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REVIEW ARTICLE

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MicroRNAs in breast cancer: Roles, functions, and mechanism of actions

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Abstract

Breast cancer is one of the most lethal malignancies in women in the world. Various factors are involved in the development and promotion of the malignancy; most of them involve changes in the expression of certain genes, such as microRNAs (miRNAs). MiRNAs can regulate signaling pathways negatively or positively, thereby affecting tumorigenesis and various aspects of cancer progression, particularly breast cancer. Besides, accumulating data demonstrated that miRNAs are a novel tool for prognosis and diagnosis of breast cancer patients. Herein, we will review the roles of these RNA molecules in several important signaling pathways, such as transforming growth factor, Wnt, Notch, nuclear factor-κ B, phosphoinositide-3-kinase/Akt, and extracellular-signal-regulated kinase/mitogen activated protein kinase signaling pathways in breast cancer.

KEYWORDS

biomarker, cancer, diagnosis, microRNAs, prognosis, signal pathway

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1 | INTRODUCTION

Breast cancer is commonly invasive neoplasms in women (Yahya & Elsayed, 2015). Various factors play a role in the development and promotion of breast cancer; most of them involve changes in the expression of certain genes, including those encoding noncoding RNAs (ncRNAs; Wang et al., 2017). Recently, many studies have elucidated the key roles of microRNAs (miRNAs) in controlling gene expression during cancer development. MiRNAs are small subclass of ncRNAs with almost 19–24 nucleotides (Chen, Fan, & Song, 2016). Multigene regulatory features of these small RNA molecules allow them to change signaling pathways, facilitate or block signal transmission to downstream effectors in various ways. MiRNAs can regulate key signaling pathways positively or negatively, therefore they can affect tumorigenesis (Hu, Markowitz, & Wang, 2016; Zarredar et al., 2018). Various signaling pathways have been elucidated in the cell, most of them are important to a cascade of biological events and gene expression. These signaling pathways often consist of a number of signaling molecules which are not involved in transcription, directly; they can eventually change gene expression because these signaling molecules are capable to regulate transcription factors directly or indirectly (Eyvazi, Kazemi, Dastmalchi, & Bandehpour, 2018; Peng, Koirala, & Mo, 2017). Arising evidence suggests that miRNAs are involved in various pathways. Studies exhibited various functions of specific miRNAs in different cancers as well as breast cancer (Hrdlickova, de Almeida, Borek, & Withoff, 2014; Mulrane, Klinger, McGee, Gallagher, & O'Connor, 2014; Payandeh et al., 2019). MiRNAs play different roles in diverse mechanisms and signaling pathways in breast cancer and repress protein (Tarhriz et al., 2019). Herein, we will review the roles of the involvement of miRNAs in the regulation of several key signaling pathways in breast cancer.

2 | MiRNA: A BRIEF OVERVIEW

MiRNAs, as one of the most important groups of ncRNAs are involved in different biological activities and target a broad range of genes, with main contributions in these processes, particularly carcinogenesis (Yahya & Elsayed, 2015). Like other RNA molecules, the transcription of these molecules is mediated by RNA polymerases such as II and III (Eyvazi et al., 2019). The product of this enzyme is a large primary transcript (pri-miRNA), with a cap on its 5′ end and a poly A tail on 3′ end. A microprocessor complex containing two main components including protein DGCR8 and RNase Drosha cleaves the pri-miRNAs into precursor miRNA (pre-miRNA), which have a stem-loop structure. Then, after pri-miRNA is transported to the cytoplasm through the function of Ran/GTP/exportin 5 complex, it is subjected to the enzymatic reaction catalyzed by a RNase III enzyme (Dicer) and produces an unstable miRNA/miRNA* duplex. One substrate of this duplex is selected as mature miRNA molecule and is guided to the target messenger RNA (mRNA) by a protein complex called RISC. MiRNAs interact with the 3′-untranslated region (3′-UTR) of target mRNA and cause translational suppression or mRNA decomposition with regard to the grade of miRNA-mRNA complementarity (Figure 1; Mulrane et al., 2014). Dysregulation in miRNAs expression pattern has been reported to exert considerable impact on hallmarks of cancer, such as inducing invasion and metastasis. The underlying mechanisms for this dysregulation include amplification or deletion of miRNA genes, deregulation of several important transcription factors, including p53 and c-Myc, dysregulated epigenetics changes, such as global genomic DNA hypomethylation, tumor suppressor genes hypermethylation and impairing the patterns of histone modification, and defects in miRNA biogenesis machinery (Majidinia & Yousefi, 2016).

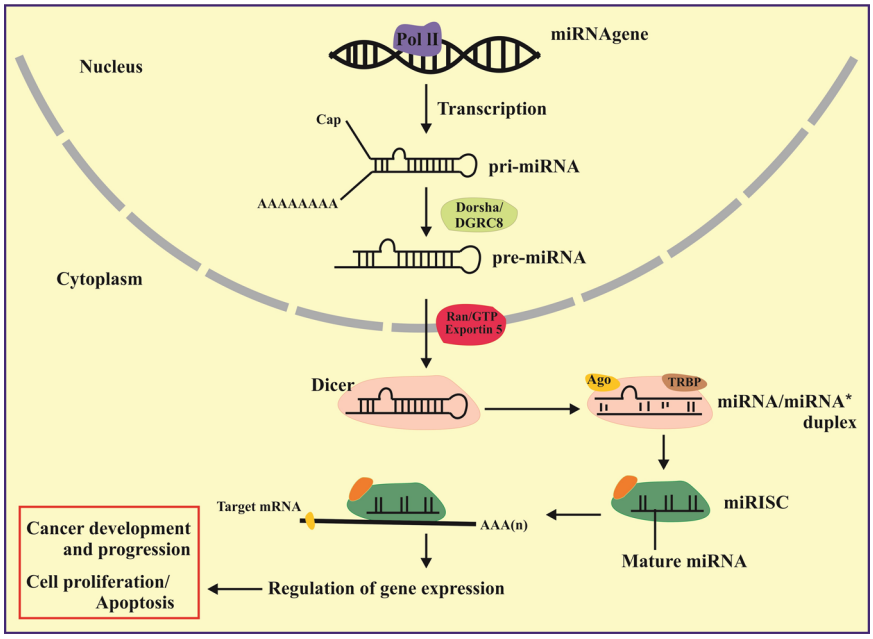

FIGURE 1 Biogenesis of miRNAs. miRNA, microRNA

3 | CROSSTALK BETWEEN VARIOUS SIGNALING PATHWAYS AND miRNAs IN BREAST TUMOR

Table 1 summarized the interplay between various signaling pathways with different miRNAs, which implicated in breast cancer initiation and progression.

3.1 | Interaction among miRNAs and transforming growth factor in breast tumor

Transforming growth factor β (TGF-β) is a component of the great group of polypeptide growth factors. TGF-β signaling pathway performs a dual function in early and advanced stages of cancer: it hinders growth and proliferation in early-stage cancer cells, and increases metastasis and invasion in late-stage tumor cells (Chen, Zhou et al., 2016). TGF-β is also contributes to epithelial–mesenchymal transition (EMT) in breast cancer (Yahya & Elsayed, 2015). TGF-β signaling pathway is capable to control and reciprocally can be controlled by multiple molecules that miRNAs seem to be one of the most noticeable of them (Smith, Agarwal, & Bhowmick, 2017). The miR-200 family frustrates the EMT process by the prevention of TGF-β signaling (Chen, Zhou et al., 2016; Pecot et al., 2013). Zinc-finger e-box binding homeobox 1 (ZEB1) is a central activator of EMT that stimulates migration of breast tumor by the direct blocking of the expressions of miR-141 and miR-200c. Reciprocally, the miRs can also hamper ZEB and TGF-β expressions (Burk et al., 2008; Chen, Zhou et al., 2016). Furthermore, it is necessary to mention that the elevated phosphorylation of SMAD5 by the heterotetrameric complex of bone morphogenetic proteins (BMPs) stimulates cancer progression (Peng et al., 2016). Interestingly, the miR-200 family supports mesenchymal to epithelial transition through the decline of the inhibitory effect of BMP-2 signaling on epithelial genes expression (Perdigao-Henriques et al., 2016). As an oncogenic miRNA, miR-106b-25 can down-regulate SMAD7 protein, which is well recognized that mediates destruction of the TGF-β receptor 1(TGF-βR1), resulting in elevated levels of the TGF-βR1 and triggers TGF-β pathway in breast tumor cells (Gong et al., 2015; Smith et al., 2012). Y. Li et al. (2014) reported the expression of miR-424/503 cluster is elevated in metastatic breast tumor. Both miR-424 and miR-503 restrain SMAD7 and Smad ubiquitination regulatory factors (Smurf—two negative regulators of TGF-β signaling—then resulted in the hyperactivation of this signaling pathway and enhance breast tumor metastasis (Y. Li et al., 2014). MiR-21 boosts migration and invasion of breast tumor cell induced by TGF-β and epidermal growth factor (EGF). These events can be mediated by the downregulation of SMAD7 that is the straight downstream target of miR-21 (Han et al., 2016; Qian et al., 2009). Evidence illustrated that miR-206 is the main estrogen receptor (ER)-related miRNA and its expression is diminished in ERα-positive breast tumor (Adams, Furneaux, & White, 2007; Kondo, Toyama, Sugiura, Fujii, & Yamashita, 2008). The miRNA inhibits TGF-β activity and also the expression of SMAD2, SMAD4, and neuropilin-1, and causes the blocking of migration, and invasion. Furthermore, the overexpression of miR-206 lessens N-cadherin and vimentin, however it amplifies E-cadherin in ER-positive breast cancer cells (Yin et al., 2016). According to Ying, Sun, and He (2017), miR-137 arrests protein translation of BMP-7, as an antagonist of the effects of TGF-β1 in breast cancer, via direct interplaying to 3′-UTR of BMP-7 mRNA and resulted in the augmentation of invasiveness and EMT in breast tumor cells (Ying et al., 2017). MiR-520/373 family exerts a metastasis-suppressive impact in ER-negative breast tumor cells. These miRNAs abrogate metastasis and invasion of breast tumor thorough the negative control of TGF-βR2 (Keklikoglou et al., 2012). SMAD3-dependent migration is elevated by miR-191 in breast cancer through the stimulation of TGF-β2 expression under hypoxia. This miRNA also targets and negatively controls human antigen R (HuR). In fact, HuR as a breast cancer-related RNA binding protein can abate TGF-β2 in hypoxia conditions. Therefore, miR-191 regulates TGF-β signaling through two direct and indirect mechanisms (Nagpal et al., 2015). Recently, studies found that TGF-β pathway can also modulate miRNAs in breast tumor (Chen, Zhou et al., 2016; Smith et al., 2017). The TGF-β/SMAD4 pathway provokes promoter activity of miR-155, which in turn prompts EMT, invasion, and metastasis through the downregulation of RhoA (Kong et al., 2008). Importantly, TGF-β has a positive effect on miR-181a expression in triple-negative breast cancers (TNBCs). Mutually, high expression of miR-181a intensified the TGF-β function to stimulate breast cancer metastasis by the enhancement of EMT process and the decrease of the proapoptotic molecule Bim expression, which brought metastatic cells resistance to anoikis (Neel & Lebrun, 2013; Taylor, Sossey-Alaoui, Thompson, Danielpour, & Schiemann, 2013). MiR-10b is one of the target genes of TGF-β1 that its expression is higher in breast tumor tissues and cells. This miRNA is correlated with EMT and the promotion of breast tumor. Suppression of can miR-10b expression enhances E-cadherin expression (Han et al., 2014). Ma et al. (2016) supported that miR-487a is an oncomiR that can induce the TGF-β1-mediated EMT, invasion and migration by reducing a tumor suppressor MAGI-2 expression level. Furthermore, they showed that TGF-β1 compels the promoter activity of miR-487a through transcription factor (Juric et al., 2016). PHACTR-1 as a novel pathway performs a fundamental function in arrangement of cell migration in invasive breast tumors. TGF-β negatively controls miR-584 expression and upregulates PHACTR1 expression. The protein is a direct downstream target of miR-584. These events lead to the promotion of cell migration in breast tumors (Fils-Aime et al., 2013).

3.2 | The interaction between Wnt/β-catenin signaling pathway and miRNAs in breast tumor

The Wnt/β-catenin signaling pathway is a crucial pathway in cells. Evidence from multiple studies show that miRNAs can control Wnt/β-catenin cascade during cancer progression (Ye et al., 2014). MiR-23a promotes the TGF-β1-induced breast tumorogenesis via the straight repression of the cytoplasmic domain of E-cadherin (CDH)-1 which is a key protein in EMT process. Interestingly, the suppression of CDH1 leads to the activation of the signaling (Ma et al., 2017). Cao et al. (2017) illustrated that miR-4469 negatively regulates the expression of cyclin-dependent kinase (CDK)-3 in breast cancer metastasis. Besides, higher expression levels of CDK3

TABLE 1 A list of miRNAs which interact with various signaling pathways in breast cancer

Type of signaling Pathway	miRNAs	Alteration of expression	Potential Targets	Functions of miRNAs in breast cancer	References
TGF-β	miR-200 family	Downregulated	ZEB1, TGF-β2, BMP2	miR-200 ⟞ TGF-β2/BMP2/ZEB1 → EMT	(Chen et al., 2016), (Burk et al., 2008)
	miR-21	Upregulated	SMAD7	miR-21 ⟞ SMAD7 ⟞ TGFβ/EGF-dependent invasion/migration	(Han et al., 2016)
	miR-137	Upregulated	BMP7	miR-137 ⟞ BMP7 ⟞ Invasion/EMT	(Ying et al., 2017)
	miR-520/373 family	Downregulated	TGF-βR2	miR-520/373 ⟞ TGFBR2 → Metastasis/invasion	(Keklikoglou et al., 2012)
	miR-191	Upregulated	TGF-β2, HuR	miR-191 → TGF-β2 → Migration	(Nagpal et al., 2015)
	miR-155	Upregulated	C/EBPβ, RhoA	TGF-β → miR-155 ⟞ C/EBPβ ⟞ EMT/invasion/metastasis	(Johansson et al., 2013)
	miR-181a	Upregulated	Bim	TGF-β ↔ miR-181a ⟞ Bim → Reduced the metastatic potential/sensitized metastatic cells to anoikis	(Taylor et al., 2013)
	miR-487a	Upregulated	MAGI2	miR-487a ⟞ MAGI2 ⟞ TGF-β1-induced EMT/migration/invasion	(Ma et al., 2016)
	miR-584	Downregulated	PHACTR1	TGF-β ⟞ miR-584 ⟞ PHACTR1 → Migration	(Fils-Aimé et al., 2013)
	miR-106b-25 cluster	Upregulated	SMAD7	miR-106b-25 ⟞ SMAD7 ⟞ TGF-β pathway → EMT	(Gong et al., 2015), (Smith et al., 2012)
	miR-206	Downregulated	NRP1, SMAD2	miR-206 ⟞ NRP1/SMAD2 → TGF-β pathway → Migration/invasion/EMT	(Yin et al., 2016), (Kondo et al., 2008)
	miR424–503 cluster	Upregulated	SMAD7, Smurf 2	miR424–503 ⟞ SMAD7/Smurf 2 ⟞ TGF-β pathway → Metastasis	(Li et al., 2014)
Wnt/β-catenin	miR-23a	Upregulated	CDH1	miR-23a ⟞ CDH1 ⟞ β-catenin → TGF-β1-induced EMT/metastasis/migration/invasion	(Ma et al., 2017)
	miR-4469	Upregulated	CDK3	miR-4469 ⟞ CDK3 ⟞ β-catenin → Cell motility/invasive ability	(Cao et al., 2017)
	miR-27a	Upregulated	SFRP1	miR-27a ⟞ SFRP1 ⟞ Wnt/β-catenin pathway → Proliferation/migration/invasion	(Kong et al., 2017)
	miR-34a	Downregulated	Wnt1	miR-34a ⟞ Wnt1 → Proliferation/progression	(Si et al., 2016)
	miR-1229	Upregulated	GSK-3β, APC, ICAT	miR-1229 ⟞ GSK-3β/APC/ICAT ⟞ Wnt/β catenin pathway → Proliferation	(Tan et al., 2016)
	miR-224	Downregulated	Fizzled 5	miR-224 ⟞ Fizzled 5 → Migration/proliferation	(Liu et al., 2016)
	miR-148a	Downregulated	Wnt1	miR-148a ⟞ Wnt1 → Migration/invasion	(Jiang, He, Ma, et al., 2016)
	miR-494	Downregulated	CXCR4	miR-494 ⟞ CXCR4 → Wnt/β-catenin pathway → Proliferation/migration/invasion	(Song, Liu, Wang et al., 2015)
	miR-1	Downregulated	Fizzled 7, TNSK2	miR-1 ⟞ Fizzled 7/TNSK2 → Wnt/β-catenin pathway → Stemness/proliferation/migration of breast CSCs	(Liu, Hu et al., 2015)
	miR-100	Downregulated	Frizzled 8	miR-100 ⟞ Frizzled 8 → Migration/invasion	(Jiang, He, Guan et al., 2016)
	miR-301a	Upregulated	PTEN		(Ma, Li, Wu, & Meng, 2014)

(Continues)

TABLE 1 (Continued)

Type of signaling Pathway	miRNAs	Alteration of expression	Potential Targets	Functions of miRNAs in breast cancer	References
				miR-301a ⟞ PTEN ⟞ Wnt/β-catenin pathway → Invasion/metastasis	
	miR-374a	Upregulated	WIF1, Wnt5, PTEN	miR-374a ⟞ WIF1/Wnt5/PTEN ⟞ Wnt/β catenin pathway → EMT/metastasis	(Cai et al., 2013)
	miR-142	Upregulated	APC	miR-142 ⟞ APC ⟞ Wnt/β-catenin pathway → Clonogenicity of BCSCs/tumor growth	(Isobe et al., 2014)
PI3K/Akt/mTOR	miR-147	Downregulated	Akt	miR-147 ⟞ Akt phosphorylation → Proliferation/invasion/migration	(Zhang, Zhang et al., 2016)
	miR-21	Upregulated	PTEN, PIK3R1	miR-21 ⟞ PTEN ⟞ PI3K/Akt/mTOR pathway ⟞ Apoptosis/autophagy	(Yu et al., 2016), (Yan et al., 2016)
				miR-21 ⟞ PIK3R1 ⟞ PI3K/Akt pathway → EMT/invasion/migration	
	miR-99a	Downregulated	mTOR	miR-99a ⟞ mTOR → Invasion/migration/cell viability	(Yang et al., 2014), (Hu et al., 2014)
	miR-122	Downregulated	IGF1R	miR-122 ⟞ IGF1R → PI3K/Akt/mTOR/p70S6K pathway → Proliferation/tumorigenesis	(Wang et al., 2012)
	miR-184	Downregulated	Akt2, TSC2, PRAS40	miR-184 ⟞ Akt2 → PI3K/AKT/mTORC1 pathway → Proliferation/self-renewal of TNBC	(Phua et al., 2015)
	miR-214	Upregulated	PTEN	miR-214 ⟞ PTEN ⟞ PI3K/Akt pathway → Cell viability/resistance to apoptosis	(Wang, Li, Chen, Zhu, & Gu, 2016)
	miR-100	Downregulated	IGF2, mTOR	miR-100 ⟞ IGF2 → Tumorigenesis	(Zhang, Zhao et al., 2016), (Gebeshuber & Martinez, 2013)
				miR-100 ⟞ mTOR ⟞ Paclitaxel-induced cell cycle arrest and apoptosis	
	miR-106b, miR-93	Upregulated	PTEN	miR-106b, miR-93 ⟞ PTEN ⟞ PI3K/Akt pathway → Migration/invasion/proliferation	(Li et al., 2017)
	miR-10b	Upregulated	PTEN	miR-10b ⟞ PTEN ⟞ PI3K/Akt pathway → Self-renewal ability of breast CSCs	(Bahena-Ocampo et al., 2016)
	miR-130b	Upregulated	PTEN	miR-130b ⟞ PTEN ⟞ PI3K/Akt pathway → Drug resistance/proliferation	(Miao et al., 2017)
	miR-221/222 cluster	Upregulated	PTEN	miR-221/222 ⟞ PTEN ⟞ Akt phosphorylation → Proliferation/invasion/migration	(Li et al., 2016)
	miR-409-3p	Downregulated	Akt1	miR-409–3p ⟞ Akt1 → Proliferation/invasion/migration	(Zhang, Liu, Xu, & Yang, 2016)
	miR-133a	Downregulated	EGFR	miR-133a ⟞ EGFR → EGFR/Akt pathway → Cell cycle/proliferation	(Cui et al., 2013)
	miR-564	Downregulated	AKT2, GNA12, GYS1, SRF	miR-564 ⟞ AKT2/GNA12/GYS1/SRF → PI3K pathway → Proliferation/EMT/migration/invasion	(Mutlu et al., 2016)

(Continues)

TABLE 1 (Continued)

Type of signaling Pathway	miRNAs	Alteration of expression	Potential Targets	Functions of miRNAs in breast cancer	References
Notch	miR-34a	Downregulated	Notch1	miR-34a ⟞ Notch1 → Proliferation/migration/invasion/stemness	(Park et al., 2014), (Kang et al., 2015)
	miR-139–5p	Downregulated	Notch1	miR-139–5p ⟞ Notch1 → Proliferation/invasion/metastasis	(Zhang et al., 2015)
	miR-9	Downregulated	Notch1	miR-9 ⟞ Notch1 → Metastasis	(Mohammadi-Yeganeh et al., 2015)
	miR-200	Downregulated	Jag1, Maml3, Maml2	miR-200 ⟞ Jag1/Maml3/Maml2 → Proliferation/EMT/stemness	(Brabletz et al., 2011)
	miR-130b-3p	Downregulated	DLL1	miR-130b-3p ⟞ DLL1 → Invasion/migration	(Shui et al., 2017)
	miR-101	Downregulated	EYA1	miR-101 ⟞ EYA1 → Notch pathway → Proliferation/block apoptosis	(Guan et al., 2016)
NF-κB	miR-29a	Downregulated	TNFR1	miR-29a ⟞ TNFR1 → Proliferation	(Zhao et al., 2017)
	miR-1246	Upregulated	PRKAR1A, PPP2CB	miR-1246 ⟞ PRKAR1A/PPP2CB ⟞ NF-κB → Proinflammatory responses	(Bott et al., 2017)
	miR-181b	Downregulated	CCL18	miR-181b ⟞ CCL18 → NF-κB → Proliferation/migration/invasion	(Wang, Wang, Chen, & Ji, 2016)
	miR-449a	Upregulated	CRIP2	miR-449a ⟞ CRIP2 ⟞ IL-6/IL-8/VEGF → Viability/clonogenicity/migration/invasion/tumor angiogenesis	(Shi et al., 2016)
	miR-362–5p	Upregulated	CYLD	miR-362–5p ⟞ CYLD ⟞ NF-κB → Proliferation/invasion/migration	(Ni et al., 2016)
	miR-892b	Downregulated	TAK1, TAB3, TRAF2	miR-892b ⟞ TRAF2/TAK1/TAB3 → NF-κB pathway → Tumor growth/metastasis/angiogenesis	(Jiang, Yu et al., 2016)
	miR-146a/b	Downregulated	IRAK1, TRAF6	FOXP3 → miR-146a/b ⟞ IRAK1/TRAF6 → NF-κB → Proliferation/invasion/metastasis	(Etikala et al., 2015), (Runhua Liu et al., 2015)
	miR-200b	Downregulated	IKBKB, IKK-β	miR-200b ⟞ IKBKB/IKK-β → NF-κB pathway → Cell growth/migration	(Wu et al., 2016)
	miR-30c-2–3p	Downregulated	TRADD, CCNE1	miR-30c-2–3p ⟞ TRADD → NF-κB pathway → Invasion/proliferation	(Shukla et al., 2015)
	miR-502–5p	Downregulated	TRAF2	miR-502–5p ⟞ TRAF2 → NF-κB pathway → Proliferation/block early apoptosis	(Sun et al., 2014)
Ras/Raf/MEK/ERK	miR-506	Downregulated	IQGAP1	miR-506 ⟞ IQGAP1 → ERK/MAPK pathway → Proliferation/invasion	(Sun et al., 2015)
	miR-30c	Downregulated	KRas	miR-30c ⟞ KRas → Proliferation	(Tanic et al., 2012)
	Let-7a	Downregulated	KRas	Let-7a ⟞ KRas → ERK/MAPK pathway → Proliferation/sphere size	(Xu et al., 2015)
	miR-200c	Downregulated	KRas	miR-200c ⟞ KRas → ERK pathway → Proliferation	(Song, Liu, Pei et al., 2015), (Kopp et al., 2014)

(Continues)

TABLE 1 (Continued)

Type of signaling Pathway	miRNAs	Alteration of expression	Potential Targets	Functions of miRNAs in breast cancer	References
	miR-134	Downregulated	KRas	miR-134 ⟞ KRas → Growth/invasion/migration	(Su et al., 2017)
	miR-1	Downregulated	KRas, MALAT1	miR-1 ⟞ KRas/MALAT1 → Growth/metastasis	(Liu, Li et al., 2015)
	miR-199a/b-3p	Downregulated	PAK4	miR-199a/b-3p ⟞ PAK4 → Raf/MEK/ERK pathway → Proliferation/invasion/migration	(Li et al., 2015)
	miR-543	Downregulated	ERK2	miR-543 ⟞ ERK2 → Proliferation	(Chen et al., 2017)
	miR-148a, miR-152	Downregulated	IGF1R, IRS1	miR-148a/152 ⟞ IGF1R/IRS1 → Proliferation/colony formation/tumor angiogenesis	(Xu et al., 2013)

Abbreviations: APC, adenomatous polyposis coli; BMP, bone morphogenic protein; CCL18, chemokine ligand 18; CDH1, cytoplasmic domain of E-cadherin 1; CDK3, cyclin-dependent kinase 3; C/EBPβ, CCAAT-enhancer binding protein beta; CRIP2, cysteine-rich protein 2; CXCR4, chemokine (C-X-C motif) receptor; CYLD, cylindromatosis; CCNE1, cyclin E1; DLL1, delta-like 1; EGFR, epidermal growth factor receptor; EMT, epithelial–mesenchymal transition; EYA1, eyes absent 1; ERK/MAPK, extracellular-signal-regulated kinase/mitogen activated protein kinase; GNA12, guanine nucleotide binding protein subunit α 12; GSK-3β, glycogen synthase kinase 3; GYS1, glycogen synthase 1; HuR, human antigen R; ICAT, inhibitor of β-catenin and T cell factor; IGF1R, insulin-like growth factor 1 receptor; IκBκB, inhibitor of nuclear factor κ B kinase subunit β; IQGAP1, IQ motif containing GTPase activating protein 1; IRS1 insulin receptor substrate 1; Jag1, Jagged-1; MAGI2, membrane-associated guanylate kinase inverted 2; Maml2/3, mastermind-like transcriptional coactivator 2/3; MALAT1, metastasis associated lung adenocarcinoma transcript 1; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; NRP1, neuropilin-1; PHACTR1, protein phosphatase and actin regulator 1; PIK3R1, phosphoinositide-3-kinase regulatory subunit 1 (α); PPP2CB, PP2A catalytic subunit β; PRAS40, proline-rich Akt substrate of 40 kDa; PRKAR1A, cAMP-dependent protein kinase Type I-α regulatory subunit; SFRP1, secreted frizzled-related proteins 1; Smurf2, smad ubiquitination regulatory factor 2; SRF, serum response factor; TAB3, TAK1-binding protein3; TAK1, transforming growth factor β-activated kinase1; TGF-βR, transforming growth factor β receptor; TRADD, TNFRSF1A-associated via death domain; TNFR1, tumor necrosis factor receptor 1; TNSK2, tankyrase-2; TRAF2, TNF receptor-associated factor 2; TSC2, tuberous sclerosis complex 2; VEGF, vascular endothelial growth factor; ZEB1, zinc-finger e-box binding homeobox 1.

blocks tumorogenesis of breast tumor cells via blocking of Wnt/β-catenin pathway by controlling the phosphorylation level of low-density LRP-6, the expression of Axin1 and disheveled (Dvl)-2, and the suppression of β-catenin. Consequently, miR-4469 straightly targets the 3′-UTR of CDK3 and plays a stimulatory function in breast tumor by the initiation of Wnt/β-catenin pathway (Cao et al., 2017). sFRPs are endogenous Wnt antagonists which can regulate the pathway. Notably, sFRP1 is a novel target of miR-27a (Guo et al., 2014). MiR-27a upregulation elevates protein expressions of β-catenin and Wnt and causes the triggering of Wnt/β-catenin cascade through the inhibition of sFRP1 to provoke the migration and invasion of breast tumor (Kong, Xue, Zhang, & Su, 2017). Among the miRNAs, miR-34a is a pivotal anti-oncogene miRNAs (Wu, Fu, Xiao, Wu, & Wu, 2014). Wnt1 is a target of miR-34a. High expression of miR-34a restrains the proliferation of cancer stem cells, EMT and promotion of breast tumor via the inactivation of the pathway (Si et al., 2016). Tan et al. (2016) found that the miR-1229 expression remarkably increased in breast tumor is related to worse survival. They also represented a new relationship among miR-1229 and the pathway (Tan et al., 2016). The hindrance of the expression of three critical negative regulators, including GSK3β, APC, ICAT by the upregulation of miR-1229 propel the pathway. This process brings about miR-1229-mediated promotion of cell proliferation in breast tumor (Carotenuto et al., 2014; Tan et al., 2016). The expression of miR-224 is conversely linked the progression of breast tumors. The overexpression of miR-224 suppresses the signaling via the reduction of FZD-5 expression and subsequently, blocks of migration and proliferation of breast tumor cells (Liu, Liu, Shen, Zhang, & Han, 2016). A novel research gave additional evidence that high expression of miR-148a blocks tumorogenesis of breast tumor cells by direct interaction with Wnt1 and inactivation of the pathway. Meanwhile, the elevated expression of miR-148a can diminish β-catenin, MMP-7, and TCF-4 (Chen, Song, & Wang, 2013; Jiang, He, Ma et al., 2016). MiR-494 targets CXCR4 (Song, Liu, Wang et al., 2015). It has been established that SDF-1 signaling via CXCR4 provokes progression and metastasis in a diversity of malignancies particularly breast tumor. Overexpression of miR-494 is able to restrain tumorigenesis of breast tumor via blocking CXCR4 mediated-Wnt/β-catenin pathway (Smith et al., 2004; Song, Liu, Wang et al., 2015). Liu et al. (2015) displayed a converse relation among the expression of miR-1 and aggressiveness of breast tumor. MiR-1 downregulates FZD-7 and tankyrase-2 expressions to inhibit the pathway. Overexpression of miR-1 compels apoptosis and prevents of proliferation of cells (Tarhriz et al., 2018). Hence, miR-1 is a negative moderator of the pathway can prevent BCSCs stemness, migration, and proliferation (Liu, Hu et al., 2015). FZD-8 is a critical receptor in this pathway which is straightly targeted by miR-100. An elevated level of miR-100 has an inhibitory effect on Wnt/β-catenin pathway function via the downregulation of FZD-8 expression; lead the hindrance of tumorigenesis (Jiang, He, Guan et al., 2016). As an oncomiR, miR-301a was found to down-regulate PTEN, as a negative regulator of the signaling, and activate the pathway cascade to provoke breast tumorigenesis (Sosman et al.,

2014). It is identified that miR-374a is linked to metastasis and EMT of breast cancer (Ye et al., 2014). Several negative modulators of the signaling for example WIF-1, Wnt5A, and PTEN are repressed by miR-374a. As a result of the suppression of Wnt pathway inhibitors, miR-374a helps distant metastasis and EMT (Cai et al., 2013; Ye et al., 2014). MiR-142 affects Wnt signaling function and plays a substantial effect on the beginning and development of breast tumor. In this context, Isobe et al. (2014) proved that miR-142 is upregulated in human BCSCs. This miRNA diminishes APC level and resulted in the initiation of the canonical the signaling pathway in the normal and malignant mammary cells (Isobe et al., 2014). Therefore, finding the relationship between miRNAs and regulators of Wnt/β-catenin signaling is a main subject in breast cancer investigation.

3.3 | The interaction between phosphoinositide-3-kinase-AKT-mammalian target of rapamycin pathway and miRNAs in breast tumor

Phosphoinositide-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) is an important pathway which contributes to the tumorigenesis (Eyvazi et al., 2019). It is well established that a number of miRNAs can target the key components of this pathway (Tarhriz et al., 2019a). The expression of miR-147 in breast tumor cells prevents tumorigenesis by restraining Akt/mTOR signaling pathway (Zhang, Zhang, & Liu, 2016). Recently, evidence emphasized that miR-21 induces PI3K/Akt signaling pathway through interaction with several targets (Yan et al., 2016; Yu et al., 2016). In this context, a study confirmed that silencing of miR-21 restrains PI3K/Akt/mTOR pathway via targeting PTEN and promote the activation of apoptosis and autophagy in breast tumor cells (Yu et al., 2016). MiR-99a directly targets mTOR and attenuates mTOR, p-4E-BP-1, and p-S6K-1 amount in breast tumor cells (Hu, Zhu, & Tang, 2014). MiR-99a overexpression hinders invasion and tumorigenesis of breast tumor cells by targeting mTOR as a downstream target of the pathway (Yang, Han, Cheng, Zhang, & Wang, 2014). downregulation of miR-122 has been shown in breast tumor. Amendment of miR-122 expression blocks tumorigenesis of breast tumor cell via targeting insulin-like growth factor 1 receptor (IGF1R) and preventing PI3K/Akt/mTOR/p70S6K cascade (Wang, Wang, & Yang, 2012). MiR-184 as a putative mammary tumor suppressor performs a central function in inhibiting the proliferation and self-renewal of TNBC through interaction with Akt2, TSC-2, PRAS40, and the negative control of the PI3K/Akt/mTOR complex (mTORC)-1 (Phua et al., 2015). As an oncomiR, miR-214 reduces PTEN expression straightly targeting PTEN 3′-UTR in breast tumor cells (Schwarzenbach, Milde-Langosch, Steinbach, Muller, & Pantel, 2012; Wang, Li et al., 2016). As a result of PTEN downregulation, miR-214 stimulates cell viability and elevates the improvement of breast tumor via the positive regulation of PI3K/Akt signaling (Wang, Li et al., 2016). MiR-100 has been emerged to target various proteins of IGF/mTOR signaling in different tumors (Gebeshuber & Martinez, 2013; Zhang, Zhao et al., 2016). According to Gebeshuber et al study overexpression of miR-100 remarkably attenuates the expression of IGF2 in breast tumor cells, resulting in the suppression of breast tumorigenesis (Gebeshuber & Martinez, 2013). PTEN is target of miR-130b and miR-10b (Miao et al., 2017). It has been revealed that miR-130b is overexpressed in TNBC (Chang et al., 2015). MiR-130b promotes drug resistance and inhibits apoptosis in breast cancer tumors by silencing PTEN through PI3K/Akt (Miao et al., 2017). MiR-221/222 is characterized as oncogenic miRNAs that negatively control PTEN. Notably, miR-221/222 cluster promotes tumorogenessis of BCSCs thorough targeting the pathway (Li et al., 2016). MiR-133a is a tumor suppressor miRNA and it is reduced in breast tumor (Cui, Zhang, Shan, Zhou, & Zhou, 2013; Wu, Wang et al., 2012). In this regard, Cui et al. (2013) proposed that the augmentation of miR-133a expression hinders proliferation of breast tumor cells by the interaction of EGF receptor (EGFR) through the negative modulation of EGFR/Akt. According to the mentioned evidence, miRNAs as bona fide regulators of PI3K/Akt/mTOR pathway are capable to be used in diagnostic of breast tumor.

3.4 | The link between Notch pathway and miRNAs in breast tumor

Notch signaling pathway modulates several processes like proliferation, differentiation, and apoptosis of cell. The interplay between the Notch pathway and miRNAs is linked with the progression of various malignancies, particularly breast cancer. Among the diverse signaling pathways, Notch signaling is the main pathway which sustains stem cell properties (Kang et al., 2015). MiR-34a as a part of the miR-34 family performs a monumental function in sustaining breast cancer stem cells (Kang et al., 2015; Park et al., 2014). In this context, Kang et al. (2015) exhibited that miR-34a hampers breast cancer stemness through the suppression of Notch1 (Kang et al., 2015). Moreover, the previous study also showed that miR34a-Notch1 axis is a novel candidate for anti-breast cancer stemness therapies (Park et al., 2014). MiR-139-5p directly targets Notch1 in breast tumor and links to the decreased expression of MMP protein. Meanwhile, MMPs has a fundamental function in the modulation of cancer progerestion. Recent evidence reported that induced expression of target of Notch1 gene by MMP2, MMP7, and MMP9 causes the development of tumorigenesis. Hence, miR-139-5p as a tumor suppressor miRNA can hinder migration of breast tumor via the decreasing of Notch1 expression to inhibit the expression of MMP2, MMP7, and MMP9 (Zhang et al., 2015). Mohammadi-Yeganeh, Mansouri, and Paryan (2015) proposed that the interaction of miR-9 and Notch1 can be a good factor in breast tumor treatment. MiR-9 expression is declined and Notch1 expression increased in TNBC. MiR-9 can reduce metastatic behavior in TNBC via direct targeting of Notch1 (Mohammadi-Yeganeh et al., 2015). MiR-200 family interplays with not only ZEB1 but also some parts of Notch pathway like Jagged-1, mastermind-like transcriptional coactivator (Maml)-2 and Maml3 in breast cancer (Brabletz et al., 2011; Rizzo et al., 2008). Importantly, miR-200 family hampers the expression of Notch pathway components, which are key mediators for cancer cell proliferation, survival,

and stemness (Brabletz et al., 2011). ZEB1 can indirectly stimulate Notch signaling via the repression of miR-200 expression (Brabletz et al., 2011; Burk et al., 2008). MiR-130b-3p directly targets delta-like (DLL)-1 that is the ligand of the Notch pathway, in breast tumor cells. Shui et al. (2017) elucidated that the negative regulation of DLL1 by miR-130b-3p can alleviate breast carcinoma cell migration and invasion (Shui et al., 2017). In addition, regulatory impact of miR-130b-3p on the function of MMP9, MMP13, and vascular endothelial growth factor (VEGF) may be linked to the repressing effect of this miRNA on breast carcinoma cells (Ren et al., 2015; Shui et al., 2017). Downregulation of miR-101 in breast tumor can provoke tumorigenesis by directly targeting eyes absent (EYA)-1 via the Notch signaling pathway. MiR-101 reduces the protein expression of EYA1 and, thereby, Notch as a downstream signaling pathway of EYA1, that is mediated by the regulatory effects of miR-101 (Guan et al., 2016). ADAM12 as a breast cancer-related gene is upregulated in human breast tumors. Li, Solomon, Duhachek Muggy, Sun, and Zolkiewska (2011) observed miR-29 family has a function in high expression of ADAM12 by Notch. Remarkably, Notch activates nuclear factor κ B (NF-κB) which downregulates miR-29 and negative modulator of ADAM12, therefore, amplifies its expression. Collectively, the dialog between miRNAs and Notch signaling pathway requires further studies to represent potential new therapeutic approaches in breast cancer therapy.

3.5 | The relationship between NF-κB pathway and miRNAs in breast tumor

NF-κB pathway affects numerous processes, such as growth of cell, cancer metastasis, and inflammation. The NF-κB signaling pathway is strongly influenced by miRNAs and has a major function in the tumorigenesis of diverse cancers, particularly breast tumor (Wu et al., 2016). Zhao et al. (2017) revealed the tumor suppressor role of miR-29a is probably through controlling NF-κB signaling pathway. Tumor necrosis factor receptor 1 (TNFR-1) is a principal receptor in NF-κB pathway which is targeted by miR-29a, directly. In addition to TNFR1, cyclin D1 and Bcl-2/Bax are also reduced by expression of miR-29a. Hence, higher expression of miR-29a promotes the blocking proliferation, cell cycle, and increasing of apoptosis in MCF-7 cells (Zhao et al., 2017). MiR-1246 is a novel oncomiR in breast cancer that increases NF-κB signaling independent of tumor necrosis factor α (TNF-α). In fact, cAMP-dependent protein kinase type 1 subunit α (PRKAR1A) as the regulatory subunit of PKA and also PP2A PPP2CB as the catalytic subunit of PP2A are negative regulators of NF-κB signaling that are directly targeted by miR-1246 (Bott et al., 2017; Gao, Hibi, Cueno, Asamitsu, & Okamoto, 2010; Seshacharyulu, Pandey, Datta, & Batra, 2013). As a result of downregulation of these negative regulators, miR-1246 causes the augmentation of NF-κB pathway by phosphorylation of the NF-κB p65 subunit (p65) in mesenchymal stem/stromal cells. Consequently, this miRNA promotes breast cancer progression and cancer-related inflammation in a p65-dependent manner (Bott et al., 2017). The secretion of chemokine ligand (CCL)-18 by tumor-associated macrophages (TAMs) stimulates the activation of NF-κB, which provokes tumorigenesis (Chen et al., 2011). A recent study suggested that miR-181b abrogates CCL18-induced breast tumor cell metastasis through stopping NF-κB expression (Wang, Wang et al., 2016). A study by Shi et al. (2016) highlighted miR-449a that its level is elevated in breast cancer tissues. They also represented that miR-449a directly interacts with a transcription factor named cysteine-rich protein (CRIP)-2 which functions as a critical suppressor of NF-κB-mediated proangiogenic factors (Shi et al., 2016). The overexression of miR-449a stimulates breast cancer cell development and clonogenicity through abrogation of CRIP2 and leads to NF-κB/p65 complex that activates transcription of VEGF which is a crucial proangiogenic cytokine (Cheung et al., 2011; Shi et al., 2016). Cylindromatosis (CYLD) acts in the modulation of diverse signaling pathways, particularly NF-κB signaling. The increased of miR-362-5p leads the development of breast tumor cells via NF-κB activation and decreasing expression level of CYLD (Ni et al., 2016). The expression of miR-892b declines in breast tumor and leads to unfavorable survival. The reduction of miR-892b level maintains the NF-kB activation via the upregulation of TNF receptor-associated factor 2 (TRAF-2), TAK-1, and TAB-3 (Jiang, Yu et al., 2016). Recently, accumulating data have shown that forkhead box P3-miR-146-NF-κB axis is a novel route in breast tumor cells (Etikala, Liu, & Wang, 2015). The upregulation of miR-146a/b blocks NF-κB through the hindrance of IRAK-1 and TRAF-6 expressions; thereby miR-146a/b prevents the tumorigenesis (Etikala et al., 2015; Liu, Liu et al., 2015). Wu et al. (2015) indicated that miR-200b blocks NF-κB via reducing the expression of (IKBKB)/IKK-β and mutually, the inactivation of NF-κB downregulates the miR-200b transcription. Regarding the function of miR-200b, it can offer an encouraging therapeutic goal for improving breast tumor management (Wu et al., 2016). The over-expression of specific miRNAs for example miR-502-5p chips in the reduction of TRAF2 gene expression in breast tumor. Levels of miR-502-5p are lower in breast tumor cell lines in comparison with the noncancerous breast cell line. MiR-502-5p hampers NF-κB cascade by the prevention of TRAF2 expression. Therefore, it seems that miR-502-5p is critical for the inhibition of breast tumor cells (Sun et al., 2014). Taken together, the interplay of miRNAs and NF-κB pathway are expected to provide a new therapeutic opportunity for patients with breast tumor.

3.6 | The relationship between extracellular-signal-regulated kinase/mitogen activated protein kinase pathway and miRNAs in breast tumor

Extracellular-signal-regulated kinase (ERK)/mitogen activated protein kinase (MAPK) pathway is a main pathway related to proliferation, differentiation, and migration in breast tumor cells. Plenty of evidence suggests that several miRNAs can activate or suppress of this signaling pathway (Asghari, Haghnavaz, Baradaran, Hemmatzadeh, & Kazemi, 2016). MiR-506 represses the tumorigenesis through the negative regulation of IQ motif including IQGAP1. ERK/MAPK signaling is the downstream of IQGAP1; thus, the pathway can also be suppressed by miR-506 (Sun, Liu, Wang, & Xu, 2015). IQGAP1 directly interacts with B-Raf and activates it,

which in turn activates MEK1 and MEK2 (Ren, Li, & Sacks, 2007). KRas as a master factor of the Ras/Raf/MAPK pathway is the target of various miRNAs, such as miR-30, Let-7a, miR-200c, and miR-134 (Asghari et al., 2016). MiR-30c expression is remarkably declined in breast tumor. Higher expression of miR-30c prevents the cancer cells progression through negative regulation of KRas (Tanic et al., 2012). A new research by Xu et al. (2015) illustrated that upregulation of Let-7a reduces the size and number of mammospheres in breast cancer stem cells via KRas/MEK/ERK and KRas/NF-κB pathways respectively (Xu et al., 2015). MiR-200c is reduced in breast tumor and can repress the expression of KRas. As a result of KRas blocking, miR-200c hinders the proliferation survival and of breast tumor cells via negative control of Akt and ERK (Kopp, Wagner, & Roidl, 2014; Song, Liu, Pei et al., 2015). Importantly, miR-134 expression level is reduced in breast tumors. Su et al. (2017) observed the reduced expression of miR-134 enhances tumorogenesis of breast tumor via the upregulation of KRas (Su et al., 2017). MALAT-1 and KRas have shown to be new targets for miR-1. High expression of miR-1 restrains tumor growth and metastasis by negative control of KRas and MALAT1 in breast tumor cells (Liu, Li et al., 2015). P21-activated kinase 4 (PAK4) performs an important function through the Raf/MEK/ERK pathway in breast tumor metastasis. Interestingly, miR-199a/b-3p downregulates the expression of PAK4. Accordingly, the overexpression of miR-199a/b-3p can repress progression of breast tumor cells through inactivation of the PAK4/MEK/ERK pathway (Li, Wang, Mi, Liu, & Tan, 2015). Elevated expression of miR-543 inhibits progression of breast tumor cells by targeting of ERK2 and prevention of the MAPK/ERK pathway. In addition to ERK2, the expression of ribosomal protein S6 kinase-2 and MSK-1 as downstream factors of MAPK/ERK are reduced by enhancing of miR-543 (Chen et al., 2017). According to Xu et al. (2013), increasing of miR-148a/152 prevents the breast cancer cell progression via downregulating the expression levels of IGF1R and IRS-1 and resulting in the inactivation of Akt and MAPK/ERK pathways (Xu et al., 2013). Eventually, the relationship between miRNAs and the Ras/Raf/MEK/ERK pathway should be considered in finding potential treatment targets in breast cancer cases.

4 | MicroRNAs CAN BE NEW BIOMARKERS IN THE DIAGNOSIS OF BREAST TUMOR

Using miRNAs as diagnostic biomarkers for identification of breast tumor at early stages and also discriminating tool among breast tumor patients and noncancerous subjects have attracted attention recently (Table 2). More importantly, specific miRNAs are capable to be considered as noninvasive biomarkers that are very stable in the body fluids (Schrauder et al., 2012; Zeng et al., 2013; Zhu, Qin, Atasoy, & Sauter, 2009). Mir-21 and Mir-155 could be used as a diagnostic marker in early stage breast tumor. Tissue and blood levels of the miRNAs increased in breast cancer patients in comparison to control group (Matamala et al., 2015; Si et al., 2013). The differential expression status of specific miRNAs reveals that sometimes their detected levels in the blood and tissue samples are different. For example, a research confirmed that mir-145 is decreased in breast cancer cell, but another study confirmed that it is increased in breast cancer patients blood (Mar-Aguilar et al., 2013; Wang et al., 2009). Other examples are mir-195 and mir-181a that increased in the plasma sample of patient with breast cancer, while its expression is decreased in breast cancer tissues (Godfrey et al., 2013; Heneghan, Miller, Kelly, Newell, & Kerin, 2010; Li, Zhao et al., 2011). Mir-19a, mir-24, and mir-181b are oncogenic miRNAs that upregulated in early stages of breast tumor, while, following surgical resection and therapy, levels of these miRNAs in serum sample decreased. therefore, they can be regarded as markers for monitoring in early breast cancer (Sochor et al., 2014). In another study a new miRNA signature that distinguishes between breast cancer patient (ER-positive and early stage) and normal subject has been demonstrated. MiR-15a, miR- 18a, miR-107, and miR-425 show overexpression in patients with breast tumor in comparison with noncancerous ones, while expression levels of miR-133a, miR-139-5p, miR-143, and miR-365 have been decreased (Kodahl et al., 2014). In another study it has been revealed that expression status of eight miRNAs, such as miR-16, miR-21, miR-27a, miR-150, miR-191, miR-200c, miR-210, miR-451 are increased, but the mir-145 is down-regulated in patients with breast tumor, meanwhile it seems that combination of miR-145 and miR-451 may be useful in diagnose of patients with breast tumor (Ng et al., 2013). In a research conducted by Kai Zhang et al, they observed that serum levels of miR-30b-5p, miR-96-5p, miR-182- 5p, miR-374b-5p, and miR-942-5p were increased and miR- 204-5p and miR-4717-3p were reduced in of the breast tumor patients (Zhang et al., 2017). Furthermore, miRNAs display differential expression in different breast tumor subtypes. Geraldine et al compared the expression levels of 20 miRNAs in ER+ with ER− breast cancers. They observed 12 overexpressed and 8 low-expressed miRNAs and reported that regarded to miR-190b high expression and specificity in patients with ER+ breast cancer, it can be used for monitoring and discriminating ER+ from ER− breast cancers (Cizeron-Clairac et al., 2015). The miRNA profiles were verified in the 29 tissues of early-stage breast cancer. In addition, it have been demonstrated that MiR-342 upregulated in ER and HER2+ luminal B breast cancer, but this miRNA reduced in TNBC. Furthermore, miR-520g overexpressed in ER and PR tumors (Lowery et al., 2009). Cluster-mir-17-92 has an oncogenic role, and an upregulation of approximately threefold was demonstrated in TNBC and suggested that it can be used as a strong diagnostic biomarker in TNBC for distinguishing from other subtypes of breast carcinoma (Farazi et al., 2011). Many studies identified tumor-related miRNAs in blood and tissue samples of the tumor patients and their association with tumor progression and metastasis. Roth et al. (2010) reported that the expression of miR10b, miR34a, and miR155 enhanced in metastatic samples and can be used for discriminating metastasis breast tumor patients from control group. Thereby, miRNAs as novel types of cancer biomarkers can be incorporated as novel diagnostic markers in patients with breast tumor.

TABLE 2 List of miRNAs with potential diagnostic biomarker in breast cancer

miRNAs	Type of biomarker	Biological sample	Clinicopathologic features/role in diagnosis and prognosis	Reference
miR-1, -92a, -133a, -133b	Diagnosis	Serum tissue	These miRNAs can be used as valuable marker in diagnosis of BC. Furthermore, ROC analysis derived from combinations of these miRNAs showed AUC of 0.90–0.91	(Chan et al., 2013)
miR-10b, -21, -125b, -145, -155, -191, -382	Diagnosis	Serum	These miRNAs can be detected in early stage of BC, but were not significantly associated with different stages. Importantly, a combination of miR-145, -155, -382 was indicated that better sensitivity and specificity in BC patients.	(Mar-Aguilar et al., 2013)
miR-127-3p, -148b, -376a, -376c, -409-3p, -652, -801	Diagnosis	Plasma	MiR-127-3p, -148b, -409-3p, -652, -801were associated with cancer stage (I, II), and also miR-801 was correlated with age, menopause status, tumor grade, PR status, P53, and Ki67. Meanwhile, The combination of all miRNAs showed the highest discriminatory power with AUC = 0.81.	(Cuk et al., 2013)
miR-141, -200a/b/c, -203, -210, -375	Diagnosis	Plasma	These miRNAs had higher levels in CTC-positive patients relative to CTC-negative group. Mir-200b was showed can be useful for discrimination CTC-positive patients from CTC-negative.	(Madhavan et al., 2012)
miR-126, -199a, -335	Diagnosis	Serum/Tissue	These miRNAs were significantly underexpressed in higher malignancy tumor grades relative to noncancerous tissue. Moreover, they were correlated with ER, PR status in both samples.	(Wang, Zheng, Guo, & Ding, 2010)
miR-30a, -181a, -205	Diagnosis	Serum plasma	The miR-30a was correlated with the status of ER and TNBC. miR-181a can be regarded as a diagnostic biomarker in early stage of BC.	(Guo & Zhang, 2012; Liu et al., 2013; Zeng et al., 2013)
miR-195, -182, let-7a	Diagnosis	Serum Plasma Whole blood	The expression level of miR-182 in the ER-positive patients were lower relative to ER-negative patients. The let-7a was associated with lymph node status. Besides, mir-195 was correlated with hormone receptor status.	(Heneghan et al., 2010; Wang et al., 2013)
miR-16, -222, -25, -324-3p	Diagnosis	Serum	The overexpression of these miRNAs were significantly correlated with age, menopause status and ER status in patients with BC.	(Hu et al., 2012)
miR-505-5p, -96-5p	Diagnosis	Plasma	These miRNAs can be detected in early stage of BC.	(Matamala et al., 2015)
miR-215, -299-5p, -411	Diagnosis	Serum	These miRNAs in serum of patients with BC, particular metastatic BC, can be used as a valuable biomarker.	(van Schooneveld et al., 2012)
miR-199a, -29c, -424	Diagnosis	Serum	The serum level of mir-199a were elevated in patients at all stages, but miR-29c and -424 levels were elevated in patients only at stages I and II.	(Zhang et al., 2015)
miR-1246, -1307-3p, -4634, -6861-5p, -6875-5p	Diagnosis	Serum	These miRNAs can be used to detect BC in the early stages, and also discriminate BC from other cancer. Furthermore, This combination had a high sensitivity, specificity and accuracy (97, 82, 89%, respectivvely) for BC.	(Shimomura et al., 2016)
miR-15, -18, -107, -425	Diagnosis	Serum	These miRNAs can differentiate early stage of ER-positive patients with BC from healthy subjects.	(Kodahl et al., 2014)
miR-139-5p, -143, -365	Diagnosis	Serum	These miRNAs can differentiate early stage of ER-positive patients with BC from healthy subjects.	(Kodahl et al., 2014)
miR-30b-5p, -69-5p,182-5p, -374b-5p, -942-5p	Diagnosis	Whole blood	These five miRNAs can be regarded as a novel candidate biomarker for BC at the early stage.	(Zhang et al., 2017)

(Continues)

TABLE 2 (Continued)

miRNAs	Type of biomarker	Biological sample	Clinicopathologic features/role in diagnosis and prognosis	Reference
miR-374, -666-5p, -451, -148a, -27a	Diagnosis	Serum	The miR-451, -148a, -27a tended to be significantly expressed in serum between BC group and healthy one.in addition, miR-451, -27a displayed significantly different expression between the benign breast tumor patients and the healthy ones. And also the expression levels of miRNAs were nor significantly different between the pre- and postoperative groups.	(Luo et al., 2014)
miR-141, -200a/b/c, -375, -801	Prognosis	Plasma	These miRNAs was associated with PFS and OS	(Madhavan et al., 2012)
miR-516-3p, -210, -128	Prognosis	Tissue	The miR-516-3p and -128 were correlated with aggressiveness of lymph node-negative/ER-positive BC, and also mir-210 was associated with aggressiveness and metastatic capability of lymph node-negative/ER-positive BC.	(Foekens et al., 2008)
miR-27b, -128a, 135a, -144, -150, -210, -342, -767-3p	Prognosis	Tissue	The miR-210, -144, -27b were correlated with distant relapse in ER-negative of BC. Furthermore, miR-767-3p and -128a were associated with distant relapse in ER-positive of BC. Finally, miR-150 and -342 reduced distant relapse in ER-negative of BC	(Foekens et al., 2008)
miR-126, -335	Prognosis	Tissue	The loss expression of miR-126,-335 was associated with unfavorable DMFS	(Tavazoie et al., 2008)
miR-181d, -195–5p, -146-5p	Prognosis	Tissue	The low-expression of miR-195-5p and -181d were associated with unfavorable patient survival. But overexpression of miR-146a-5p displayed a relationship with unfavorable survival in HER2-positive patients.	(Tashkandi et al., 2015)
miR-342, -205, let-7b	Prognosis	Tissue/cell line	The higher expression level of miR-342 was associated with favorable survival in patients with BC. Similarly, let-7b and miR205 expression were associated with increased RFS and OS	(Leivonen et al., 2014; Quesne et al., 2012)
miR-124, -206	Prognosis	Tissue	These miRNAs associated with positive outcome. Hence, increased expression of miR-124, -206 correlated with increased OS and decreased TNM and LNM stage.	(Dong, Chen, Wang, & Zhang, 2015; Y. Li, Hong, & Yu, 2013)
miR-29b, -27a	Prognosis	Tissue	The low-expression of miR-29b, -27a associated with decreased DFS and OS.	(Shinden et al., 2015; Tang et al., 2012)
let-7c, miR-99a, -125b	Prognosis	Tissue	These miRNAs regulate HER2 protein expression and also when lost may cause to unfavorable outcome for patients of subtype luminal A of BC	(Bailey, Westerling, & Brown, 2014)
miR-421, -486, -503, -720, -1303	Prognosis	Tissue	The five-miRNA signature was showed that were associated with pathological tumor size and PR status. Meanwhile, these miRNAs were correlated with MFS	(Lerebours et al., 2013)
miR-10, -34a, -155	Prognosis	Serum	The increase expression of these miRNAs associated with tumor progression and metastasis in patients of BC	(Roth et al., 2010)
miR-18b, -103, -107, -652	Prognosis	Serum	These four miRNAs associated with negative outcome. Hence, all of these miRNAs can be used as a novel prognostic biomarker in patients with TNBC. Furthermore, the serum level of miRNAs closely linkage RFS and OS in TNBC.	(Sahlberg et al., 2014)
miR-16, -374a/b, -497	Prognosis	Tissue	These miRNAs identified as protective miRNAs that were associated DDFS in patients with TNBC.	(Cascione et al., 2013)

(Continues)

TABLE 2 (Continued)

miRNAs	Type of biomarker	Biological sample	Clinicopathologic features/role in diagnosis and prognosis	Reference
miR-376b, -409-5p, -410, -193-3p, -432, -381,	Prognosis	Tissue	MiR-193a, -409-5p and -410 associated with unfavorable prognosis in TNBC. Furthermore, miR-376b and -381 correlated with worse prognosis in ER-negative/TNBC. Besides, only mir-432 had a closely relationship with DMFS in ER-negative of patients with BC.	(de Rinaldis et al., 2013)
miR-21, -181a, -221/222 cluster	Prognosis	Tissue/cell line	The high expression of miR-21, -181a, -221/222 cluster associated with LNM, advanced tumor stage and also unfavorable prognosis in patients with BC.	(Yan et al., 2008; Kaiyuan Zhang, Zhang, Liu, Xiong, & Zhang, 2014)
miR-601, -34b	Prognosis	Tissue	The low-expression of miR-601 associated with distant metastasis and poor DMFS in BC. The miR-34b expression correlated with DFS and OS of patients with TNBC.	(Svoboda et al., 2012)
miR-146, -638, -301a	Prognosis	Tissue	The overexpression of miR-146, -638 closely associated with better OS in TNBC. Moreover, the upregulation of miR-301a correlated with poor prognosis in TNBC.	(Yu et al., 2014; Zavala et al., 2016)

Abbreviations: AUC, area under the ROC curve; BC, breast cancer; DDFS, distant disease-free survival; DMFS, distal metastasis-free survival; ER, estrogen receptor; LNM, lymph node metastasis; miRNA, microRNA; MFS, metastasis-free survival; OS, overall survival; PR, progesterone receptor; RFS, relapse free-survival; ROC, receiver operating characteristic; TNBC, triple-negative breast cancer; TNM, tumor node metastasis.

4.1 | Five-microRNAs as new biomarkers in breast tumor prognosis

The miRNA expression is linked in clinical characteristics and prognosis in different types of breast tumor (Table 3). Briefly, here we point on the specific miRNAs roles in breast cancer prognosis. Several studies reported that specific miRNAs correlated with the favorable prognosis (Leivonen et al., 2014; Tashkandi, Shah, Patel, & Chen, 2015). Mir-30 family has been shown that could be considered as a good prognostic marker in many studies. D'Aiuto found the expression of miR-30e in specific-subtype of the tumor was linked to a good prognosis (Buffa et al., 2011). In another study it has been found that miR-30a downregulated in primary breast tumor relative to the noncancerous tissues. Furthermore, the miRNA was conversely linked in lung metastasis in the population of breast tumor patients. MiR-30a repressed proliferation and metastasis by affecting metadherin (MTDH). As a result, overexpression of mir-30 family was linked to a favorable prognosis in breast tumor (Zhang et al., 2014). Let-7b and miR-205 have been confirmed to be linked with prognosis in breast tumor. Moreover, recently a study showed expression of let-7b was higher in benign breast disease relative to breast cancer samples. In addition, its expression in breast tumor patients was conversely correlated with overall survival (OS) and relapse free-survival (RFS). Therefore, dysregulation of these two miRNAs are capable to used biomarkers in the patients. Ma et al. (2017) in a cohort study demonstrated several miRNAs that are linked to RFS. They revealed that mir-135 in ER-negative patients, and mir-342 and mir-150 was notability correlated with favorable prognosis in ER-positive breast tumor patients (Buffa et al., 2011). Mir-375 and mir-497 are tumor-suppressive miRNAs that can be regarded as a prognostic marker in this tumor (Shen et al., 2012; van Schooneveld et al., 2015). Hence, a study showed mir-497 downregulated in breast tumor tissues relative to noncancerous tissues. Furthermore patients with increased miR-497 displayed better disease-free survival (DFS) and OS relative to the low-expression cases of it, and also decreasing of miR-497 was remarkably linked to shorter OS and DFS in breast cancer (Wang, Li, Wang, & Wang, 2013). Additionally, Xiwei Wu et al analyzed approximately 800 miRNAs in serum of 42 Stage II and III patients with breast tumor. In their report higher levels of mir-375 reflect more positive clinical outcome (Wu, Somlo et al., 2012). Many studies showed that specific miRNAs are unfavorable prognostic biomarkers in this malignancy (Blenkiron et al., 2007; Madhavan et al., 2012; Yu et al., 2014). Another study pointed that overexpression of the microRNA was linked in shorter DFI in the TNBC and HER2-negative subtypes of breast cancer (Markou, Yousef, Stathopoulos, Georgoulias, & Lianidou, 2014). Tatsuya Toyama et al. showed in TNBC patients, expression of mir-210 was increased relative to estrogen receptor-positive/HER2-negative patients, and also they reported that its low-expression significantly related to favorable DFS and OS than those have higher miR-210 expression in TNBC (Toyama et al., 2012). Meanwhile, according to results of two meta-analysis study and other evidence mir-210 may be a prognostic biomarker in particular subtype of breast tumor (M. Li et al., 2014; Wang et al., 2014). Florence Lerebours et al analyzed

TABLE 3 List of miRNAs with potential prognostic biomarker in breast cancer

LncRNA	Expression in breast cancer	Type of sample	Clinicopathologic features/role in diagnosis and prognosis	References
ANRIL, SOX2OT, PTPRG-AS1, ANRASSF1,	Upregulated	Tissue	Potential biomarkers for breast cancer diagnosis. ANRASSF1 expression associated with Her2/neu status. ANRIL and ANRASSF1 expressions were higher in TNBC.	(Iranpour et al., 2016)
α-HIF	Upregulated	Tissue/cell line	Associated with poor DFS prognosis in breast cancer.	(Cayre, Rossignol, Clottes, & Penault-Llorca, 2003; Gutschner & Diederichs, 2012)
BC040587	Downregulated	Tissue/cell line	Expression of BC040587 was associated with tumor differentiation and menopausal status. Moreover, the expression level of BC040587 was significantly correlated with unfavorable prognosis and it was revealed as a prognostic biomarker breast cancer.	(Chi et al., 2014)
BC200	Upregulated	Tissue	The expression of BC200 in ER positive is higher than ER-negative tumors. BC200 expression may be as a molecular tool in the diagnosis and prognosis biomarker of breast cancer.	(Iacoangeli et al., 2004; Singh et al., 2016)
CCAT1	Upregulated	Tissue	The overexpression of CCAT1 was correlated with TNM stage, lymph node metastasis and differentiation grade. The upregulation of CCAT1 associated with OS and progression-free survival. Therefore, it has a potential prognostic biomarker in breast cancer patients.	(Zhang, Liu, Li, & Li, 2015)
CCAT2	Upregulated	Tissue/cell line	*CCAT2* is not a certain prognostic biomarker for breast cancer progression, but for LNP, CMF treated patients, the expression of *CCAT2* may predict poor survival and metastasis.	(Redis et al., 2013)
EFNA3	Upregulated	Tissue	*EFNA3* is induced by HIF in human tumors and this induction is predictive of unfavorable prognosis and elevated risk of metastasis. Furthermore, overexpression of *EFNA3* has a robust correlation with shorter MFS in breast cancer patients.	(Gómez-Maldonado et al., 2015)
EGOT	Downregulated	Tissue	Expression changes of EGOT associated with malignant status as well as the unfavorable prognosis for OS in breast cancer. Low-expression of EGOT has the strong correlation with lymph node metastasis, tumor size and Ki-67 expression.	(Xu et al., 2015)
EPB41L4A-AS2	Downregulated	Cell line	The Overexpression of EPB41L4A-AS2 inhibits tumor cell growth in breast cancer and also is correlated with favorable prognosis in breast cancer. Meanwhile, it can be used as a prognostic biomarker in breast cancer patients.	(Xu et al., 2016)
FGF14-AS2	Downregulated	Tissue	It Has been reported that can be regarded as a prognostic biomarker in breast cancer, and was associated with worse prognosis survival in breast cancer.	(Yang et al., 2016)
GAS5	Downregulated	Blood/tissue	The plasma level of GAS5 changes with surgery. The circulating GAS5 suggests had the potential to assess the preoperative condition of breast cancer patients, as well as it has the potential as a prognostic and diagnostic biomarker in breast cancer patients.	(Han, Ma, Liu, & Zhou, 2016)

(Continues)

TABLE 3 (Continued)

LncRNA	Expression in breast cancer	Type of sample	Clinicopathologic features/role in diagnosis and prognosis	References
H19 KCNQ1OT1 HOTAIR	Upregulated	Blood/tissue/ cell line	These lncRNAs were overexpressed significantly in IBC and DCIS relative to normal tissue. Furthermore, these lncRNAs implicated in breast tumorigenesis. Moreover, upregulation of HOTAIR has been indicated in ER-positive and TNBC. Besides, these three lncRNAs can be considered as a biomarker for diagnosis of breast cancer.	(Tao, He, & Chen, 2015; Zhang et al., 2015)
IRAIN	Downregulated	Tissue	It can be used as a novel prognostic biomarker in breast cancer.	(Kang et al., 2015)
LINC00617	Upregulated	Tissue/cell line	It Promotes migration and invasion of breast cancer cells and induces EMT. The overexpression of Linc00617 was significantly correlated with advanced tumor grade and lymph node metastasis. Furthermore, it may serve as a prognostic factor in breast cancer.	(Li et al., 2017)
linc-ITGB1	Upregulated	Tissue/cell line	Involved in the promotion of cell proliferation and metastasis in breast cancer tumorigenesis. It can be used as a novel diagnostic biomarker in breast cancer patients.	(Yan et al., 2017)
lincRNA-BC2, lincRNA-BC5	Upregulated	Tissue	The Expression level of lincRNA-BC2significantly correlated with LNM, but lincRNA-BC5 expression was significantly higher in grade III. These two lncRNAs have been reported as biomarkers for diagnosis of breast cancer.	(Amorim, Salta, Henrique, & Jerónimo, 2016)
lincRNA-BC8, lincRNA-BC4	Downregulated	Tissue	LincRNA-BC8 was inversely associated with progesterone receptor expression. Meanwhile, the expression status of lincRNA-BC4 was significantly lower in grade III of breast cancer. These two lncRNAs have been reported as two biomarkers for diagnosis of breast cancer	(Ding et al., 2014)
LINC00628	Downregulated	Tissue/cell line	Downregulation of LINC00628 has an unfavorable prognosis and lower OS rate, and associated with LNM. It is a potential biomarker for prognosis of breast cancer.	(Chen et al., 2017)
TUG1	Upregulated	Tissue/cell line	The overexpression of TUG1 was associated with distant metastasis, tumor size, and TNM staging. It can be regarded as a diagnostic marker in breast cancer patients.	(Li, Liu, Xiao, & Xu, 2017)
AK058803	Dysregulated	Tissue/cell line	The expression of AK058003 increased in the breast cancer tissue, especially in cases that had lymph node metastasis. Furthermore, it plays a regulatory role in proliferation, invasion and metastasis by regulating SNCG expression. Therefore, it can be regarded as a diagnostic and prognostic biomarker in breast cancer patients.	(He & Wang, 2015)
LOC554202	Dysregulated	Tissue/cell line	LOC554202 associated with tumor size and pathological stage. Moreover, it may be as a novel biomarker for breast cancer diagnosis.	(Shi et al., 2014)
MALAT1	Dysregulated	Tissue/cell line	The downregulation of MALAT1 may serve as a prognostic factor in breast cancer.as well as low-expression of MALAT1 was correlated with the unfavorable prognosis in breast cancer patients. In TNBC, MALAT1 was	(Jin, Lu, Lin, & Ma, 2016; S. Xu et al., 2015)

(Continues)

TABLE 3 (Continued)

LncRNA	Expression in breast cancer	Type of sample	Clinicopathologic features/role in diagnosis and prognosis	References
			upregulated and Patients with the overexpression of MALAT1 had worse OS time than those with low-expression of it.	
MEG3	Downregulated	Tissue	The overexpression of MEG3 was significantly correlated with the TNM stage, LNM, and molecular subtypes. Furthermore, patients with lower expression of lncRNA MEG3 had poor OS, and RFS rates.it can be a novel diagnostic and prognostic biomarker in breast cancer.	(Shi, Xia, Yin, Qi, & Xing, 2016)
snaR	Upregulated	Cell line	It plays an important role in progression of HER2-positive breast cancer cell. Furthermore, it may be as a candidate for diagnostic biomarker in HER2-positive breast cancer patients.	(Lee et al., 2017)
MVIH	Upregulated	Tissue/cell line	The overexpression of MVIH was associated with Ki67 expression. Furthermore, patients with high expression levels of MVIH indicated the unfavorable OS and DFS.	(Lei et al., 2016)
RP11–445H22.4	Upregulated	Tissue	It associated with ER, PR and menopausal status of the breast cancer patients. Meanwhile, the circulating blood levels of it can be considered as a biomarker for diagnosis in breast cancer patients.	(Xu et al., 2015)
HULC	Upregulated	Tissue/cell line	The overexpressed in TNBC and associated with malignant status and as well as unfavorable prognosis in patients with TNBC.	(Shi, Xiao, Ding, Qin, & Huang, 2016)
SPRY4-IT1	Upregulated	Tissue/cell line	The high expression of SPRY4-IT1 was correlated with a larger tumor size as well as, an advanced tumor stage in breast cancer patients.it can be used as a new biomarker for prognosis of breast cancer.	(Shi et al., 2015)
UCA1	Upregulated	Tissue/cell line	It may serve as a potential biomarker for the detection of breast cancer patients from healthy subjects.(as a diagnostic factor)	(Xue, Chen, & Li, 2016)
Z38	Upregulated	Cell line	The expression changes of Z38 may be a novel biomarker for the early diagnosis of breast cancer tumor	(Deng et al., 2016)

Abbreviations: DCIS, ductal carcinoma in situ; DFS, disease free-survival; ER, estrogen receptor; IBC, inflammatory breast cancer; lncRNA, long noncoding RNA; LNM, lymph node metastasis; miRNA, microRNA; OS, overall survival; RFS, relapse free-survival; TNBC, triple-negative breast cancer; TNM, tumor node metastasis.

expression of 804 miRNAs in 12 inflammatory breast tumor compared with 31 non-IBC and eight healthy samples. Many studies confirmed that mir-9, mir-155, mir-122, and mir-27b are miRNAs that were linked in unfavorable prognosis in breast cancer (Kong et al., 2014; Shen et al., 2014; Wu, Somlo et al., 2012; Zhou et al., 2012). Mir-9 has a function in breast tumorogenesis. In a study, it is reported that upregulation of miR-9 was linked in breast tumor local recurrence of ER-positive patients. Alao, it is reported patients with lower expression of miR-9 had favorable local recurrence-free survival (Zhou et al., 2012). upregulation of miR-155 was significantly related in unfavorable prognosis in breast tumor patients (Chen, Wang, & Tang, 2012). Several microRNAs can be as prognostic factors in subtypes of breast tumor. Marie Tuomarila and colleagues demonstrated that over-expression and under-expression of mir-200c were importantly related with reduced survival in progesterone-negative and reduced survival in PR-positive patients, respectively. In addition, they reported that in PR-negative groups, overexpression of this miRNA was associated with shorter RFS, and also increased local recurrence (Tuomarila et al., 2014). Another research reported that expression changes of mir-222 are linked in tumor stage, high Ki-67, and HER2. Mir-222 expression level was linked in HER2+ subtypes and luminal B relative to TNBC and luminal A. So, overexpression of miR-222 had an unfavorable prognosis only in the hormone receptor-positive subtype (Han et al., 2017). In TNBC mir-301a and mir-34b were significantly linked in prognosis. Marek Svoboda et al. analyzed expression levels of mir-34 family in 39 tissue sample of TNBC patients. In their study expression levels of mir-34b conversely linked in DFS and OS (Svoboda et al., 2012). Moreover, another study indicated that overexpression of miR-301a was remarkably linked in unfavorable prognosis (Yu et al., 2014). Zavala et al. illustrated miR-146a and miR-638 were overexpressed TNBC. Furthermore, expression of both miRNAs in this patients is linked in BRCA1 expression and overexpression of miR-146a and miR-638 was linked in a favorable OS relative to the group with normal BRCA1 and low-expression of both miRNAs (Zavala, Pérez-Moreno, Tapia, Camus, & Carvallo, 2016). Accumulating evidence suggest that detecting breast cancer in early-stage involved in favorable disease outcome as well as prolonged patient survival. Furthermore, new clinical investigations conducted on biological fluid-specific miRNAs, get to the conclusion that miRNAs are potential novel prognostic markers for various cancers, especially breast tumor.

5 | CONCLUSION

Breast cancer is affecting over 1.5 million women each year, and also is responsible for the large number of cancer-related deaths in women. In the disease, various alterations occur in the expression of coding and noncoding genes. Although many of protein-coding genes are effective in cancer progression and several mechanisms that alter the ability of the progression of cancer, the molecular determinants of cancer progression remain unknown. MiRNAs have provided new insight into cancer biology and offer new opportunity as tools for diagnosis and prognosis when there is a correlation between their expression and promotion of cancers. It has been shown that there is a significant relationship between signaling pathways involved in breast tumor including TGF-β, Wnt/β-catenin, PI3K/Akt/mTOR, Notch, NF-κB, ERK/MAPK pathways, and miRNA.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

M. A., V. R., N. T., F. J., and S. S. prepared the writing and drafting. H. S., M. B., and S. E. colected the data. T. Y., A. K., and M. Y. completed the review and editing. A. G. and A. M. completed the revision and M. N. and M. E. prepared the figures and tables, M. M. and A. S. supervised the data. B. Y. critically revised the data.

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