Received: 25 December 2018 | Revised: 27 March 2019 | Accepted: 10 April 2019

DOI: 10.1002/jcp.28742

REVIEW ARTICLE

WILEY Journal of Cellular Physiology

The role of inflammation and its related microRNAs in breast cancer: A narrative review

Alireza Bahiraee[1] | Reyhane Ebrahimi[2] | Raheleh Halabian[1] | Amirsaeed Sabeti Aghabozorgi[3] | Jafar Amani[1]

[1]Applied Microbiology Research Center, Systems Biology and Poisonings Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran

[2]Department of Clinical Biochemistry, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

[3]Department of Medical Genetics, Faculty of Medicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran

Correspondence
Jafar Amani, Applied Microbiology Research Center, Systems Biology and Poisonings Institute, Baqiyatallah University of Medical Sciences, Vanak Sq., Molasadra St. Tehran P.O. Box 19395-5487, Iran.
Email: jafar.amani@gmail.com

Abstract

Breast cancer is recognized as the most common type of cancer among women with a high rate of mortality all over the world. Over the past years, growing attention has been regarded to realize more about the mechanisms underlying the disease process. It is revealed that the progression of breast cancer may be strongly linked to chronic inflammation owing to the role of inflammatory factors in genetic instability and subsequent cancer predisposition. Although the association between breast cancer and inflammatory pathways has been well-defined now, only recent evidence pointed towards the inflammation-related microRNAs (miRNAs) as potential biomarkers and therapeutic targets involved in the crosstalk of multiple pathways during breast cancer development. Moreover, the practical interactions between these miRNAs and inflammatory factors are also a little characterized. In this review, we intended to describe the effects of predominant inflammatory pathways such as cytokines, phosphoinositide 3-kinase/protein kinase B, and nuclear factor kappa B in association with tumor promoting and tumor suppressing miRNAs on breast cancer progression. Providing new studies in the field of combining biomarkers for early diagnosis, prognosis, and monitoring breast cancer are very important. Notably, understanding the underlying mechanisms of miRNAs as a possible link between inflammation and tumorigenesis may offer a novel insight for combating this epidemic.

KEYWORDS

breast cancer, cytokines, inflammation, microRNA, nuclear factor kappa B

1 | INTRODUCTION

Breast cancer with a growing rise in both developed and developing countries triggers a large rate of mortality as the second leading cause of death among women worldwide. This epidemic is growing rapidly so that it is replacing cardiovascular diseases as the first cause of death (Patnaik, Byers, DiGuiseppi, Dabelea, & Denberg, 2011). Although the early diagnosis may reduce the death rates due to breast cancer, prevention and control of this disease are still a public concern. There are different factors interfering with processes involved in breast cancer development and considering them may give a noble insight for improving outcomes that breast cancer patients receive (Shah, Rosso, & Nathanson, 2014).

Abbreviations: 3′-UTR, 3′-untranslated region; 53BP1, p53-binding protein-1; Bcl-xL, B-cell lymphoma-extra large; EMT, epithelial–mesenchymal transition; IKK, IκBα kinase; IL, interleukin; IκBα, NF-κB inhibitor α; JAK, Janus kinase; miRNA, microRNA; NF-κB, nuclear factor kappa B; PI3K, phosphoinositide 3-kinase; PIP3, phosphatidyl-inositol,3,4,5 triphosphate; PKB/Akt, protein kinase B; PTEN, phosphatase and tensin homolog; RelA, v-rel avian reticuloendotheliosis viral oncogene homolog A; RIP, receptor interacting protein; SOCS, suppressor of cytokine signaling; STAT3, signal transducer and activator of transcription 3; TAK1, transforming growth factor β-activated kinase 1; TGF-β, transforming growth factor-β; TNBC, triple-negative breast cancer; TNF-α, tumor necrosis factor-α; TNFR, tumor necrosis factor receptor; TRADD, TNFR1-associated death domain protein; TRAF, TNF receptor-associated factor.

It is revealed that tumorigenic signaling pathways are not sufficient for a complete breast tumor progression, suggesting the contribution of supportive signals mostly produced from the tumor inflammatory microenvironment. Innate and acquired immune systems are important mechanisms playing a critical role in the responses to tumorigenesis, and the effect of the immune system and inflammatory factors on tumor cells especially breast cancer cells has been the subject of many studies nowadays. Inflammation is a response of the immune system to external or internal stimuli that removes the aggressor and restores the physiology of the body. However, in pathological states, chronic inflammation may be a major driver of consequent diseases (Ben-Baruch, 2003). It is known that one of the main problems of breast cancer as well as other types of cancer is that primary breast tumor cells can attack to surrounding tissues and progress cancer in the other parts of the body which is known as metastasis (Scully, Bay, Yip, & Yu, 2012). Inflammation is an important cause of cancer development and also metastasis progression. Inflammatory factors along with their receptors are involved in the development of breast cancer in various aspects, including promoting cell proliferation, differentiation, tumor metastasis, angiogenesis, and fine-tuning the inflammatory microenvironment in the involved tissue (Allen & Jones, 2015). Aaltomaa et al. (1992) defined inflammatory infiltrate as a prognostic marker in breast cancer for the first time. Because that, there are numerous studies revealed the role of different inflammatory pathways in preinvasive and invasive breast cancer (Allen & Jones, 2015). Despite many progressions in the field of breast cancer related to inflammation, the underlying mechanisms of this malignancy have remained largely unknown and need to be fully understood. Although inflammatory pathways are one of the known processes contributing to cancer progression, there is also a need for the contribution of specific genetic and epigenetic modifications to lead a benign tumor to become malignant. One of these epigenetic modifications are microRNA (miRNA or miR) molecules which regulate many cancer development pathways (You & Jones, 2012). In this review, we will discuss the involvement of main inflammatory pathways and miRNAs in breast cancer progression, which may help us to understand about the etiology of breast cancer, as well as to improve the early diagnosis and treatment of this epidemic.

2 | CYTOKINES

Lymphocytes and macrophages secrete different cytokines with several common structural and functional features. Cytokines are biologically active at extremely low concentrations and can change the activity of their target cells by binding to the cell surface receptors. Moreover, their function may be additive, synergistic or antagonistic. Various cytokines such as tumor necrosis factor-α (TNF-α), transforming growth factor-β (TGF-β), and interleukins (ILs) like IL-6 play an important role in regulating the immune system and are overexpressed under pathological conditions. These cytokines are recognized as key factors in breast cancer development and metastasis through regulating the inflammatory tumor microenvironment (Kishimoto, Taga, & Akira, 1994).

2.1 | Tumor necrosis factor-α

TNF-α as a multifunctional cytokine contributes to different cancers development. There are two types of receptors for TNF-α biological activity, tumor necrosis factor receptor 1 (TNFR1) and TNFR2 (D. Liu, Wang, & Chen, 2016). TNF-α binds to TNFR1 and promotes the sequential recruitment of the proteins TNFR1-associated death domain protein (TRADD), receptor interacting protein (RIP), and TNFR-associated factor 2 (TRAF2) to the membrane as illustrated in Figure 1. Next, TRAF2 triggers the activation of IκBα kinase (IKK) and subsequent nuclear factor kappa B (NF-κB) through a transforming growth factor β-activated kinase 1 (TAK1)-dependent pathway (Shostak & Chariot, 2011). There is a controversy about the role of TNFR1 in controlling breast cancer. Some studies support its tumor-promoting role by activating the NF-κB signaling pathway (Rivas et al., 2008), whereas others support its tumor suppressive role by inducing breast cancer cells apoptosis (Smolnikar, Loffek, Schulz, Michna, & Diel, 2000). The participation of TNF-α in stimulating several signaling pathways connecting inflammation, cell growth, and survival to breast cancer has been revealed by several studies (D. Liu et al., 2016).

2.2 | Transforming growth factor-β

The pleiotropic cytokine TGF-β promotes metastasis in breast cancer. Under physiological conditions, the function of this cytokine is strongly controlled by a complex regulatory network. But when these inhibitory regulators are suppressed, TGF-β would be overactivated leading to tumor growth. It is known that during breast cancer progression, TGF-β becomes a key developer of epithelial–mesenchymal transition (EMT), invasion and metastasis (Barcellos-Hoff & Akhurst, 2009).

2.3 | IL-1, IL-8, IL-11, and IL-23

Several ILs are reported to control the inflammatory tumor microenvironment. IL-1, IL-8, IL-11, and IL-23 are important factors involved in tumor progression. They can affect inflammation, invasion, and metastasis in the tumor microenvironment to increase the potential of breast tumorigenesis. Moreover, higher levels of these ILs have been observed in breast cancer cells compared to normal cells and they all can be used as biomarkers predicting this type of cancer (Esquivel-Velázquez et al., 2015).

2.4 | IL-6/signal transducer and activator of transcription 3 signaling pathway

Among different ILs, IL-6 is one of the most studied and effective factors playing a role as a double-edged sword in the pathogenesis of breast cancer. IL-6 is a pleiotropic cytokine regulating

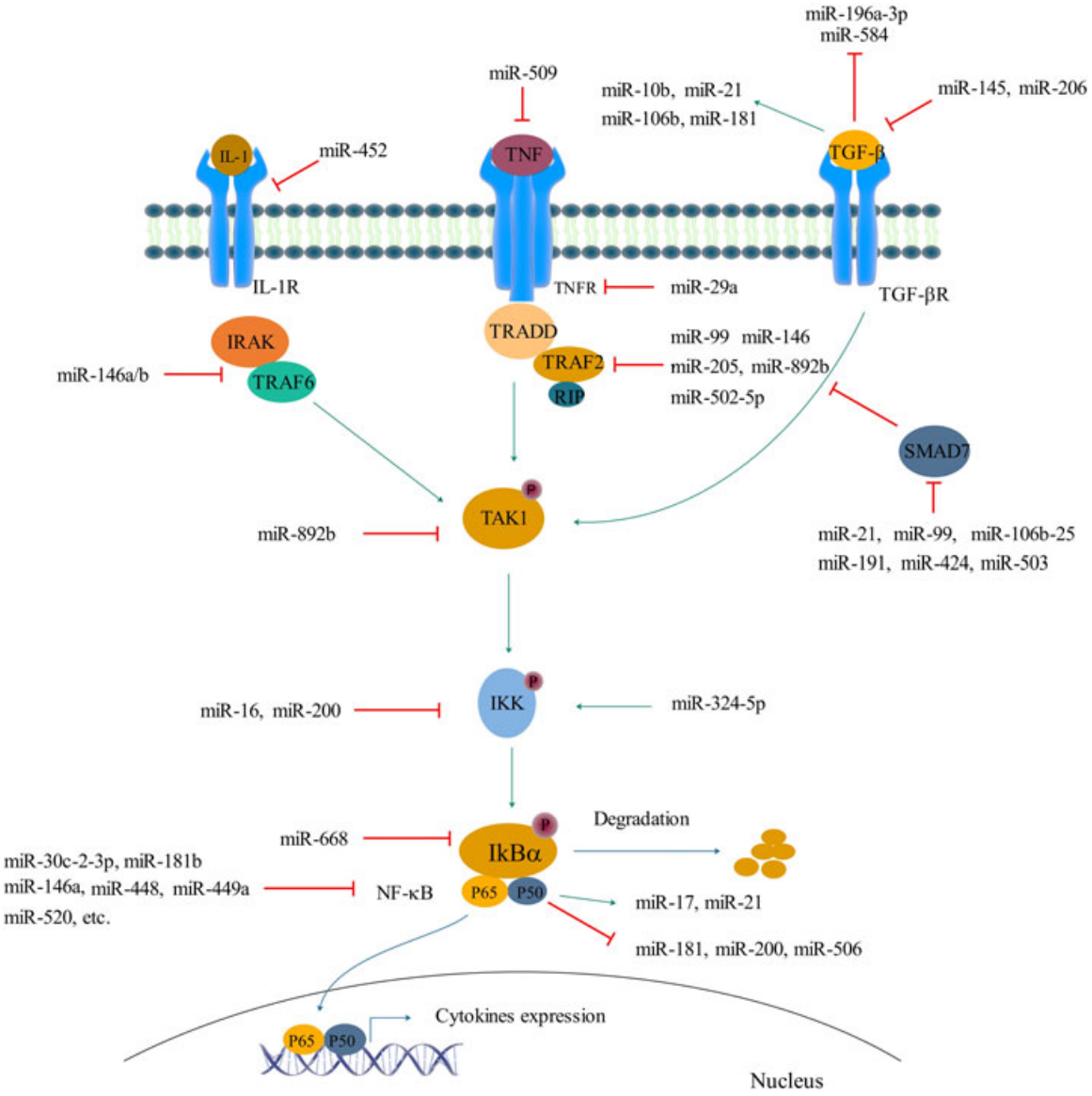

FIGURE 1 A schematic representation of different cytokines signaling pathways leading to the activation of IKK/NF-κB signaling pathway along with all inflammation-related miRNAs which may regulate or be regulated by these factors and play significant roles in breast cancer development. IKK: IκBα kinase; IL: interleukin; IRAK: IL-1 receptor-associated kinase; miRNA: microRNA; NF-κB: nuclear factor kappa B; RIP: receptor interacting protein; SMAD: suppressor of mothers against decapentaplegic; TAK: transforming growth factor β-activated kinase; TGF-β: transforming growth factor-β; TNF: tumor necrosis factor; TNFR: tumor necrosis factor receptor; TRAF: TNF receptor-associated factor; TRADD: TNFR1-associated death domain protein [Color figure can be viewed at wileyonlinelibrary.com]

multiple biological activities. Over the past years, opposing functions of IL-6 have been revealed and both tumorigenic and antitumorigenic effects of IL-6 have been reported in experiments related to breast cancer (Knupfer & Preiss, 2007). IL-6 may inhibit apoptosis through increasing the expression of antiapoptotic proteins including B-cell lymphoma-extra large (Bcl-xL) and Bcl-2 and then, may trigger cell survival through signal transducer and activator of transcription 3 (STAT3)-dependent pathway (Leu, Wong, Chang, Huang, & Hu, 2003). Hence, it seems that a higher expression of IL-6 is involved in resistance to chemotherapy (Conze et al., 2001). IL-6 also plays a critical role in metastasis through decreasing E-cadherin expression and breast cell adhesion (Asgeirsson, Olafsdottir, Jonasson, & Ogmundsdottir, 1998). IL-6 overexpression induces the Janus kinase (JAK)/STAT3 signaling pathway, which causes the translocation of phospho-STAT3 into the nucleus and transactivation of proteins-mediated proliferation, differentiation, and survival. STAT3 is a member of the STAT protein family and is an imperative molecule for supporting pluripotency in embryonic stem cells. Hyperactivation of STAT3 has been observed in many types of cancer. Then, it can be regarded as a target for the treatment of tumor cells. IL-6 also has a positive feedback loop with NF-κB through a mechanism by that suggests STAT3 activation (Johnson, O'Keefe, & Grandis, 2018) as shown in Figure 2.

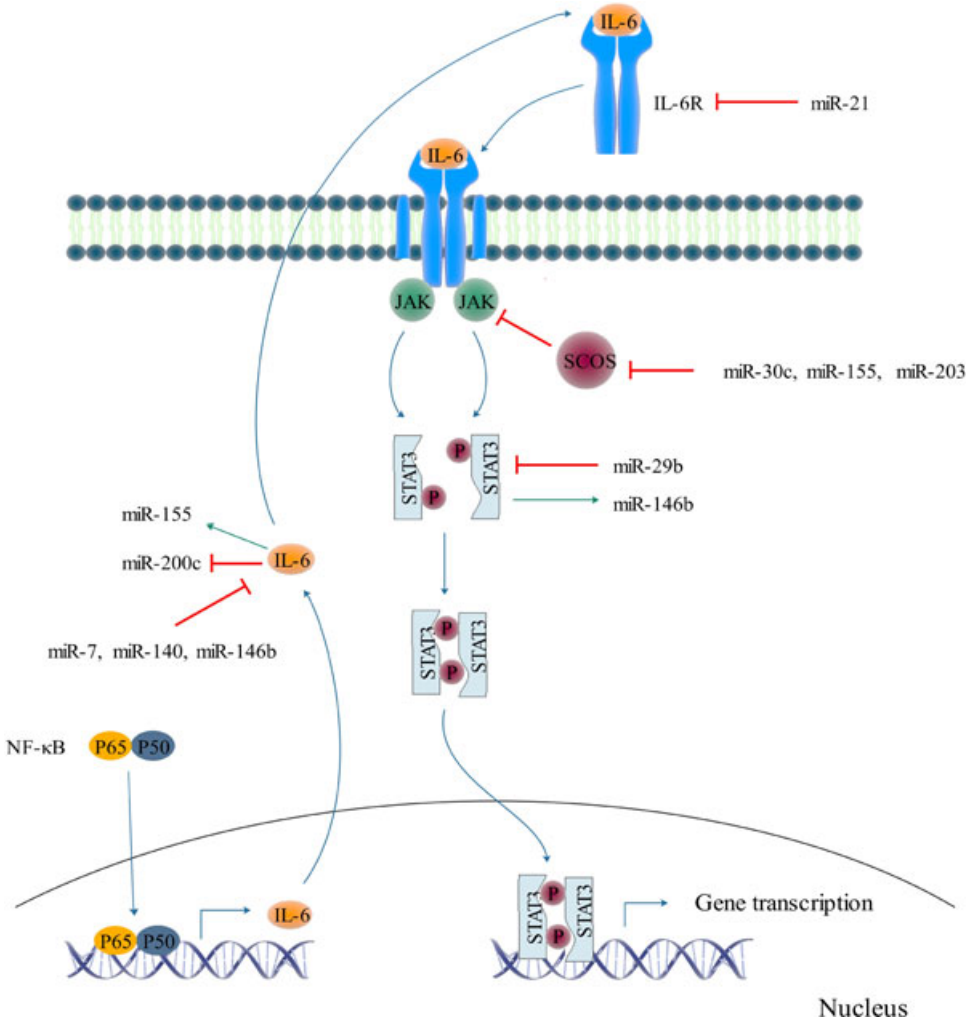

FIGURE 2 A schematic overview of the involved tumorigenic and antitumorigenic miRNAs in the IL-6/STAT3 signaling pathway with a probable occurrence in breast cancer cells. IL: interleukin; JAK: Janus kinase; miRNA: microRNA; NF-κB: nuclear factor kappa B; SCOS: suppressor of cytokine signaling; STAT3: signal transducer and activator of transcription 3 [Color figure can be viewed at wileyonlinelibrary.com]

Cytokines activating the JAK-STAT signaling pathway are negatively regulated by suppressor of cytokine signaling (SOCS) proteins particularly, SOCS1 and SOCS3. These proteins are effective suppressors of JAKs and play important roles in inflammation, as well as tumorigenesis (Inagaki-Ohara, Kondo, Ito, & Yoshimura, 2013). A lower expression of SOCS1–3 was detected in less than 50% of breast cancer cases. This may result from genetic or epigenetic changes of SOCS1–3 including the promoter hypermethylation. Indeed, Sutherland et al. observed higher methylation of SOCS1 promoter in 9% of the studied breast tumor samples. This may lead to the activation of the JAK-STAT signaling pathway and stimulation of cell proliferation and tumorigenesis (Sutherland et al., 2004).

Previous studies emphasized the antitumorigenic properties of the proteins involved in the IL-6/STAT3 signaling pathway in breast cancer. IL-6 along with STAT3 may create the inflammatory mechanism underlying cancer progression (Barclay, Anderson, Waters, & Curlewis, 2009). There are several reported miRNAs now that have been indicated in the IL-6/STAT3 signaling pathway and we will describe them later.

2.5 | Phosphatase and tensin homolog/ phosphoinositide 3-kinase/protein kinase B signaling pathway

Phosphatase and tensin homolog (PTEN)/phosphoinositide 3-kinase (PI3K)/protein kinase B (PKB/Akt) signaling pathway plays an important role in controlling multiple biological processes like cell growth, proliferation, differentiation, and apoptosis. This pathway is recognized as the main survival cascade activated in cancer. PTEN is a multifunctional tumor suppressor deleted on chromosome 10 in many types of cancer including breast tumors. The substrate of PTEN is the product of PI3K, means phosphatidyl-inositol,3,4,5 triphosphate (PIP3). Then, this phosphatase opposes the activity of PI3K. The lipid PIP3 triggers the recruitment of Akt to the cell membrane

where it is stimulated by other kinases also induced by PIP3. The serine/threonine kinase Akt phosphorylates many proteins related to mentioned biological processes. Mammalian target of rapamycin (mTOR) can be stimulated indirectly by AKT in response to stress, growth factors, or DNA damage. After activation, mTOR can affect many cellular processes including cell proliferation and growth. Previous studies reported that mTOR may also have a critical role in the regulation of metastasis. Importantly, the overexpression of mTOR contributes to the development of many cancers including breast cancer (Hare & Harvey, 2017). Remarkably, one of the most important factors activated by Akt is NF-κB through phosphorylation and consequent degradation of its inhibitor, NF-κB inhibitor α (IκBα). As it is known, NF-κB activation is crucial for PI3K/Akt-induced tumorigenesis. Moreover, any component of this pathway may undergo modifications like mutation, deletion or promoter methylation which prepare them to induce tumorigenic properties in various cells. The loss of PTEN activity and hyperactivity of PI3K and Akt are reported in triggering breast cancer (Georgescu, 2010). Hence, studies considering the PTEN/PI3K/Akt pathway and their regulatory molecules as important targets for breast cancer progression are required.

2.6 | IKK/NF-κB signaling pathway

NF-κB is a well-known proinflammatory transcription factor that controls various significant biological and pathological processes, such as the development of invasive breast cancer cells. The NF-κB family contains five subunits which are p65 (RelA), RelB, c-Rel, p105/p50 (NF-κB1), and p100/p52 (NF-κB2). The first three mentioned proteins are produced as mature and active proteins and have the transactivation domains, while two latter ones are synthesized as inactive proteins and lack the transactivation domains. Homo- or heterodimerization of these subunits create the NF-κB complex (Shih, Tsui, Caldwell, & Hoffmann, 2011; Shostak & Chariot, 2011).

NF-κB is activated by two recognized pathways, named classical or canonical and alternative or noncanonical pathways. The activation of these pathways is both depended on phosphorylation and degradation of an inhibitory molecule and consequent releasing of NF-κB to translocate into the nucleus and induce target genes such as IL-6. However, they are different in the factors inducing them and also the identity of their mediated downstream proteins. The canonical pathway is usually produced by exogenous ligands or cytokines including TNF-α and IL-1. These inflammatory cytokines activate IKK through a cascade depending on TNFR1, TRADD, TRAF2, RIP, and TAK1 proteins and cause to the phosphorylation and degradation of IκBα as an inhibitory molecule of NF-κB. Then, activated NF-κB having RelA-p50 heterodimer translocates into the nucleus. The noncanonical pathway triggers the stimulation of RelB-p52 heterodimer derived from RelB-p100 through TRAF2/NF-κB inducing kinase-dependent pathway, which leads to the translocation of this dimer into the nucleus. Next, NF-κB induces the gene expression related to cell proliferation, inflammation, and innate immunity (Shostak & Chariot, 2011; Tegowski & Baldwin, 2018).

There are different regulators affecting the strength and duration of NF-κB signaling pathway under biological and pathological conditions. As mentioned above, several signaling pathways including TNF-α, IL-1, and TGF-β appear with the NF-κB signaling pathway in developing a tumor. Dysregulation of NF-κB is a shared process in a variety of cancers and its expression is reported to be constitutively high in different breast cancer subtypes (Hoesel & Schmid, 2013; W. Wang, Nag, & Zhang, 2015). However, the exact mechanisms underlying the abnormal activation of NF-κB signaling pathway in breast cancer are not fully understood. There is growing evidence that many miRNAs may regulate or be regulated by the NF-κB signaling pathway and we will discuss them later.

3 | miRNAs AS A NOVEL CLASS OF MOLECULES LINKING BREAST CANCER AND INFLAMMATION

Posttranslational modifications are heritable changes in gene expression without directly altering the original DNA sequence. These modifications are natural processes which can undergo various factors and conditions including age, diet, inflammation, and disorders like cancer. The most important posttranslational modifications are methylation, acetylation, and noncoding RNAs (Goldberg, Allis, & Bernstein, 2007).

There are many protein-coding and noncoding RNAs with gene expression related to disease states. Among them, miRNAs are endogenous small noncoding molecules with a length of approximately 18–22 nucleotides that regulate a wide range of physiological and pathological processes including cell proliferation, differentiation, apoptosis, and tumorigenesis. These small modulatory RNAs are highly conserved and usually have a complementary site in their "seed" sequences which interacts with the 3′-untranslated region (3′-UTR) of target messenger RNA and leads to its inhibition. A large number of miRNAs have an abnormal expression in many kinds of diseases, including cancer (Lu et al., 2005). Today, because of the tumorigenic as well as antitumorigenic properties of miRNAs, their expression profile in cancer has become a new subject for investigation to reveal the connections between miRNAs and their target genes remarkably in breast cancer (Kanwal & Gupta, 2010). Although different cancers can show common abnormal miRNAs expression, cancer-specific miRNAs are the main molecules in determining the disease state. In general, miRNAs create multiple regulatory networks involving transcription factors with the aim of inducing or reducing inflammatory and tumorigenic processes (Schetter, Heegaard, & Harris, 2010). Alterations of miRNAs expression profile in breast cancer have been reviewed elsewhere (Hamam et al., 2017; Kaboli, Rahmat, Ismail, & Ling, 2015). But in this review, we will focus on the involvement of inflammation and its related miRNAs in breast cancer and describe their applications to clinical approaches, particularly their potential to be diagnostic biomarkers and therapeutic targets. Hence, we will emphasize the miRNAs involved in inflammatory and tumorigenic pathways in the next sections (also see the data summarized in Table 1).

TABLE 1 Dysregulated miRNAs regulating/regulated by inflammation in breast cancer

Pathway	miRNA	Regulating/regulated by	Expression pattern	References
Cytokines	*miR-509*	*TNF-α*	Down	Xing et al. (2015); G. Zhang, Liu, Han, Wang, and Yang (2016)
	miR-29a	*TNFR*	Down	Zhao et al. (2017)
	miR-10b	*TGF-β*	Up	X. Han et al. (2014)
	miR-21	*TGF-β*	Up	M. Han et al. (2016); Qian et al. (2009)
	miR-106b	*TGF-β*	Up	Gong et al. (2015); Smith et al. (2012)
	miR-181	*TGF-β*	Up	Neel and Lebrun (2013)
	miR-196a-3p	*TGF-β*	Down	Chen et al. (2017); Fils-Aimé et al. (2013)
	miR-584	*TGF-β*	Down	Chen et al. (2017); Fils-Aimé et al. (2013)
	miR-145	*TGF-β*	Down	Ding et al. (2017)
	miR-206	*TGF-β, IL-11*	Down	Samaeekia et al. (2016); Yin et al. (2016)
	miR-99	*TGF-β*	Up	Turcatel, Rubin, El-Hashash, and Warburton (2012)
	miR-191	*TGF-β*	Up	Nagpal et al. (2015)
	miR-424	*TGF-β*	Up	Y. Li et al. (2014)
	miR-503	*TGF-β*	Up	Y. Li et al. (2014)
	miR-452	*IL-1R/IL-1, IL-8*	Down	Abrahamsson et al. (2017)
	miR-17	*IL-8*	Down	Yu et al. (2010)
	miR-20	*IL-8*	Down	Yu et al. (2010)
	miR-124	*IL-11*	Down	Cai et al. (2018)
	miR-30c	*IL-11*	Down	Bockhorn et al. (2013)
IL-6/STAT3	*miR-21*	*IL-6R*	-	Khori et al. (2015); P. Li et al. (2016); W. Wang et al. (2018)
	miR-30c	*SOCS3*	Up	Yen et al. (2016)
	miR-155	*SOCS1, IL-6*	Up	S. Jiang et al. (2010); Kim et al. (2016); Lei et al. (2016)
	miR-203	*SOCS3*	Up	P. Li et al. (2016); Muhammad, Bhattacharya, Steele, and Ray (2016)
	miR-29b	*STAT3*	Down	Y. Liu, Zhang, Sun, Su, and You (2017)
	miR-146b	*STAT3, IL-6*	Down	Al-Ansari and Aboussekhra (2015); Xiang et al. (2014)
	miR-200c	*IL-6*	Down	Rokavec, Wu, and Luo (2012)
	miR-7	*RAF1*	Down	Hsiao et al. (2015)
PTEN/PI3K/Akt	*miR-590*	*PI3K*	Up	Sheikholeslami, Nabiuni, and Arefian (2017)
	miR-21	*PTEN*	Up	Khaidakov and Mehta (2012); Niu et al. (2012); X. Wang et al. (2017)
	miR-132	*PTEN*	Up	Xie et al. (2018)
	miR-212	*PTEN*	Up	Xie et al. (2018)
	miR-221	*PTEN*	Up	B. Li et al. (2017)
	miR-222	*PTEN*	Up	B. Li et al. (2017)
	miR-141	*Akt*	Up	Choi et al. (2016)
	miR-200	*Akt*	Up	Choi et al. (2016)
	miR-429	*Akt*	Up	Choi et al. (2016)
	miR-100	*mTOR*	Down	G. Zhang et al. (2016)
	miR-125b	*mTOR*	Down	Vilquin et al. (2015)
	miR-15	*mTOR*	Down	Janaki Ramaiah et al. (2014)
	miR-16	*mTOR*	Down	Janaki Ramaiah et al. (2014)
IKK/NF-κB	*miR-146*	*TRAF2, IRAK1, TRAF6, NF-κB*	Down	X. Li et al. (2012); Y. Li et al. (2015); R. Liu et al. (2015); Tanic, Zajac, Gómez-López, Benítez, and Martínez-Delgado (2012)

(Continues)

TABLE 1 (Continued)

Pathway	miRNA	Regulating/regulated by	Expression pattern	References
	miR-99	*TRAF2, NF-κB*	Down	Tanic et al. (2012); Turcatel et al. (2012)
	miR-205	*TRAF2*	Down	Tanic et al. (2012)
	miR-892b	*TRAF2, TAK1*	Down	L. Jiang et al. (2016)
	miR-502–5p	*TRAF2*	Down	L. -L. Sun et al. (2014)
	miR-16	*IKK*	Down	Tang et al. (2016)
	miR-200	*IKK, NF-κB*	Down	Y. Sun et al. (2018); Teng, Mei, Hawthorn, and Cowell (2014); H. Wu et al. (2016)
	miR-324–5p	*IKK*	Up	Song et al. (2015)
	miR-668	*IκBα*	Up	Luo, Ding, Li, and Yao (2017)
	miR-17	*NF-κB*	Up	Niu et al. (2012); Zhong et al. (2017)
	miR-21	*NF-κB*	Up	Niu et al. (2012); Zhong et al. (2017)
	miR-181	*NF-κB*	Down	L. Wang, Wang, Chen, and Ji (2016); Kastrati, Canestrari, and Frasor (2015)
	miR-506	*NF-κB*	Down	Arora et al. (2013)
	miR-448	*NF-κB*	Down	Mak et al. (2013)
	miR-30c	*NF-κB*	Down	Shukla et al. (2015)
	miR-520	*RelA*	Down	Keklikoglou et al. (2012)
	miR-373	*RelA*	Down	Keklikoglou et al. (2012)

Note. IL: interleukin; IRAK1: IL-1 receptor-associated kinase 1; IκBα: NF-κB inhibitor α; IKK: IκBα kinase; mTOR: mammalian target of rapamycin; miRNA: microRNA; NF-κB: nuclear factor kappa B; PI3K: phosphoinositide 3-kinase; PKB/Akt: protein kinase B; PTEN: phosphatase and tensin homolog; RAF1: rapidly accelerated fibrosarcoma 1; RelA: v-rel avian reticuloendotheliosis viral oncogene homolog A; SOCS: suppressor of cytokine signaling; STAT3: signal transducer and activator of transcription 3; TAK1: transforming growth factor β-activated kinase 1; TGF-β: transforming growth factor-β; TNF-α: tumor necrosis factor-α; TNFR: tumor necrosis factor receptor; TRAF: TNF receptor-associated factor.

4 | miRNAs AND CYTOKINES

Several mechanisms involving the posttranscriptional regulation of cytokines such as TNF-α, TGF-β, and ILs via miRNAs have been reported regarding their important roles in various pathological conditions. Interestingly, the link between miRNAs and these cytokines appears to reveal a complex relationship in breast cancer development (Asirvatham, Magner, & Tomasi, 2009).

4.1 | miRNAs and TNF-α

TNF-α as a highly expressed cytokine in breast cancer can be regulated by some miRNAs. A study identified miR-509 as a tumor suppressor with an inhibitory effect on brain metastasis in patients with primary breast cancer through regulating TNF-α which is involved in brain invasion (Xing et al., 2015). Moreover, the inhibitory effects of miR-509 on cell proliferation and invasion of triple-negative breast cancer (TNBC) cells were also reported by suppressing TNF-α levels. TNBC is more common among breast cancer subtypes with a higher risk of death. Considering these studies, a higher expression of miR-509 in primary breast cancer tumors may prevent metastasis through regulating TNF-α (G. Zhang et al., 2016). In addition, binding of miR-29a to the 3′-UTR of TNFR1 gene reduced cell proliferation and induced apoptosis in primary breast cancer samples and Michigan Cancer Foundation-7 (MCF-7) cells as a known human breast cancer cell line (Zhao et al., 2017).

4.2 | miRNAs and TGF-β

There are many miRNAs implicated in the TGF-β signaling pathway which can both regulate or be regulated by this cytokine. For instance, miR-10b (X. Han et al., 2014), miR-21 (Qian et al., 2009), miR-106b (Gong et al., 2015), and miR-181 (Neel & Lebrun, 2013) are represented as cell metastasis promoters for developing metastatic breast cancer and are regulated by TGF-β. In addition, other miRNAs involved in breast tumorigenesis are miR-21 (M. Han et al., 2016), mir-99 (Turcatel et al., 2012), miR-106b-25 (Smith et al., 2012), miR-191 (Nagpal et al., 2015), miR-424, and miR-503 (Y. Li et al., 2014), which activate the TGF-β signaling pathway through targeting and suppressing suppressor of mothers against decapentaplegic as an inhibitor of this cytokine. A higher expression of these miRNAs is also observed in metastatic compared to primary breast cancers which suggest their possible role in developing metastasis in peripheral tissues. Hence, these miRNAs may predict the development of metastatic breast cancer from primary tumor cells. miR-200c and miR-340 were also reported to have indirect feedback suppression

with the TGF-β signaling pathway (Bai et al., 2014; Hou et al., 2016). Moreover, two miRNAs, miR-145 (Ding et al., 2017) and miR-206 (Yin et al., 2016) were revealed to act as tumor suppressors by regulating TGF-β. Other studies also demonstrated that miR-196a-3p and miR-584 act as anticancer factors and are downregulated by TGF-β in breast cancer cells (Chen et al., 2017; Fils-Aimé et al., 2013). Decreased levels of these miRNAs were associated with metastatic breast cancer mediated by the prometastatic signaling pathway of TGF-β.

4.3 | miRNAs and IL-1, IL-8, IL-11, and IL-23

Recent studies suggest that miRNAs may have an important role in the ILs status related to breast cancer and then, may contribute to tumorigenesis. For example, a study showed that miR-452 was in a negative correlation with the IL-1R/IL-1 ratio and IL-8. Thus, its downregulation might increase the risk of developing breast cancer in postmenopausal women (Abrahamsson, Capodanno, Rzepecka, & Dabrosin, 2017). It was also reported that miR-17 and miR-20 inhibited some inflammatory cytokines including IL-8 through direct binding to the 3′-UTR, then controlled the invasion of neighboring cells in breast cancer (Yu et al., 2010). Another study revealed the inhibitory effect of miR-124 on bone metastases development through suppression of IL-11 in breast cancer (Cai et al., 2018). A lower expression of these miRNAs was connected to the development of metastatic breast cancer. Moreover, miR-30c as a known prognostic marker of breast cancer indirectly targeted IL-11 and then, reduced chemotherapy resistance in patients with primary breast cancer (Bockhorn et al., 2013). IL-11 was also characterized as an oncogenic target for miR-206 which triggered a decrease in the invasion of breast cancer cells (Samaeekia et al., 2016) and as mentioned before, a lower level of miR-206 was associated with a higher probability of metastatic breast tumor development. Remarkably, a binding site in the 3′-UTR of the IL-23 receptor gene was identified for miRNAs binding with a possible contribution to the progression of breast cancer (L. Wang et al., 2012). The inflammation-related miRNAs involved in the cytokines signaling pathways are presented in Figure 1.

4.4 | miRNAs and IL-6/STAT3 signaling pathway

Numerous individual miRNAs are identified as target proteins of the IL-6/STAT3 signaling pathway involved in the progression of breast cancer. miR-155 is revealed to be overexpressed in breast cancer type 1-deficient tumors (Kim et al., 2016). Importantly, a study showed the important role of miR-155 in promoting breast cancer by targeting SOCS1 as a tumor suppressor gene. Moreover, they stated that IL-6 would also stimulate miR-155 expression and consequent progression of breast cancer (S. Jiang et al., 2010). Another study on human breast cancer showed an inhibitory effect on the levels of IL-1, IL-6, and the JAK-STAT3 signaling pathway, using a novel photosensitizer named 3B which downregulated miR-155-5p (Lei et al., 2016). Therefore, these studies suggest the positive correlation between miR-155 expression and IL-6/STAT3 signaling pathway in primary breast cancer. There are other investigations performed in line with the cancerous effects of miRNAs. In a study, a sesquiterpenoids compound named isolinderalactone decreased miR-30c expression and then, caused to an increase in SOCS3 levels, a decrease in STAT3 phosphorylation, and an increase in TNBC cells apoptosis (Yen et al., 2016). The regulatory role of low miR-29b expression in promoting metastatic breast cancer by upregulation and activation of the STAT1 pathway has been illustrated too (Y. Liu et al., 2017).

Remarkably, a recent study stated the multiple antitumorigenic effects of endogenous kallistatin protein on the expression of different miRNAs including miR-21 and miR-203 in breast cancer cells which triggered a decrease in Akt phosphorylation along with an alteration in Bcl-2 expression and also an increase in SOCS3 expression (P. Li et al., 2016). Previous studies also demonstrated the direct inhibition of SOCS3 by miR-203 in MCF-7 cells (Muhammad et al., 2016). However, there is still a controversy about the role of miR-21 linked to IL-6 and STAT protein in breast cancer. For example, it was reported that miR-21 underwent the antitumorigenic effects of both interval exercise and tamoxifen along with a decrease in IL-6, NF-kB, and STAT3 levels in mice model of breast cancer (Khori et al., 2015). In contrast, another study revealed the inhibitory effect of miR-21 on proliferation and invasion of endothelial progenitor cells which consequently decreased venous thrombosis by direct targeting IL-6R (W. Wang et al., 2018). Altogether, miR-21 may play a critical role in breast cancer metastasis in association with inflammatory pathways.

In addition to the remarkable role of miR-146 in NF-κB signaling pathway which we will discuss later, this miRNA is also investigated in several studies regarding the IL-6/STAT3 signaling pathway. Interestingly, a higher methylation of miR-146b promoter was identified in primary breast cancer which had a negative feedback loop with activation of NF-κB, STAT3, and IL-6. As a tumor suppressor marker, miR-146 is a direct STAT3 target gene. Moreover, its promoter methylation caused to the upregulation of NF-κB and the subsequent induction of phospho-STAT3 dimer formation along with an increase in the migration and invasion of breast cancer cells (Xiang et al., 2014). A specific sequence at the 3′-UTR of IL-6 was also recognized for binding miR-146b-5p to be regulated by different tumor suppressors such as p16 protein. In addition, using curcumin ameliorated tumorigenic properties through activating this pathway (Al-Ansari & Aboussekhra, 2015). There are also other tumor-suppressing miRNAs studied in association with the IL-6/STAT3 signaling pathway. For instance, miR-7 was reported as a negative regulator of IL-6 by direct binding to the 3′-UTR of its upstream mediator, rapidly accelerated fibrosarcoma 1. Thus, it seems to have antitumorigenic and antimetastatic effects in primary breast cancer cells (Hsiao et al., 2015). Moreover, a feedback loop was reported between miR-200c and IL-6 in both human and mouse breast cancer cells in which IL-6 caused to the inhibition of miR-200c and after activation of inflammatory and tumorigenic pathways, and in turn, the promoter demethylation and activation of IL-6 occurred (Rokavec et al., 2012). The interactions between these miRNAs and IL-6/STAT3 signaling pathway are illustrated in Figure 2.

4.5 | miRNAs and PTEN/PI3K/AKT signaling pathway

One of the most studied miRNAs linked to the association between PTEN/PI3K/Akt cascade and breast cancer progression is miR-21. There is a study reporting the anti-inflammatory and antitumorigenic effects of curcumin in suppressing miR-21 and regulating its target gene, PTEN (X. Wang et al., 2017). It was also demonstrated that DNA damage increased histone H3 phosphorylation which subsequently enhanced the recruitment of NF-κB and STAT3 on the open chromatin structure of miR-21 promoter to upregulate its expression. Consequently, miR-21 induced cell metastasis through suppressing PTEN expression (Niu et al., 2012). In addition, in MCF-10A cells treated with oxidized low-density lipoprotein, an increase in miR-21 expression along with the inhibition of PTEN as its target gene was reported which was followed by the PI3K/Akt signaling pathway activation (Khaidakov & Mehta, 2012). As described earlier, miR-21 along with several inflammatory pathways has a significant role in breast cancer metastasis.

Furthermore, other studies indicated the inhibitory effects of miR-221 and miR-222 on their target gene PTEN along with an increase in the phosphorylation of Akt and subsequent overexpression of NF-κB p65 which promoted the invasion of breast cancer cells (B. Li et al., 2017). In line with drug resistance, miR-132 and miR-212 are reported to be overexpressed in conditions of doxorubicin (an antitumor drug for breast cancer)-resistant MCF-7 cells which targeted PTEN and subsequently induced NF-κB and antiapoptotic proteins (Xie et al., 2018).

Other studies also supported the role of miRNAs in breast cancer by regulating PI3K or Akt proteins. For instance, a study on breast cancer cell lines indicated that miR-590 is both anti-inflammatory and antitumorigenic factor through downregulating PI3K (Sheikholeslami et al., 2017) and resulted to a decrease in the metastatic ability of breast cells. Moreover, the mediatory effects of miR-126 on the suppression of the PI3K/Akt signaling pathway and NF-κB levels by mango polyphenolics were investigated in BT474 breast cancer cells and xenografts of mice (Banerjee, Kim, Krenek, Talcott, & Mertens-Talcott, 2015). miRNAs 141, 200a, 200b, 200c, and 429 enhanced the invasion of TNBC cells through phosphorylation and activation of Akt. In addition, a higher expression of these miRNAs was reported in metastatic cancer relative to primary tumor samples. Indeed, overexpression of miR-200 in primary breast cancer was linked to a higher risk of metastasis (Antolín et al., 2015; Choi et al., 2016). Another study used pomegranate polyphenols as antitumorigenic agents which repressed breast cancer cell proliferation, induced apoptosis, and decreased inflammation through downregulating the miR-155/PI3K/Akt/NF-κB signaling pathway (Banerjee, Talcott, Safe, & Mertens-Talcott, 2012). A summary of the regulatory functions of these miRNAs on the PTEN/PI3K/Akt signaling pathway is presented in Figure 3.

As described earlier, Akt can have different downstream effects including activating mTOR. Several studies indicated the role of miRNAs in the regulation of mTOR and further cell proliferation and apoptosis in breast cancer. For instance, miR-100 and miR-125b had an inhibitory effect on the expression of mTOR with low expression in both primary breast cancer samples and cell lines (Vilquin et al., 2015; B. Zhang et al., 2016). Other studies have also reported the inhibitory role of miR-15 and miR-16 in the metastasis of breast cancer cells (Janaki Ramaiah et al., 2014).

4.6 | miRNAs and IKK/NF-κB signaling pathway

A variety of studies are presented now considering the role of miRNAs in interactions between the NF-κB signaling pathway and developing breast cancer. In this manner, some miRNAs may show antitumorigenic effects while others may not (J. Wu, Ding, Yang, Guo, & Zheng, 2018). Here, we will first discuss the tumor suppressor miRNAs-mediating NF-κB signaling pathway in breast cancer models and next, we will bring some miRNAs with tumorigenic properties.

The potential role of TRAF2 in activating NF-κB through direct interaction with various TNFRs has been described before. Moreover, its regulatory effect on inducing cancer properties has been discovered too (L. Zhang, Blackwell, Altaeva, Shi, & Habelhah, 2011). Several studies indicated the mediatory role of different miRNAs on NF-κB and subsequent cancer development through targeting TRAF2. For instance, miR-502-5p has a binding site in the 3′-UTR of TRAF2 gene with an inhibitory effect. Then, it acted as a tumor suppressor for regulating the development of metastatic breast cancer through suppressing NF-κB-induced tumorigenic pathways. Indeed, miR-502-5p had a lower level in metastatic breast cancer cells compared with nonmalignant cells (L. -L. Sun et al., 2014). Remarkably, miR-892b was reported as an important suppressor of NF-κB through direct targeting its mediators means TRAF2 and TAK1. Therefore, it inhibits tumor growth, invasion, and angiogenesis. But, the promoter of miR-892b was suppressed by methylation in primary breast cancer samples compared to normal tissues in an association with a greater metastatic capacity (L. Jiang et al., 2016). Another study introduced TRAF2 as a target gene for binding miRNAs 99, 146, and 205 which subsequently regulated NF-κB activity in HCC1937 breast cancer cells (Tanic, Zajac, Gómez-López, Benítez, & Martínez-Delgado, 2012). Forkhead box P3 is a tumor suppressor and proapoptotic protein acting by binding to the miR-146a promoter, increasing miR-146a/b expression, and downregulating IL-1R-associated kinase 1 and TRAF6, two factors contributed in NF-κB activation in MCF-7 cells (R. Liu et al., 2015). It was also reported that p53-binding protein-1 (53BP1) as a potential tumor suppressor has lower expression in cancerous cells. Accordingly, this factor inhibited NF-κB through overexpression of miR-146a in breast cancer (X. Li et al., 2012). On the other hand, a study revealed the binding site of NF-κB on the miR-146a promoter in tumor-associated macrophages with an inhibitory influence (Y. Li et al., 2015). Altogether, these studies showed that miRNAs 146 and 205 are downregulated in primary breast cancer compared to normal breast tissues suggesting their applicable role in tumorigenesis.

Several studies reported the negative association between miR-200 and NF-κB in the invasion of breast cancer cells. Indeed, miR-200

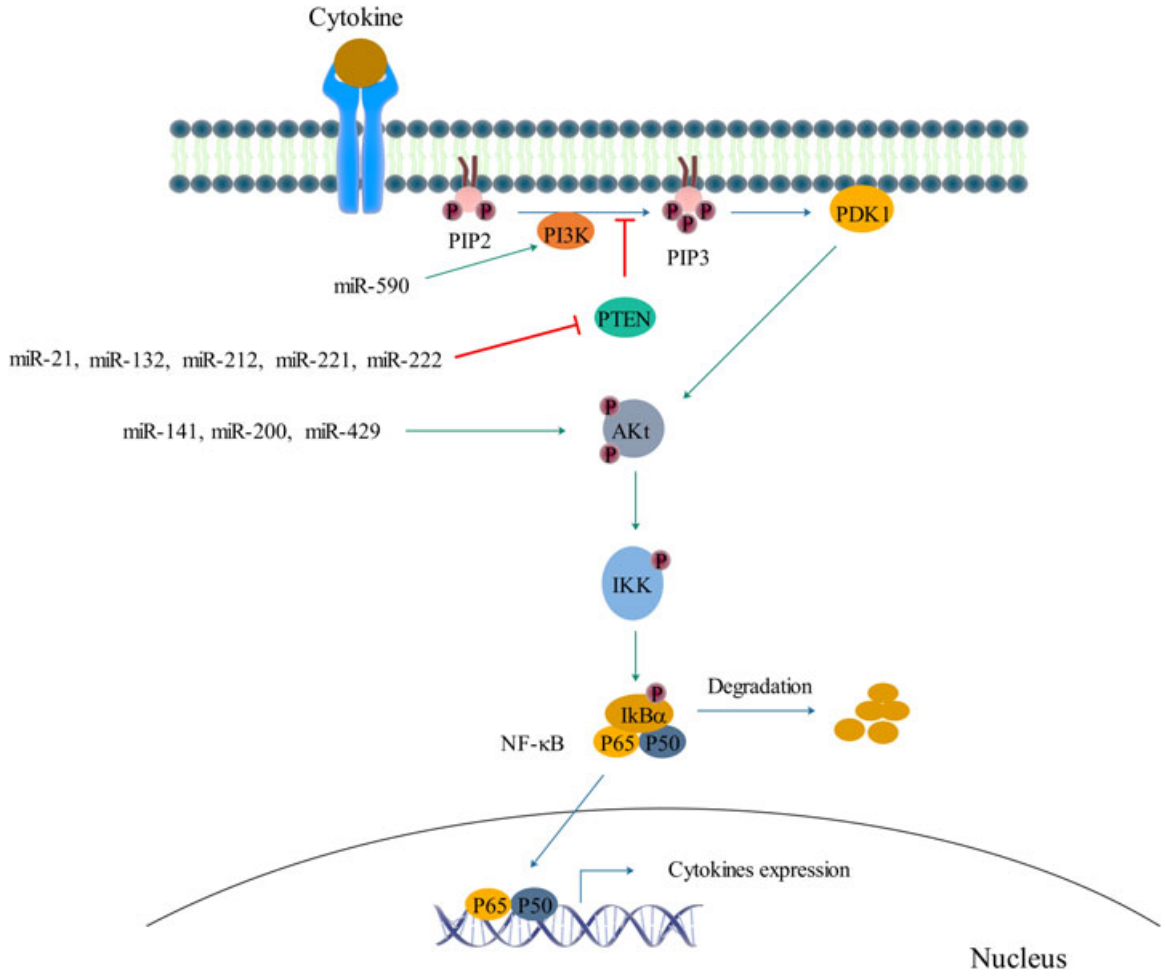

FIGURE 3 A schematic representation of the involved miRNAs in stimulating or inhibiting target genes in the PTEN/PI3K/Akt signaling pathway which may happen in both primary and metastatic breast cancer development. Akt: protein kinase B; IKK: IκBα kinase; miRNA: microRNA; NF-κB: nuclear factor kappa B; PI3K: phosphoinositide 3-kinase; PIP3: phosphatidyl-inositol,3,4,5 triphosphate; PTEN: phosphatase and tensin homolog [Color figure can be viewed at wileyonlinelibrary.com]

showed an undetectable expression in the poorly differentiated tumor cells (Teng, Mei, Hawthorn, & Cowell, 2014). Remarkably, there was a feedback loop between miR-200b expression and NF-κB activation, in which the 3′-UTR of IKK acted as a direct target for binding miR-200b and with its inhibition, NF-κB activity and subsequent breast cancer progression were reduced (H. Wu et al., 2016). Moreover, miRNAs 200b and 200c were reported to target IKK to control MCF-7 cell growth (Y. Sun et al., 2018). In turn, the promoter of miR-200b had a putative binding site for NF-κB with an inhibitory effect on its expression (H. Wu et al., 2016). Another miRNA, miR-16 was able to sensitize breast cancer cells to the treatment by chemotherapy medication paclitaxel leading to cell apoptosis via direct targeting IKK (Tang et al., 2016).

It was reported that miR-181b as a cytokine-responsive miRNA inhibited the migration of breast cancer cells by binding to the 3′-UTR of NF-κB gene (L. Wang et al., 2016). Another study revealed that NF-κB in consistency with estrogen receptor-inhibited miR-181 expression to upregulate its target gene pleckstrin homology-like domain, family A, member 1, as a stem cell marker involved in the survival of breast cancer cells (Kastrati, Canestrari, & Frasor, 2015). The possible inhibitory effect of miR-520 and miR-373 on the metastatic ability of primary breast cancer cells was also demonstrated through direct suppressing of RelA which mediates NF-κB activation and subsequent production of IL-6 and IL-8 (Keklikoglou et al., 2012). In addition, miR-30c was identified as an important inhibitor of NF-κB signaling pathway which decreased the expression of IL-6 and IL-8 and reduced the proliferation of TNBC cells (Shukla et al., 2015). NF-κB expression and tumorigenesis were also inhibited by pterostilbene as an antioxidant component of blueberries through upregulation of miR-448 (Mak et al., 2013). Moreover, it was characterized that the relative amount of miR-448 was lower in the high metastatic breast cancer cell lines compared to the low metastatic breast cancer cell lines. Another study indicated that NF-κB has a binding site at the upstream of tumor suppressor miR-506 promoter which inhibits its expression in breast cancer cells. Furthermore, miR-506 had an inhibitory effect on the invasion and migration of high metastatic breast cancer cells through regulating EMT-related genes (Arora, Qureshi, & Park, 2013).

In line with the tumorigenic properties of miRNAs, a study on sinomenine as a tumor suppressor isoquinoline showed that it had an inhibitory effect on invasion and metastasis of breast cancer cells and induced their apoptosis through suppressing miR-324-5p expression and IKK phosphorylation. On the other hand, this miRNA increased the separation of NF-κB and IκBα by targeting IKK phosphorylation which was inhibited by sinomenine (Song et al., 2015). IκBα was reported as a direct target of miR-668 in promoting radioresistance of breast cancer MCF-7 and T-47D cells. Then, this miRNA activated NF-κB through suppressing its inhibitor, IκBα (Luo et al., 2017). NF-κB was also revealed to bind miR-17 and miR-21 promoters and, thereby contributed to the invasion of breast cancer cells through targeting E-cadherin and PTEN, respectively (Niu et al., 2012; Zhong et al., 2017). The regulatory functions of these miRNAs on the NF-κB signaling pathway are depicted in a summarized manner in Figure 1.

As described earlier, metastasis as a complex process involves the separation of cancer cells from the primary tumor and their moving through the bloodstream to invade and grow within the peripheral tissues and to form a metastatic tumor. This crucial process emphasizes the early diagnosis of breast cancer to reduce death rates (Scully et al., 2012). In this review, we described the specific roles of various miRNAs in the development of primary and metastatic breast tumors in relation with main inflammatory pathways such as cytokines, PTEN/PI3K/Akt, and IKK/NF-κB. We indicated that inflammatory-miRNAs such as miR-30, miR-146, miR-205, and and so forth have been found to have an abnormal expression in primary breast cancer suggesting their applicable role in these type of cancers. Therefore, they may be used as a prognostic tool for monitoring primary breast cancer. Moreover, clinical observations indicated that some miRNAs with an unusual level in primary breast cancer can trigger a more probability of developing metastasis through regulating inflammatory pathways. Among these miRNAs, miR-7, miR-373, miR-509, miR-520, miR-892b, and and so forth have been found to be lower and miR-25, miR-99, miR-191, miR-424, miR-503, and and so forth have been found to be higher in primary breast cancer associated with a greater risk of metastasis. Furthermore, among miRNAs with an abnormal level in metastatic breast tumors, we declared miR-10, miR-106, miR-181, and and so forth to be upregulated and miR-124, miR-206, miR-502-5p, and and so forth to be downregulated associated with predominant inflammatory pathways. Therefore, screening of miRNA expression profiling regarding both primary and metastatic breast cancer may eventually lead to give an applicable approach for predicting the breast tumor metastasis and also to prevent such metastasis development from primary tumor cells.

5 | CONCLUSION

As the most frequently occurring cancer in women all over the world, breast cancer provides a challenging public health problem which demands great attention. Growing evidence suggests that tumorigenic pathways are not completely sufficient for breast cancer progression, and the contribution of inflammation, as well as specific genetic and epigenetic modifications, are required too. This review summarized the present state of information on the molecular interactions between miRNAs and the predominant inflammatory pathways including IL-6/STAT3, PTEN/PI3K/Akt, and IKK/NF-κB in breast cancer. In summary, it seems likely that miRNAs can directly control the key target proteins or their regulators in the inflammatory pathways. In turn, the main components of these pathways may also regulate noncoding RNAs. Considering the tumorigenic and antitumorigenic effects of miRNAs in association with the inflammatory pathways, miRNAs seem to be promising biomarkers for predicting the clinical outcome of breast cancer. Collectively, our review may provide remarkable information for understanding the underlying mechanisms of miRNAs as a possible link between inflammation and tumorigenesis to give a noble insight in the field of combining biomarkers for early diagnosis, prognosis, and monitoring breast cancer.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

A. B. and R. E. wrote the whole manuscript. R. H. edited the manuscript. A. S. A. designed the table and figures. J. A. supervised the project and approved its submission. All authors reviewed and approved the manuscript.

ORCID

Alireza Bahiraee http://orcid.org/0000-0001-6041-8378
Raheleh Halabian http://orcid.org/0000-0002-3363-8276

REFERENCES

Aaltomaa, S., Lipponen, P., Eskelinen, M., Kosma, V. M., Marin, S., Alhava, E., & Syrjänen, K. (1992). Lymphocyte infiltrates as a prognostic variable in female breast cancer. *European Journal of Cancer*, *28a*(4-5), 859–864.

Abrahamsson, A., Capodanno, A., Rzepecka, A., & Dabrosin, C. (2017). Downregulation of tumor suppressive microRNAs in vivo in dense breast tissue of postmenopausal women. *Oncotarget*, *8*(54), 92134.

Al-Ansari, M. M., & Aboussekhra, A. (2015). miR-146b-5p mediates p16-dependent repression of IL-6 and suppresses paracrine procarcinogenic effects of breast stromal fibroblasts. *Oncotarget*, *6*(30), 30006.

Allen, M. D., & Jones, L. J. (2015). The role of inflammation in progression of breast cancer: Friend or foe? (Review). *International Journal of Oncology*, *47*(3), 797–805. https://doi.org/10.3892/ijo.2015.3075

Antolín, S., Calvo, L., Blanco-Calvo, M., Santiago, M. P., Lorenzo-Patiño, M. J., Haz-Conde, M., & Valladares-Ayerbes, M. (2015). Circulating miR-200c and miR-141 and outcomes in patients with breast cancer. *BMC Cancer*, *15*(1), 297. https://doi.org/10.1186/s12885-015-1238-5

Arora, H., Qureshi, R., & Park, W.-Y. (2013). miR-506 regulates epithelial-mesenchymal transition in breast cancer cell lines. *PLoS One*, *8*(5), e64273.

Asgeirsson, K. S., Olafsdottir, K., Jonasson, J. G., & Ogmundsdottir, H. M. (1998). The effects of IL-6 on cell adhesion and e-cadherin expression in breast cancer. *Cytokine*, *10*(9), 720–728. https://doi.org/10.1006/cyto.1998.0349

Asirvatham, A. J., Magner, W. J., & Tomasi, T. B. (2009). miRNA regulation of cytokine genes. *Cytokine*, *45*(2), 58–69. https://doi.org/10.1016/j.cyto.2008.11.010

Bai, W. D., Ye, X. M., Zhang, M. Y., Zhu, H. Y., Xi, W. J., Huang, X., & Yang, A. G. (2014). miR-200c suppresses TGF-β signaling and counteracts trastuzumab resistance and metastasis by targeting ZNF217 and ZEB1 in breast cancer. *International Journal of Cancer*, *135*(6), 1356–1368.

Banerjee, N., Kim, H., Krenek, K., Talcott, S. T., & Mertens-Talcott, S. U. (2015). Mango polyphenolics suppressed tumor growth in breast cancer xenografts in mice: Role of the PI3K/AKT pathway and associated microRNAs. *Nutrition Research*, *35*(8), 744–751.

Banerjee, N., Talcott, S., Safe, S., & Mertens-Talcott, S. U. (2012). Cytotoxicity of pomegranate polyphenolics in breast cancer cells in vitro and vivo: Potential role of miRNA-27a and miRNA-155 in cell survival and inflammation. *Breast Cancer Research and Treatment*, *136*(1), 21–34.

Barcellos-Hoff, M. H., & Akhurst, R. J. (2009). Transforming growth factor-beta in breast cancer: Too much, too late. *Breast Cancer Research*, *11*(1), 202. https://doi.org/10.1186/bcr2224

Barclay, J. L., Anderson, S. T., Waters, M. J., & Curlewis, J. D. (2009). SOCS3 as a tumor suppressor in breast cancer cells, and its regulation by PRL. *International Journal of Cancer*, *124*(8), 1756–1766. https://doi.org/10.1002/ijc.24172

Ben-Baruch, A. (2003). Host microenvironment in breast cancer development: Inflammatory cells, cytokines and chemokines in breast cancer progression: Reciprocal tumor-microenvironment interactions. *Breast Cancer Research*, *5*(1), 31–36. https://doi.org/10.1186/bcr554

Bockhorn, J., Dalton, R., Nwachukwu, C., Huang, S., Prat, A., Yee, K., & Swanson, K. E. (2013). MicroRNA-30c inhibits human breast tumour chemotherapy resistance by regulating TWF1 and IL-11. *Nature Communications*, *4*, 1393.

Cai, W.-L., Huang, W.-D., Li, B., Chen, T.-R., Li, Z.-X., Zhao, C.-L., & Xiao, J.-R. (2018). MicroRNA-124 inhibits bone metastasis of breast cancer by repressing Interleukin-11. *Molecular cancer*, *17*(1), 9.

Chen, Y., Huang, S., Wu, B., Fang, J., Zhu, M., Sun, L., & Guo, L. (2017). Transforming growth factor-β1 promotes breast cancer metastasis by downregulating miR-196a-3p expression. *Oncotarget*, *8*(30), 49110.

Choi, S. K., Kim, H. S., Jin, T., Hwang, E. H., Jung, M., & Moon, W. K. (2016). Overexpression of the miR-141/200c cluster promotes the migratory and invasive ability of triple-negative breast cancer cells through the activation of the FAK and PI3K/AKT signaling pathways by secreting VEGF-A. *BMC Cancer*, *16*(1), 570.

Conze, D., Weiss, L., Regen, P. S., Bhushan, A., Weaver, D., Johnson, P., & Rincon, M. (2001). Autocrine production of interleukin 6 causes multidrug resistance in breast cancer cells. *Cancer Research*, *61*(24), 8851–8858.

Ding, Y., Zhang, C., Zhang, J., Zhang, N., Li, T., Fang, J., & Tang, S. (2017). miR-145 inhibits proliferation and migration of breast cancer cells by directly or indirectly regulating TGF-β1 expression. *International Journal of Oncology*, *50*(5), 1701–1710.

Esquivel-Velázquez, M., Ostoa-Saloma, P., Palacios-Arreola, M. I., Nava-Castro, K. E., Castro, J. I., & Morales-Montor, J. (2015). The role of cytokines in breast cancer development and progression. *Journal of Interferon and Cytokine Research*, *35*(1), 1–16. https://doi.org/10.1089/jir.2014.0026

Fils-Aimé, N., Dai, M., Guo, J., El-Mousawi, M., Kahramangil, B., Neel, J.-C., & Lebrun, J.-J. (2013). Micro-RNA-584 and the protein phosphatase and actin regulator 1 (PHACTR1): New signaling route through which transforming growth factor-beta mediates the migration and actin dynamics of breast cancer cells. *Journal of Biological Chemistry*, *288*(17), 11807–11823.

Georgescu, M. M. (2010). PTEN tumor suppressor network in PI3K-Akt pathway control. *Genes Cancer*, *1*(12), 1170–1177. https://doi.org/10.1177/1947601911407325

Goldberg, A. D., Allis, C. D., & Bernstein, E. (2007). Epigenetics: A landscape takes shape. *Cell*, *128*(4), 635–638.

Gong, C., Qu, S., Liu, B., Pan, S., Jiao, Y., Nie, Y., & Song, E. (2015). miR-106b expression determines the proliferation paradox of TGF-β in breast cancer cells. *Oncogene*, *34*(1), 84–93.

Hamam, R., Hamam, D., Alsaleh, K. A., Kassem, M., Zaher, W., Alfayez, M., & Alajez, N. M. (2017). Circulating microRNAs in breast cancer: Novel diagnostic and prognostic biomarkers. *Cell Death & Disease*, *8*, e3045. https://doi.org/10.1038/cddis.2017.440

Han, M., Wang, F., Gu, Y., Pei, X., Guo, G., Yu, C., & Wang, Y. (2016). MicroRNA-21 induces breast cancer cell invasion and migration by suppressing smad7 via EGF and TGF-β pathways. *Oncology Reports*, *35*(1), 73–80.

Han, X., Yan, S., Weijie, Z., Feng, W., Liuxing, W., Mengquan, L., & Qingxia, F. (2014). Critical role of miR-10b in transforming growth factor-β1-induced epithelial–mesenchymal transition in breast cancer. *Cancer Gene Therapy*, *21*(2), 60–67.

Hare, S. H., & Harvey, A. J. (2017). mTOR function and therapeutic targeting in breast cancer. *American Journal of Cancer Research*, *7*(3), 383–404.

Hoesel, B., & Schmid, J. A. (2013). The complexity of NF-κB signaling in inflammation and cancer. *Molecular Cancer*, *12*, 86. https://doi.org/10.1186/1476-4598-12-86

Hou, L.-K., Yu, Y., Xie, Y.-G., Wang, J., Mao, J.-F., Zhang, B., & Cao, X.-C. (2016). miR-340 and ZEB1 negative feedback loop regulates TGF-β-mediated breast cancer progression. *Oncotarget*, *7*(18), 26016–26026.

Hsiao, Y.-C., Yeh, M.-H., Chen, Y.-J., Liu, J.-F., Tang, C.-H., & Huang, W.-C. (2015). Lapatinib increases motility of triple-negative breast cancer cells by decreasing miRNA-7 and inducing Raf-1/MAPK-dependent interleukin-6. *Oncotarget*, *6*(35), 37965–37978.

Inagaki-Ohara, K., Kondo, T., Ito, M., & Yoshimura, A. (2013). SOCS inflammation, and cancer. *JAK-STAT*, *2*(3), e24053. https://doi.org/10.4161/jkst.24053

Janaki Ramaiah, M., Lavanya, A., Honarpisheh, M., Zarea, M., Bhadra, U., & Bhadra, M. P. (2014). miR-15/16 complex targets p70S6 kinase 1 and controls cell proliferation in MDA-MB-231 breast cancer cells. *Gene*, *552*(2), 255–264. https://doi.org/10.1016/j.gene.2014.09.052

Jiang, L., Yu, L., Zhang, X., Lei, F., Wang, L., Liu, X., & Li, J. (2016). miR-892b silencing activates NF-κB and promotes aggressiveness in breast cancer. *Cancer Research*, *76*(5), 1101–1111.

Jiang, S., Zhang, H.-W., Lu, M.-H., He, X.-H., Li, Y., Gu, H., & Wang, E.-D. (2010). MicroRNA-155 functions as an OncomiR in breast cancer by targeting the suppressor of cytokine signaling 1 gene. *Cancer Research*, *70*(8), 3119–3127.

Johnson, D. E., O'Keefe, R. A., & Grandis, J. R. (2018). Targeting the IL-6/JAK/STAT3 signalling axis in cancer. *Nature Reviews Clinical Oncology*, *15*(4), 234–248. https://doi.org/10.1038/nrclinonc.2018.8

Kaboli, P. J., Rahmat, A., Ismail, P., & Ling, K.-H. (2015). MicroRNA-based therapy and breast cancer: A comprehensive review of novel therapeutic strategies from diagnosis to treatment. *Pharmacological Research*, *97*, 104–121. https://doi.org/10.1016/j.phrs.2015.04.015

Kanwal, R., & Gupta, S. (2010). Epigenetics and cancer. *Journal of Applied Physiology*, *109*(2), 598–605.

Kastrati, I., Canestrari, E., & Frasor, J. (2015). PHLDA1 expression is controlled by an estrogen receptor-NFκB-miR-181 regulatory loop and is essential for formation of ER+mammospheres. *Oncogene*, *34*(18), 2309–2316.

Keklikoglou, I., Koerner, C., Schmidt, C., Zhang, J., Heckmann, D., Shavinskaya, A., & Schneeweiss, A. (2012). MicroRNA-520/373 family functions as a tumor suppressor in estrogen receptor negative breast cancer by targeting NF-κB and TGF-β signaling pathways. *Oncogene*, *31*(37), 4150–4163.

Khaidakov, M., & Mehta, J. L. (2012). Oxidized LDL triggers pro-oncogenic signaling in human breast mammary epithelial cells partly via stimulation of MiR-21. *PLoS One*, *7*(10), e46973.

Khori, V., Shalamzari, S. A., Isanejad, A., Alizadeh, A. M., Alizadeh, S., Khodayari, S., & Sohanaki, H. (2015). Effects of exercise training together with tamoxifen in reducing mammary tumor burden in mice: Possible underlying pathway of miR-21. *European Journal of Pharmacology*, *765*, 179–187.

Kim, S., Song, J. H., Kim, S., Qu, P., Martin, B. K., Sehareen, W. S., & Chang, S. (2016). Loss of oncogenic miR-155 in tumor cells promotes tumor growth by enhancing C/EBP-β-mediated MDSC infiltration. *Oncotarget*, *7*(10), 11094–11112.

Kishimoto, T., Taga, T., & Akira, S. (1994). Cytokine signal transduction. *Cell*, *76*(2), 253–262.

Knupfer, H., & Preiss, R. (2007). Significance of interleukin-6 (IL-6) in breast cancer (review). *Breast Cancer Research and Treatment*, *102*(2), 129–135. https://doi.org/10.1007/s10549-006-9328-3

Lei, K., Du, W., Lin, S., Yang, L., Xu, Y., Gao, Y., & Qian, X. (2016). 3B, a novel photosensitizer, inhibits glycolysis and inflammation via miR-155-5p and breaks the JAK/STAT3/SOCS1 feedback loop in human breast cancer cells. *Biomedicine & Pharmacotherapy*, *82*, 141–150.

Leu, C. M., Wong, F. H., Chang, C., Huang, S. F., & Hu, C. P. (2003). Interleukin-6 acts as an antiapoptotic factor in human esophageal carcinoma cells through the activation of both STAT3 and mitogen-activated protein kinase pathways. *Oncogene*, *22*(49), 7809–7818. https://doi.org/10.1038/sj.onc.1207084

Li, P., Guo, Y., Bledsoe, G., Yang, Z., Chao, L., & Chao, J. (2016). Kallistatin induces breast cancer cell apoptosis and autophagy by modulating Wnt signaling and microRNA synthesis. *Experimental Cell Research*, *340*(2), 305–314.

Li, Y., Li, W., Ying, Z., Tian, H., Zhu, X., Li, J., & Li, M. (2014). Metastatic heterogeneity of breast cancer cells is associated with expression of a heterogeneous TGF-β-activating miR-424-503 gene cluster. *Cancer research*, *canres*, *0389*, 2014.

Li, B., Lu, Y., Yu, L., Han, X., Wang, H., Mao, J., & Li, C. (2017). miR-221/222 promote cancer stem-like cell properties and tumor growth of breast cancer via targeting PTEN and sustained Akt/NF-κB/COX-2 activation. *Chemico-biological Interactions*, *277*, 33–42.

Li, X., Xu, B., Moran, M. S., Zhao, Y., Su, P., Haffty, B. G., & Yang, Q. (2012). 53BP1 functions as a tumor suppressor in breast cancer via the inhibition of NF-κB through miR-146a. *Carcinogenesis*, *33*(12), 2593–2600.

Li, Y., Zhao, L., Shi, B., Ma, S., Xu, Z., Ge, Y., & Shi, J. (2015). Functions of miR-146a and miR-222 in tumor-associated macrophages in breast cancer. *Scientific Reports*, *5*, 18648.

Liu, R., Liu, C., Chen, D., Yang, W.-H., Liu, X., Liu, C.-G., & Liu, Y. (2015). FOXP3 controls an miR-146/NFκB negative feedback loop that inhibits apoptosis in breast cancer cells. *Cancer Research*, *75*(8), 1703–1713.

Liu, D., Wang, X., & Chen, Z. (2016). Tumor necrosis factor-alpha, a regulator and therapeutic agent on breast cancer. *Current Pharmaceutical Biotechnology*, *17*(6), 486–494.

Liu, Y., Zhang, J., Sun, X., Su, Q., & You, C. (2017). Down-regulation of miR-29b in carcinoma associated fibroblasts promotes cell growth and metastasis of breast cancer. *Oncotarget*, *8*(24), 39559–39570.

Lu, J., Getz, G., Miska, E. A., Alvarez-Saavedra, E., Lamb, J., Peck, D., & Ferrando, A. A. (2005). MicroRNA expression profiles classify human cancers. *Nature*, *435*(7043), 834–838.

Luo, M., Ding, L., Li, Q., & Yao, H. (2017). miR-668 enhances the radioresistance of human breast cancer cell by targeting IκBα. *Breast Cancer*, *24*(5), 673–682.

Mak, K. K., Wu, A. T., Lee, W. H., Chang, T. C., Chiou, J. F., Wang, L. S., & Chao, T. Y. (2013). Pterostilbene, a bioactive component of blueberries, suppresses the generation of breast cancer stem cells within tumor microenvironment and metastasis via modulating NF-κ B/microRNA 448 circuit. *Molecular Nutrition & Food Research*, *57*(7), 1123–1134.

Muhammad, N., Bhattacharya, S., Steele, R., & Ray, R. B. (2016). Anti-miR-203 suppresses ER-positive breast cancer growth and stemness by targeting SOCS3. *Oncotarget*, *7*(36), 58595.

Nagpal, N., Ahmad, H. M., Chameettachal, S., Sundar, D., Ghosh, S., & Kulshreshtha, R. (2015). HIF-inducible miR-191 promotes migration in breast cancer through complex regulation of TGFβ-signaling in hypoxic microenvironment. *Scientific Reports*, *5*, 9650.

Neel, J.-C., & Lebrun, J.-J. (2013). Activin and TGFβ regulate expression of the microRNA-181 family to promote cell migration and invasion in breast cancer cells. *Cellular Signalling*, *25*(7), 1556–1566.

Niu, J., Shi, Y., Tan, G., Yang, C. H., Fan, M., Pfeffer, L. M., & Wu, Z.-H. (2012). DNA damage induces NF-κB-dependent microRNA-21 upregulation and promotes breast cancer cell invasion. *Journal of Biological Chemistry*, *287*(26), 21783–21795355495.

Patnaik, J. L., Byers, T., DiGuiseppi, C., Dabelea, D., & Denberg, T. D. (2011). Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: A retrospective cohort study. *Breast Cancer Research*, *13*(3), R64. https://doi.org/10.1186/bcr2901

Qian, B., Katsaros, D., Lu, L., Preti, M., Durando, A., Arisio, R., & Yu, H. (2009). High miR-21 expression in breast cancer associated with poor disease-free survival in early stage disease and high TGF-β1. *Breast Cancer Research and Treatment*, *117*(1), 131–140.

Rivas, M. A., Carnevale, R. P., Proietti, C. J., Rosemblit, C., Beguelin, W., Salatino, M., & Schillaci, R. (2008). TNF alpha acting on TNFR1 promotes breast cancer growth via p42/P44 MAPK, JNK, Akt and NF-kappa B-dependent pathways. *Experimental Cell Research*, *314*(3), 509–529. https://doi.org/10.1016/j.yexcr.2007.10.005

Rokavec, M., Wu, W., & Luo, J.-L. (2012). IL6-mediated suppression of miR-200c directs constitutive activation of inflammatory signaling circuit driving transformation and tumorigenesis. *Molecular Cell*, *45*(6), 777–789.

Samaeekia, R., Adorno-Cruz, V., Bockhorn, J., Chang, Y.-F., Huang, S., Prat, A., & Zheng, H. (2016). miR-206 inhibits stemness and metastasis of breast cancer by targeting MKL1/IL11 pathway. *Clinical Cancer Research*, *23*, 1091–1103.

Schetter, A. J., Heegaard, N. H., & Harris, C. C. (2010). Inflammation and cancer: Interweaving microRNA, free radical, cytokine and p53 pathways. *Carcinogenesis*, *31*(1), 37–49. https://doi.org/10.1093/carcin/bgp272

Scully, O. J., Bay, B. H., Yip, G., & Yu, Y. (2012). Breast cancer metastasis. , *9*(5), 311–320*Cancer Genomics & Proteomics*

Shah, R., Rosso, K., & Nathanson, S. D. (2014). Pathogenesis, prevention, diagnosis and treatment of breast cancer. *World Journal of Clinical Oncology*, *5*(3), 283–298. https://doi.org/10.5306/wjco.v5.i3.283

Sheikholeslami, A., Nabiuni, M., & Arefian, E. (2017). Suppressing the molecular signaling pathways involved in inflammation and cancer in breast cancer cell lines MDA-MB-231 and MCF-7 by miR-590. *Tumor Biology*, *39*(4. 1010428317697570

Shih, V. F., Tsui, R., Caldwell, A., & Hoffmann, A. (2011). A single NFkappaB system for both canonical and non-canonical signaling. *Cell Research*, *21*(1), 86–102. https://doi.org/10.1038/cr.2010.161

Shostak, K., & Chariot, A. (2011). NF-κB, stem cells and breast cancer: The links get stronger. *Breast Cancer Research*, *13*(4), 214. https://doi.org/10.1186/bcr2886

Shukla, K., Sharma, A. K., Ward, A., Will, R., Hielscher, T., Balwierz, A., & Keklikoglou, I. (2015). MicroRNA-30c-2-3p negatively regulates NF-κB signaling and cell cycle progression through downregulation of TRADD and CCNE1 in breast cancer. *Molecular Oncology*, *9*(6), 1106–1119.

Smith, A. L., Iwanaga, R., Drasin, D. J., Micalizzi, D. S., Vartuli, R. L., Tan, A.-C., & Ford, H. L. (2012). The miR-106b-25 cluster targets Smad7, activates TGF-β signaling, and induces EMT and tumor initiating cell characteristics downstream of Six1 in human breast cancer. *Oncogene*, *31*(50), 5162–5171.

Smolnikar, K., Loffek, S., Schulz, T., Michna, H., & Diel, P. (2000). Treatment with the pure antiestrogen faslodex (ICI 182780) induces tumor necrosis factor receptor 1 (TNFR1) expression in MCF-7 breast cancer cells. *Breast Cancer Research and Treatment*, *63*(3), 249–259.

Song, L., Liu, D., Zhao, Y., He, J., Kang, H., Dai, Z., & Zan, Y. (2015). Sinomenine inhibits breast cancer cell invasion and migration by suppressing NF-κB activation mediated by IL-4/miR-324-5p/CUEDC2 axis. *Biochemical and Biophysical Research Communications*, *464*(3), 705–710.

Sun, L.-L., Wang, J., Zhao, Z.-J., Liu, N., Wang, A.-L., Ren, H.-Y., & Wan, E.-H. (2014). Suppressive role of miR-502-5p in breast cancer via down-regulation of TRAF2. *Oncology Reports*, *31*(5), 2085–2092.

Sun, Y., Yang, D., Xi, L., Chen, Y., Fu, L., Sun, K., & Qin, Y. (2018). Primed atypical ductal hyperplasia-associated fibroblasts promote cell growth and polarity changes of transformed epithelium-like breast cancer MCF-7 cells via miR-200b/c-IKKβ signaling. *Cell Death & Disease*, *9*(2), 122.

Sutherland, K. D., Lindeman, G. J., Choong, D. Y., Wittlin, S., Brentzell, L., Phillips, W., & Visvader, J. E. (2004). Differential hypermethylation of SOCS genes in ovarian and breast carcinomas. *Oncogene*, *23*(46), 7726–7733. https://doi.org/10.1038/sj.onc.1207787

Tang, X., Jin, L., Cao, P., Cao, K., Huang, C., Luo, Y., & Li, X. (2016). MicroRNA-16 sensitizes breast cancer cells to paclitaxel through suppression of IKBKB expression. *Oncotarget*, *7*(17), 23668.

Tanic, M., Zajac, M., Gómez-López, G., Benítez, J., & Martínez-Delgado, B. (2012). Integration of BRCA1-mediated miRNA and mRNA profiles reveals microRNA regulation of TRAF2 and NFκB pathway. *Breast Cancer Research and Treatment*, *134*(1), 41–51.

Tegowski, M., & Baldwin, A. (2018). Noncanonical NF-κB in cancer. *Biomedicines*, *6*(2), 66. https://doi.org/10.3390/biomedicines6020066

Teng, Y., Mei, Y., Hawthorn, L., & Cowell, J. K. (2014). WASF3 regulates miR-200 inactivation by ZEB1 through suppression of KISS1 leading to increased invasiveness in breast cancer cells. *Oncogene*, *33*(2), 203–211.

Turcatel, G., Rubin, N., El-Hashash, A., & Warburton, D. (2012). MIR-99a and MIR-99b modulate TGF-β induced epithelial to mesenchymal plasticity in normal murine mammary gland cells. *PLoS One*, *7*(1), e31032.

Vilquin, P., Donini, C. F., Villedieu, M., Grisard, E., Corbo, L., Bachelot, T., & Cohen, P. A. (2015). MicroRNA-125b upregulation confers aromatase inhibitor resistance and is a novel marker of poor prognosis in breast cancer. *Breast Cancer Research*, *17*(1), 13–13. https://doi.org/10.1186/s13058-015-0515-1

Wang, L., Liu, W., Jiang, W., Lin, J., Jiang, Y., Li, B., & Pang, D. (2012). A miRNA binding site single-nucleotide polymorphism in the 3′-UTR region of the IL23R gene is associated with breast cancer. *PLoS One*, *7*(12), e49823.

Wang, W., Nag, S. A., & Zhang, R. (2015). Targeting the NFkappaB signaling pathways for breast cancer prevention and therapy. *Current Medicinal Chemistry*, *22*(2), 264–289.

Wang, L., Wang, Y. X., Chen, L. P., & Ji, M. L. (2016). Upregulation of microRNA-181b inhibits CCL18-induced breast cancer cell metastasis and invasion via the NF-κB signaling pathway. *Oncology Letters*, *12*(6), 4411–4418.

Wang, W., Yuan, X., Xu, A., Zhu, X., Zhan, Y., Wang, S., & Liu, M. (2018). Human cancer cells suppress behaviors of endothelial progenitor cells through miR-21 targeting IL6R. *Microvascular Research*, *120*, 21–28.

Wang, X., Hang, Y., Liu, J., Hou, Y., Wang, N., & Wang, M. (2017). Anticancer effect of curcumin inhibits cell growth through miR-21/PTEN/Akt pathway in breast cancer cell. *Oncology Letters*, *13*(6), 4825–4831.

Wu, H., Wang, G., Wang, Z., An, S., Ye, P., & Luo, S. (2016). A negative feedback loop between miR-200b and the nuclear factor-κB pathway via IKBKB/IKK-β in breast cancer cells. *The FEBS Journal*, *283*(12), 2259–2271.

Wu, J., Ding, J., Yang, J., Guo, X., & Zheng, Y. (2018). MicroRNA roles in the Nuclear Factor Kappa B signaling pathway in cancer. *Frontiers in Immunology*, *9*, 546. https://doi.org/10.3389/fimmu.2018.00546

Xiang, M., Birkbak, N. J., Vafaizadeh, V., Walker, S. R., Yeh, J. E., Liu, S., & Groner, B. (2014). STAT3 induction of miR-146b forms a feedback loop to inhibit the NF-κB to IL-6 signaling axis and STAT3-driven cancer phenotypes. *Science Signaling*, *7*(310), ra11–ra11.

Xie, M., Fu, Z., Cao, J., Liu, Y., Wu, J., Li, Q., & Chen, Y. (2018). MicroRNA-132 and microRNA-212 mediate doxorubicin resistance by down-regulating the PTEN-AKT/NF-κB signaling pathway in breast cancer. *Biomedicine & Pharmacotherapy*, *102*, 286–294.

Xing, F., Sharma, S., Liu, Y., Mo, Y.-Y., Wu, K., Zhang, Y.-Y., & Watabe, K. (2015). miR-509 suppresses brain metastasis of breast cancer cells by modulating RhoC and TNF-α. *Oncogene*, *34*(37), 4890–4900.

Yen, M.-C., Shih, Y.-C., Hsu, Y.-L., Lin, E.-S., Lin, Y.-S., Tsai, E.-M., & Kuo, P.-L. (2016). Isolinderalactone enhances the inhibition of SOCS3 on STAT3 activity by decreasing miR-30c in breast cancer. *Oncology Reports*, *35*(3), 1356–1364.

Yin, K., Yin, W., Wang, Y., Zhou, L., Liu, Y., Yang, G., & Lu, J. (2016). MiR-206 suppresses epithelial mesenchymal transition by targeting TGF-β signaling in estrogen receptor positive breast cancer cells. *Oncotarget*, *7*(17), 24537–24548.

You, J. S., & Jones, P. A. (2012). Cancer genetics and epigenetics: Two sides of the same coin? *Cancer Cell*, *22*(1), 9–20. https://doi.org/10.1016/j.ccr.2012.06.008

Yu, Z., Willmarth, N. E., Zhou, J., Katiyar, S., Wang, M., Liu, Y., & Pestell, R. G. (2010). microRNA 17/20 inhibits cellular invasion and tumor metastasis in breast cancer by heterotypic signaling. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(18), 8231–8236.

Zhang, L., Blackwell, K., Altaeva, A., Shi, Z., & Habelhah, H. (2011). TRAF2 phosphorylation promotes NF-κB-dependent gene expression and inhibits oxidative stress-induced cell death. *Molecular Biology of the Cell*, *22*(1), 128–140. https://doi.org/10.1091/mbc.E10-06-0556

Zhang, G., Liu, Z., Han, Y., Wang, X., & Yang, Z. (2016). Overexpression of miR-509 increases apoptosis and inhibits invasion via suppression of tumor necrosis factor-α in triple-negative breast cancer Hs578T cells. *Oncology Research Featuring Preclinical and Clinical Cancer Therapeutics*, *24*(4), 233–238.

Zhang, B., Zhao, R., He, Y., Fu, X., Fu, L., Zhu, Z., & Dong, J. T. (2016). MicroRNA 100 sensitizes luminal A breast cancer cells to paclitaxel treatment in part by targeting mTOR. *Oncotarget*, *7*(5), 5702–5714. https://doi.org/10.18632/oncotarget.6790

Zhao, Y., Yang, F., Li, W., Xu, C., Li, L., Chen, L., & Sun, P. (2017). miR-29a suppresses MCF-7 cell growth by downregulating tumor necrosis factor receptor 1. *Tumor Biology*, *39*(2), 1010428317692264.

Zhong, W., Chen, S., Qin, Y., Zhang, H., Wang, H., Meng, J., & Lei, Y. (2017). Doxycycline inhibits breast cancer EMT and metastasis through PAR-1/NF-κB/miR-17/E-cadherin pathway. *Oncotarget*, *8*(62), 104855.

How to cite this article: Bahiraee A, Ebrahimi R, Halabian R, Aghabozorgi AS, Amani J. The role of inflammation and its related microRNAs in breast cancer: A narrative review. *J Cell Physiol*. 2019;1–14. https://doi.org/10.1002/jcp.28742