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Role of regulatory miRNAs of the PI3K/AKT signaling pathway in the pathogenesis of breast cancer

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Abstract

Breast cancer is one of the most common tumors in women. Current data indicate that the overexpression of some microRNAs (miRNAs) is associated with breast cancer, in relation to stage, tumor size and potential for metastasis. Some studies have reported that miRNAs have critical roles in cellular processes implicated in breast cancer cell growth, migration and metastasis by targeting the PI3K/AKT oncogenic signaling pathway. Therefore, identifying novel regulatory miRNAs for this oncogenic pathway and discovery of their related target genes may represent a promising therapeutic approach for breast cancer therapy. This review highlights the recent findings about the potential role of PI3K/AKT signaling regulatory miRNAs in breast cancer tumorigenesis.

Keywords: PI3K/AKT signaling, MicroRNA, breast cancer

Introduction

Breast cancer is the most frequently diagnosed tumor in women and causes the second highest rate of mortality in women [1]. Breast cancer was identified as a heterogeneous disorder with a varying prognosis related to molecular subtypes defined by various gene expression profiles [2]. Breast cancer tumorigenesis is a multistage process which involves several genetic and epigenetic alterations [3]. The genetic changes including over expression of oncogenes or down regulation of tumor suppressors play significant roles in breast cancer pathogenesis by activation of oncogenic cascades [4]. Recent studies indicated that specific miRNAs as oncogenic factors are upregulated in breast cancer [5].

MiRNAs are endogenous small RNAs usually consisting 20-25 nucleotides that pair with the 3´-untranslated regions (UTRs) of targets mRNA, resulting in mRNA degradation or blockage of translation [6, 7]. Current studies indicate that individual miRNAs can promote or suppress certain cellular process by regulating the expression of their related mRNAs [8]. Aberrant expression of miRNAs was reported in many forms of disorders including cancer, and increasing data revealed that miRNAs can act as oncogenes or tumor suppressor genes along cancer growth and metastasis [6, 9].

It has been shown consistently that the over-expressed miRNAs can promote tumorigenesis by inducing cancer-associated pathways including PI3K/AKT/mTOR axis [9]. The regulatory function of miRNAs on the PI3K pathway resulting in breast cancer suppression, suggesting the therapeutic potency of miRNAs for breast cancer therapy.

PI3K/AKT/mTOR signaling pathway

The PI3K signaling is a central intracellular signaling axis that integrates multiple signals to induce cancer cell growth and progression [10]. Generally, the signaling pathway includes three main components comprising PI3K, AKT and mTOR.

The PI3Ks are a family of kinase enzymes that catalyzes phosphorylation of phosphatidylinositol 4,5-bisphosphate (PIP2) to form phosphatidylinositol 3,4,5-triphosphate (PIP3) [11]. This production of PIP3 promotes phosphorylation of AKT as a master regulator that can directly modulates several downstream targets including mTOR and WNT/β-catenin pathways [12]. AKT can regulate cancer cell proliferation, metabolism, apoptosis and angiogenesis [13].

The mTOR complexes are activated by AKT and regulate several cell growth functions including protein synthesis, cell survival and inhibition of autophagy [14]. Recent data indicate that PI3K signaling is frequently activated in several human malignancies including breast cancer and prolonged activation of PI3K signaling is related to a poor prognosis and resistance to chemotherapy [15, 16].

Role of PI3K/AKT signaling regulatory oncogenic miRNAs in breast cancer pathology

It is well stablished that un-controlled activation of PI3K pathway is pivotal in the development of human malignancies [9]. There are several oncoproteins and tumor suppressors involved in PI3K/AKT signaling regulation are often aberrant in breast cancer [17, 18]. Recently, increasing evidence indicated that various miRNAs can promote the PI3K/AKT signaling pathway by targeting master regulators such as PTEN. PTEN is a phosphatase enzyme which antagonizes PI3K activity through dephosphorylation of PIP3 [19]. PTEN was found to be targeted by several miRNAs including miR-21 which is over-expressed in $HER2^+$ and triple negative breast cancer resulting in tumor progression. Additionally, miR-21 inhibits autophagic cell death process by suppressing PI3K/AKT signaling through directly targeting PTEN. The over-expression of miR-21 was found to contribute to trastuzumab and tamoxifen resistance in $HER2^+$ and ER^+ tumors respectively. Therefore, targeting miR-21 or upregulation of PTEN could be effective strategy for breast cancer therapy [20-22]. Moreover, the expression of PTEN was reported to be regulated by miR-93, miR-301 and miR-106b resulting in aberrantly activation of PI3K/ AKT signaling.

Recent studies have shown that the expression level of miR-93, miR-301 and miR-106b were augmented in breast cancer patients which induces tumor cell proliferation and invasion [23, 24]. In addition, serum levesl of miR-214 were remarkably higher in breast cancer patients in compare with healthy controls. ROC analysis has indicated that the miR-214 levels can distinguish malignant tumor from benign one. Moreover, it has been shown that miR-214 serum levels were positively correlated with tumor metastasis and bad outcomes in breast cancer patients. the miR-214 induces breast cancer progression and metastasis via promoting PI3K signaling through directly targeting PTEN expression [25, 26]. The over-expression of miR-19b was also observed in patients compared to normal controls. Intriguingly, the upregulation of miR-19b was reported to be positively related to cellular proliferation and migration leading to cancer progression and metastasis. Regarding the results of survival analysis, miR-19b expression was related to a lower overall survival suggesting its prognostic potential for breast cancer patients [27]. Moreover, it has been shown that the expression of MiR-10b was associated with breast cancer cell survival and metastasis. It has been revealed that prolong expression of miR10b was closely related to upregulation of epithelial- mesenchymal transition markers in breast cancer. Inhibition of miR10b by antisense RNAs resulted in upregulation of PTEN and suppression of AKT [28]. The over-expression of miR-20b was also detected in breast cancer tissues and cell lines. Recent evidence shows that upregulation of miR-20b was related to cancer cell proliferation and colony formation. According to gene expression analysis results, upregulation of miR-20b decreased the PTEN protein level without any effect on its mRNA expression. Therefore, the anti-tumor activity of miR-20b may be caused by suppressing the translation of PTEN protein in breast cancer cells [29]. Recent investigations revealed that upregulation of certain oncogenic miRNAs resulted in drug resistance in tumor cells. For example, the expression of miR-29a, miR-222 and miR-130b were detected to be overexpressed in breast cancer which confers resistance to adriamycin during cancer therapy. The upregulation of miR-29a, miR-222 and miR-130b induces tumor cell growth by inducing PI3K/ AKT activity through targeting multiple tumor suppressors including PTEN and

GSK3β. These results suggested that miR-29a, miR-222 and miR-130b may induce multi drug resistance by targeting PTEN/ AKT/ GSK3β signaling in breast cancer cells [30-33].

Role of PI3K/AKT signaling regulatory tumor suppressor miRNAs in breast cancer pathology

Recently, mTOR signaling was recognized as a target of miR-99a which can inhibit breast cancer growth via targeting mTOR/HIF1-α signaling pathway. Recent studies revealed that the upregulation of miR-99a promotes cellular apoptosis in breast cancer stem cells indicating that miR-99a can be a prognostic biomarker for breast cancer [34, 35]. The expression of miR-122 was also reported to be downregulated in breast cancer. miR-122, as a key regulator of PI3K signaling, inhibits tumor cell proliferation via inducing G1 cell cycle arrest. These results indicate that the anti-tumor mechanism of miR-122 may be via the suppression of the AKT/mTOR/ p70s6k signaling axis [36]. Consistently, it has been reported that miR-122-3p downregulation in breast tumor cells is associated with increased tumor cell survival and metastasis. Mechanistically, upregulation of miR-122-3p induced cellular apoptosis while prevents cancer cell invasion trough targeting PI3K and EMT related proteins comprising PTEN, AKT, Vimentin and E-cadherin [37]. Furthermore, there is a negative association between miR-147 expression and breast cancer growth. The expression of miR-147 was considerably suppressed in breast cancer cells. Enforced expression of miR-147 resulted in reduced tumor progression and metastasis by targeting AKT/mTOR signaling [38]. Recent findings demonstrate that miR-200c has a regulatory effect on EMT and metastasis and enhances sensitivity of breast tumor cells to doxorubicin. Moreover, miR-200c was shown to interacts with KRAS and inhibits PI3K/AKT signaling by inducing PTEN expression in breast cancer [39, 40]. Recently, Hong et al. reported that up-regulation of miR-204-5p abrogates tumor cell growth and metastasis via repression of PI3K/AKT signaling by directly targeting PIK3CB a catalytic subunit of PI3K in breast cancer [41]. Similarly, the reduced expression of miR-409-3p was also observed in breast cancer. The *in vitro* and *in vivo* results

indicated that ectopic expression of miR-409-3p inhibited cancer cell proliferation and migration via targeting AKT1 [42]. The AKT1 was also shown to be targeted by tumor suppressor miR-215, which was implicated in regulating breast tumor cell growth and invasion [43]. Recent findings demonstrated that suppressed expression of miR-489 was related to aggressive tumor characteristics including chemoresistance and metastasis in breast cancer. Additionally, upregulation of miR-489 was shown to be related to reduced cancer cell growth by targeting PI3K pathway in breast cancer cells and tissues [44]. Furthermore, when miR-542-3p was markedly suppressed in breast cancer this was associated with resistance to trastuzumab and apoptosis following by G1 cell cycle arrest. Other studies have shown that the tumor suppressive function of miR-542-3p is mediated by inhibition of PI3K pathway [45]. The epidermal growth factor receptor (EGFR) was found to be targeted by miR-133a which is downregulated in breast cancer cells and tissues. The EGFR, is one of the major cell surface tyrosine kinase receptors, and regulates the activity of several downstream targets including PI3K and AKT. Recent study revealed that enforced expression of miR-133a promotes cell cycle arrest in G2/S phase accompanied by targeting EGFR and AKT activity in breast cancer. It has been shown that the 3 ′ -untranslated region of EGFR gene was targeted by miR-133a resulting in suppressing expression of EGFR and its downstream targets like AKT. Aberrant expression of miR-133a was also downregulates the p-AKT protein levels resulted in inhibiting nucleus translocation of p-AKT proteins [46]. In addition, miR-126 was reported to be downregulated in breast cancer patients and inhibits cancer growth and angiogenesis via targeting VEGFA /PI3K axis [47]. The VEGF growth factor was identified as one of the prominent activators of PI3K/ AKT signaling which promotes tumorigenesis by inducing vasculogenesis and angiogenesis [48]. To further identify the regulatory function of miRNAs on PI3K/AKT pathway, Mutlu et al. indicated that miR-564 suppresses tumor progression by promoting G1 cell cycle arrest. Further studies reported that enforced expression of miR-564 blocks EMT and metastasis in breast cancer cells.

Mechanistically, miR564, as a potential dual inhibitor, suppresses breast cancer progression by inhibiting PI3K and MAPK pathway components including AKT2, SRF, GNA12 and GYS1 [49]. Finally, these data suggest that miRNAs can regulate the tumorigenesis of breast cancer through targeting PI3K pathway and can be used as prognostic or diagnostic biomarkers for breast cancer therapy.

Conclusion

There is substantial evidence indicating that uncontrolled activity of oncogenic PI3K/AKT signaling is related to bad prognosis and tumor metastasis in breast cancer patients. In this review, we have summarized the recent findings on the regulatory role of miRNAs on oncogenic PI3K/AKT/mTOR signaling pathway involved in pathogenesis of breast cancer (Table 1).

Recent reports indicate that regulation of tumor suppressor or oncogenic miRNAs have the potential to have an important role in the management of breast cancer and possibly as novel potential diagnostic and prognostic markers (Figure 1). Therefore, identification and characterization of new regulatory miRNAs and their corresponding target genes may lead to developing novel miRNA-based therapeutic strategies for control pathological responses and better management of breast cancer in the future.

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Figure legends

Figure 1) The mechanisms of PI3K/AKT/mTOR regulatory miRNAs in the development of breast cancer