostic and prognostic value in BC

tissues and circulating samples, noteworthy differences in expression patterns exist between these two contexts. Most tissue-based studies indicate that miR-200 members are downregulated in BC tissues, exerting tumor-suppressive effects (90,107,108,113). Conversely, circulating miR-200 levels, particularly in plasma or serum from patients with MBC, are frequently upregulated, and high levels correlate with poorer prognosis (110,111,115-117,119). Several mechanisms may explain this discrepancy: (i) Active secretion and selective miRNA packaging: Tumor cells actively release miRNAs into extracellular vesicles, such as exosomes, influencing the TME or evading intracellular tumor-suppressive roles. For example, Liu *et al.* (79) demonstrated that BC cells selectively load miR-200c into exosomes through a Rab1A-mediated mechanism, thus reducing intracellular miR-200c levels while increasing circulating miR-200c. This 'secretory escape' could explain elevated circulating miR-200 despite suppressed tissue expression (79). (ii) Tumor heterogeneity and molecular subtype variability: BC is highly heterogeneous, and miRNA expression and functions differ across molecular subtypes (for example, luminal, HER2-positive, TNBC) (120). (iii) Sample type and detection methodology differences: Tissue samples reflect localized miRNA expression, while circulating samples represent systemic average levels. Additionally, differences in detection platforms, RNA extraction methods and normalization strategies may contribute to observed discrepancies (121).

Despite expression inconsistencies, these differences carry valuable biological and clinical insights. Elevated circulating miR-200 may indicate active secretion by tumor cells, closely linked to metastatic behavior. Therefore, clinical applications should clearly differentiate between tissue-derived and circulating miRNAs. Tissue miR-200 may be more appropriate for assessing local tumor characteristics and identifying

Table IV. Regulation of drug resistance by members of the miR-200 family.

First author/s, year	miR-200 family members	Chemotherapy drugs	Targets	Drug resistance	(Refs.)
Yu <i>et al</i> , 2018	miR-200a	PTX	TP53INP1, YAP1	↑	(123)
Hu <i>et al</i> , 2020		TAM	-	↓	(129)
Yang <i>et al</i> , 2022	miR-200b	PTX	ANLN	↓	(124)
Li <i>et al</i> , 2022		TXT	Bcl-2	↓	(125)
Chen <i>et al</i> , 2018	miR-200c	PTX	SOX2	↓	(126)
Safaei <i>et al</i> , 2022		DOX	MDR1	↓	(131)
Zhang <i>et al</i> , 2020		DOX	ANLN	↓	(132)
Alam <i>et al</i> , 2017		DOX	Moesin	↓	(133)
Duan <i>et al</i> , 2024	miR-141-3p	PTX	Keap1	↑	(127)
Tao <i>et al</i> , 2025		PTX	RAB10	↓	(128)
Song <i>et al</i> , 2019		Trastuzumab	CDK8	↓	(134)
Gao <i>et al</i> , 2019	miR-200b/c	TAM	c-MYB	↓	(130)

miR, microRNA; PTX, Paclitaxel; TXT, Docetaxel; TAM, Tamoxifen; DOX, Doxorubicin.

therapeutic targets. By contrast, circulating miR-200 serves as a non-invasive biomarker for dynamic monitoring, metastasis prediction and treatment efficacy evaluation. Future studies should further explore miR-200 expression dynamics across sample types and its specific relationships with tumor biology to advance precision clinical applications.

5. Drug resistance

Paclitaxel (PTX) is a first-line chemotherapy agent for BC treatment; however, tumor cell resistance significantly limits its clinical efficacy (122). It has been revealed that miR-200 family members play key roles in PTX resistance through multiple molecular mechanisms. Yu *et al* (123) reported that miR-200a promotes resistance of BC cells to paclitaxel, cisplatin and gemcitabine by targeting TP53INP1 and YAP1. Mechanistically, miR-200a directly inhibits TP53INP1, weakening the pro-apoptotic p73/p53 pathway, and simultaneously downregulates YAP1, reducing p73 protein stability. These coordinated effects suppress transcription of pro-apoptotic genes (for example, PUMA, Bax, Bim and Noxa), ultimately reducing chemotherapy-induced apoptosis sensitivity (123). Additionally, Yang *et al* (124) demonstrated that circ-0007331 promotes PTX resistance. Knockdown of circ-0007331 upregulates miR-200b-3p, targeting and reducing ANLN expression, thus restoring PTX sensitivity (124). Similarly, Li *et al* (125) observed significantly increased LINC00667 expression in exosomes derived from docetaxel (TXT)-resistant TNBC cells. These exosomes transfer LINC00667 to recipient TNBC cells, downregulating miR-200b-3p, elevating Bcl-2 expression, and promoting TXT resistance (125). Chen *et al* (126) demonstrated that miR-200c-3p restores PTX sensitivity by directly targeting and reducing SOX2 expression. Notably, miR-200 family members may exhibit opposing regulatory effects under specific conditions. Duan *et al* (127) reported that miR-141-3p inhibits Keap1 expression, activates the Nrf2/SLC7A11-GSH-GPX4 signaling pathway, suppresses

ferroptosis, and thus promotes paclitaxel resistance. Conversely, Tao *et al* (128) found that miR-141-3p enhances tumor cell sensitivity to PTX by suppressing autophagy through downregulation of RAB10.

The miR-200 family also plays a critical role in regulating resistance to endocrine therapies. Regarding tamoxifen (TAM) resistance, Hu *et al* (129) reported that the circ-UBE2D2/miR-200a-3p axis significantly reduces sensitivity of ER-positive BC cells to TAM (129). Gao *et al* (130) revealed that miR-200b/c targets and suppresses c-MYB, inhibiting EMT and restoring TAM sensitivity. In relation to other chemotherapies, several studies indicated that miR-200c restores sensitivity to doxorubicin by inhibiting molecules such as MDR1 (131), ANLN (132) and Moesin (133). Moreover, miR-141-3p enhances trastuzumab sensitivity by targeting and reducing CDK8 expression (134). In summary, miR-200 family members mediate BC chemotherapy resistance via multiple target genes and signaling pathways (Table IV), providing potential intervention targets to reverse resistance.

6. Conclusion

In summary, the miR-200 family acts as a critical regulator in BC initiation and progression. Through diverse molecular mechanisms, this family controls key biological processes, including cell proliferation, apoptosis, cell cycle regulation, invasion, migration and maintenance of stemness. These findings highlight the significant therapeutic potential of miR-200 and provide novel insights for molecularly targeted BC treatments. Importantly, the functional impact of the miR-200 family extends beyond BC. Extensive research demonstrates its conserved role in regulating EMT and metastasis across multiple cancer types. Such pan-cancer functional conservation suggests that research on the miR-200 family may uncover shared tumor metastasis mechanisms, offering biological insights for early prevention of cancer spread. From

a clinical translation perspective, miR-200 family members show potential as stable biomarkers for early diagnosis, dynamic monitoring, and prognosis assessment in BC, allowing integration into comprehensive screening-diagnosis-monitoring frameworks. Critically, aberrant miR-200 expression in other cancers, such as CRC (135) and cholangiocarcinoma (136), mirrors its diagnostic and prognostic significance in BC, positioning miR-200 as a potential pan-cancer early-risk marker. Notably, differential miR-200 expression between drug-sensitive and resistant cells underscores its central role in chemotherapy resistance mechanisms, providing a therapeutic target for overcoming clinical resistance. However, current research on the miR-200 family in BC faces limitations: (i) Studies primarily focus on individual miRNA functions, with insufficient exploration of synergistic or antagonistic interactions among family members. (ii) Controversy persists regarding miR-200 expression patterns and functions across BC subtypes and bodily fluids. Additionally, efficient utilization of miR-200 for early BC diagnosis and accurate prognostic assessment remain challenging. Critically, circulating miR-200 expression used for dynamic monitoring may be influenced by non-tumor factors, including treatment-related stress, inflammation, or comorbidities, impeding its specificity and reliability as a clinical biomarker. (iii) Current research remains predominantly experimental, lacking substantial integration into clinical practice. Therefore, future research should emphasize: First, mechanistically, emerging technologies such as single-cell and spatial transcriptomics should be leveraged to elucidate miR-200 expression heterogeneity among different cell types (for example, cancer cells, CAFs and TAMs) within the BC microenvironment and to clarify their intercellular communication roles, enabling a comprehensive understanding of functional complexity. Second, translational research should urgently advance three areas: (i) Developing miR-200-based interventions, such as targeted delivery systems using exosomes or lipid nanoparticles for miR-200 mimics or inhibitors; (ii) establishing standardized detection and validation systems through multicenter, multicohort studies to define absolute quantification standards and dynamic thresholds for circulating miR-200 across different BC subtypes and treatment stages; (iii) advancing precision detection technologies and constructing multifactorial dynamic monitoring models to fully harness clinical application potential. Finally, prospective clinical studies should systematically evaluate miR-200 biomarker utility throughout BC management, from prevention to diagnosis, treatment and monitoring, while exploring combined application with imaging, pathology and existing serum markers. Comprehensive and systematic investigation promises to establish novel theoretical foundations and therapeutic targets for precision BC management, ultimately improving patient outcomes.

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Authors' contributions

JL and HD were responsible for manuscript writing, conceived and designed the study. YS and JL were responsible for the collection and assembly of data. YS and HD were responsible for data analysis and interpretation. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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