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Research Article

mirna-19a-3p Promotes Malignant Progression of Breast Cancer Cells by Up Regulating PI3K-AKT-Mtor Pathway Activity Through Targeted Inhibition of PTEN

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Abstract

Breast cancer is one of the leading causes of cancer-related mortality worldwide and is the most common malignancy in women. Breast cancer is not only highly prevalent and aggressive, but also highly susceptible to recurrence and metastasis, which greatly restricts its clinical treatment outcome. In recent years, miRNAs have been shown to be closely related to the recurrence and metastasis of breast cancer. It is significant to explore the mechanism of newer miRNAs on breast cancer metastasis. Our previous study found that miR-19a-3p may be involved in breast cancer metastasis, but the exact mechanism is still exclusive. Further investigation revealed that Phosphatase and Tensin Homologs (PTEN) may be downstream targets of miR-19a-3p. Meanwhile, we examined the related research progress of downstream signaling pathways of PTEN and concluded that miR-19a-3p/PTEN may promote breast cancer metastasis through mediating PI3K/AKT/mTOR pathway. In this paper, we will comprehensively and systematically analyze and discuss how miR-19a-3p/PTEN affects breast cancer development and distant metastasis through PI3K/AKT/mTOR signaling pathway, aiming to provide novel clues and directions for the early diagnosis and treatment of breast cancer.

Keywords: Breast cancer; miR-19a-3p; PTEN; PI3K/AKT/mTOR pathway

Incidence of Breast Cancer and Current Status of Research

Breast cancer is one of the leading causes of cancer-related mortality worldwide and is the most common cancer in women. In China, breast cancer has become the most prevalent malignant tumor in women. According to the statistics of the National Cancer Center of China, breast cancer accounts for 15% of all new tumors in women and is also the leading cause of death from malignant tumors in women under 45 years of age [1,2]. More seriously, the incidence and mortality rate of breast cancer in China are increasing year by year and have a tendency to attack the younger, which seriously threatens the survival and health of women [3]. Breast cancer is highly prevalent, aggressive and prone to recurrence and metastasis. Currently, adjuvant chemotherapy and radiotherapy are the most commonly used treatment strategies after surgical resection; however, tumor recurrence often occurs after radiotherapy treatment, and recurrent breast cancer tends to have higher malignancy and worse survival and prognosis [4]. Targeted therapy is a new treatment method in addition to the three traditional treatments of surgery, radiotherapy and chemotherapy, which has strong specificity, significant efficacy and low toxic side effects. Targeted therapy has minimal damage to normal tissues and can provide a more effective approach to clinical treatment [5,6]. However, the molecular mechanisms mediating breast cancer cell metastasis are still not fully understood, and a large number of unknowns still need to be explored. Therefore, further exploration of the key regulatory genes and their signaling pathways in the process of breast cancer recurrence and metastasis has become the key to overcome the bottleneck of breast cancer treatment as early as possible, which is important for the early diagnosis and prognosis of breast cancer.

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Function and Role of miRNA in Breast Cancer

It is well known that activation of oncogenes, inactivation of suppressor genes and alteration of related apoptotic genes lead to enhanced proliferation of malignant cell and disturbed regulation of apoptosis. The expression of these oncogenes is closely related to the malignant progression of tumors [7,8]. Only 1%-2% of the

transcribed RNA in the human genome encodes proteins, and the rest RNA is called non-coding RNA (ncRNA), which has an important role in the biological processes of diseases, such as the involvement in the development of tumors. miRNA is highly conserved endogenous ncRNAs that are 2-25 bp in length [9]. By binding to the 3' untranslated region (3'UTR) of target mRNAs, miRNAs lead to degradation or reduced translation of targeted mRNAs, thereby regulating the expression of targeted genes and participating in cell development, proliferation, differentiation and apoptosis [10]. Distant invasion and metastasis are the biological features of malignant tumors. Cancer metastasis is the main cause of death in breast cancer patients. Breast cancer metastasis is often a multi-step and multi-mechanism regulatory process. In recent years, a large body of literature has reported the mechanisms of miRNAs associated with recurrence and metastasis of breast cancer. For example, Zhang et al. [11] found that miR-138 expression was down-regulated in breast cancer, and over expression of miR-138 inhibited breast cancer cell metastasis; its down-regulation suggested poor prognosis in advanced stage patients. Li et al. [12] found that miR-141 expression was down-regulated in breast cancer tumor tissues, and its expression level correlated with tumor stage; miR-141 overexpression in vitro could significantly inhibited breast cancer cell proliferation, migration and invasion. Other studies found that overexpression of miR-106b and miR-93 promoted the invasion and metastasis of breast cancer cells. While the above studies suggest that miRNAs are indeed closely related to breast cancer progression, we still hope to explore newer miRNAs and reveal the complete regulatory network and mechanisms involved in breast cancer metastasis progression.

The Mir-19a-3p Promotes Breast Cancer

Our group has been engaged in clinical and basic research in breast cancer-related fields for many years. In our previous study, we identified a miRNA, miR-19a, which is up-regulated in breast cancer and functions as an oncogene according to other literature reports and database information. Previous studies have confirmed that miR-19a can be involved as an oncogene in the regulation of cell proliferation and metastasis in a variety of malignant tumors, including breast cancer [13], ovarian cancer [14], gastric cancer [15], gallbladder cancer [16] and prostate cancer [17]. miR-19a-3p belongs to the miR-17-92 family, the miR-17-92 gene cluster, located at chromosome 13q31.3. The miR-17-92 gene cluster is a typical cluster of multiple cis-trans genes encoding six miRNAs, including miR-17-5p, miR-18a, miR-19a-3p, miR-20a-3p, miR-19b-3p and miR-92, with important biological functions [18]. The sequence of miR-17-92 gene cluster is highly conserved in all vertebrates. There are few reports related to miR-19a-3p in breast cancer metastasis, and none of them have fully explored the molecular mechanisms involved. Therefore, it is important to further investigate the downstream regulatory mechanisms of miR-19a-3p involved in breast cancer metastasis.

The Mir-19a-3p/PTEN Signaling Axis May Be Involved in Breast Cancer Metastasis

PTEN is a phosphatase gene homologous to Tensin with a deletion on chromosome 10, located on chromosome 10q23.3, consisting of 9 exons and 8 introns, and is an oncogene closely related to tumorigenesis after p53 and Rb genes [19]. PTEN has three structural domains from N-terminal to C-terminal, and its N-terminal structural domain is the phosphatase functional domain of PTEN, which accounts for about half of the protein molecule, followed by the C2 structural domain and PDZ structural domain in that order. The C2 structural domain is the lipid membrane-binding structural domain whose function is to enable PTEN to bind to the cell membrane to initiate lipid phosphatase activity, as well as to stabilize PTEN phosphatase activity, maintain the stability of PTEN, and mediate the interaction between PTEN and other proteins [20]. PTEN is the first oncogene with phosphatase activity identified to date. PTEN acts as a tumor suppressor by regulating transcription, translation, cell cycle progression, inducing cell death, stimulating angiogenesis and stem cell self-renewal [21]. PTEN plays an important role in cell growth, proliferation, survival, apoptosis, cell migration invasion, local adhesion, and angiogenesis [22,23]. PTEN proteins are homologous to the cytoskeletal protein Tensin, which is involved in extracellular matrix adhesion and thus affects cell migration and is an important molecular basis for tumor infiltration and metastasis [24,25]. PTEN is often found in the nucleus. It was initially identified as a cytosolic protein (mainly used in tumor cells). In addition to the lipid phosphatase activity of PTEN, it also plays other roles. The nuclear function of PTEN is important for the ability of PTEN to inhibit tumor development. According to reports, nuclear PTEN plays an important role in chromosome stability, DNA repair and cell cycle regulation. In the cell nucleus, PTEN directly binds to p53 to promote the stability and transcriptional activity of the tumor suppressor gene p53. Forced expression of PTEN in the nucleus results in MAP kinase-dependent inhibition of cyclin D1 expression. Nuclear expression of PTEN leads to dephosphorylation of MAP kinase. Whether this is a direct effect of PTEN protein phosphatase activity is unclear. In addition, it was also found that PTEN and E2F synergistically induce the expression of Rad51, thereby enhancing DNA repair. This relationship between PTEN and Rad51 can explain the observation that the rate of double-stranded DNA breaks increases when nuclear PTEN function is disrupted [26].

We studied the downstream regulatory mechanisms of miR-19a-3p through extensive literature research, we found that PTEN is a direct target of miR-19a-3p, and miR-19a-3p mediated hepatocellular carcinoma metastasis can be detected by over-expression or silence PTEN [27]. Jiang et al. [27] found that miR-19a-3p promotes tumor metastasis and chemoresistance in hepatocellular carcinoma through the PTEN/Akt pathway. Zhang et al. [28] found that silencing of miR-19a-3p enhanced chemosensitivity of osteosarcoma cells by increasing the expression of the tumor suppressor PTEN. The above advances suggest that miR-19a-3p and PTEN have a targeted regulatory relationship, but whether the regulatory axis constituted by both is involved in the malignant progression of breast cancer metastasis deserves further investigation.

Studies have shown that PTEN gene can inhibit breast cancer development by promoting apoptosis, inducing breast cancer cell cycle arrest, inhibiting breast cancer cell migration, and suppressing tumor angiogenesis [29]. Zhang et al. found that the expression rates of PTEN protein were 22.5%, 55.5%, and 95.0% ($p<0.05$) in breast invasive ductal carcinoma tissue, paracancerous breast tissue, and cystic hyperplasia tissue, respectively, indicating that downregulated PTEN protein was closely associated with breast cancer metastasis [30]. This suggests that the miR-19a-3p/PTEN signaling axis may be an important regulatory axis in the metastatic mechanism of breast cancer.

PTEN Mediates PI3K/AKT/Mtor Pathway to Promote Malignant Progression of Breast Cancer

It is currently believed that the downstream regulatory pathways of PTEN genes mainly include the following four important

signaling pathways. (1) P13K-AKT-mTOR signaling pathway is an important signaling regulatory pathway involved in cell proliferation, apoptosis, migration and other processes, and is a hot new target in tumor therapy [31]. P13K, as a key protein on the P13K-AKT-mTOR signaling pathway, can produce phosphatidylinositides (e.g., phosphatidyl-3, 4, 5-trisphosphate, PIP3) through phosphorylation to regulate cell survival, growth, proliferation and metabolism [32]. Protein Kinase B (PKB), also known as AKT, is a serine/threonine protein kinase that includes three main isoforms, AKTl, AKT2, and AKT3, all three of which play extremely important roles in regulating cell proliferation and metabolism [33]. Mammalian Target of Rapamycin (mTOR) is a conserved serine/threonine protein kinase that belongs to the phosphatidylinositol kinase-related kinase family. mTOR has two forms, mTORCl and mTORC2. Activated by the P13K-AKT-mTOR pathway, it further regulates downstream proteins and plays a regulatory role in a variety of physiological functions such as cell growth, proliferation, apoptosis, autophagy and cell cycle [34]. It has been shown that aberrantly activated phosphorylated mTOR regulates the downstream substrates of this pathway mainly ribosomal s6 protein kinase (S6K) and eukaryotic initiator 4E Binding Protein 1 (4EBPl) [35]. Activation of mTOR phosphorylates both S6K1 and 4EBPl proteins and promotes the translation of mRNA, resulting in the expression of a large number of proteins related to the promotion of cell growth and proliferation, leading to enhanced malignant cell proliferation [36]. (2) Raf in the Raf-MEK-ERK signaling pathway has three isoforms, ARaf, BRaf, and CRaf, whose phosphorylation leads to MEK activation [37,38]. Downstream in the MEK superfamily signaling process, it is mainly responsible for the biological information transduction initiated by MEK and is at the central part of this pathway. The downstream component ERK1/2 is involved in the regulation of mTORcL through P90RSK, inducing alterations in transcription in the nucleus, which in turn affects cell proliferation, survival, motility and angiogenesis [39,40]. (3) Focal Adhesion Kinase (FAK) of the FAK pathway is an important molecule in the integrin-mediated signaling pathway. FAK tyrosine phosphorylation activates integrins, leading to increased levels of FAK tyrosine phosphorylation and enhancing its phosphokinase activity [41]. FAK activation activates several kinases and signaling molecules associated with it, promoting cell invasion and metastasis [44]. (4) The cell cycle protein pathway is PTEN regulates the cell cycle by inducing cell Cycle-Dependent Kinase (CDK) [43]. For more detailed PTEN/ERK and PTEN/FAK pathways, please refer to the figure below. Figure 1 the role of PTEN in ERK and AFK signaling pathways. (https://www.gloriousmed.com/news/154).

PI3K/AKT/mTOR, an important intracellular signaling pathway, is aberrantly activated in breast cancer [44]. PTEN mainly acts on the target molecule PIP3 downstream of PI3K through its lipid phosphatase activity, thereby blocking the PI3K/AKT signaling pathway to achieve its tumor suppressive effect. PTEN deficiency triggers excessive activation of the PI3K pathway, which subsequently leads to the accumulation of intracellular PIP3 and activation of downstream factors such as 3-phosphatidylinositol-dependent protein kinase 1 (PDK1) as well as AKT/PKB [45]. mTOR is an important target of action downstream of AKT that can be activated by phosphorylation by AKT and affects cell proliferation through 2 different downstream pathways, Ribosomal Kinase p70s6k (RSK) and eukaryotic initiation factor 4E binding protein 1 (4E-BP-1), which regulate specific mRNAs at the translational level and protein synthesis is regulated [46]. AKT1 regulates cell survival and anti-apoptosis and

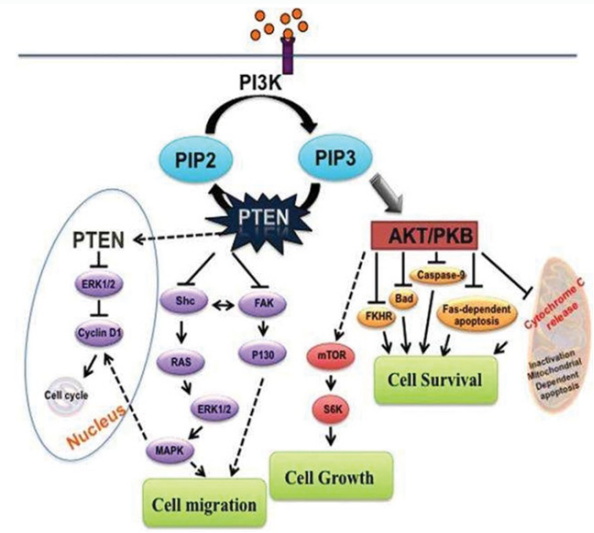

Figure 1: The role of PTEN in ERK and AFK signaling pathways.

AKT2 is mainly involved in glucose metabolism. In the PI3K/AKT pathway, AKT1 plays a role, and AKT2 does not participate in this pathway. Data shows that PTEN prefers to bind to phosphorylated Akt1, PTEN suppresses tumorigenesis by directly dephosphorylating Akt [47]. PI3K is generally activated in two ways, one by interacting with certain growth factor receptors or ligand proteins that alter its own dimeric structure, and the second activation is through direct binding of Ras to the catalytic subunit p110 leading to PI3K activation [48]. Activated PI3K produces the second messenger PIP3, which binds to AKT and PDK1, changing the structure and position of AKT, binding to PDK21 and PDK-2 on the cell membrane and undergoing phosphorylation, leading to AKT activation [49]. Activated AKT acts on a series of its downstream substrates such as bad, caspase9, Nuclear Factor kappaB (NF-κB) and Glycogen Synthase Kinase 23 (GSK23) to regulate cell proliferation, differentiation, apoptosis and migration by altering the corresponding functional states through phosphorylation [50]. The lack of PTEN expression in breast cancer patients leads to over-activation of AKT and continuous activation of PI3K/AKT signaling pathway. And other related molecules in this signaling pathway, such as PTEN, may also be efficient molecular target drugs [51]. PTEN is an oncogene with dual phosphatase activity that dephosphorylates Tyr, Ser and Thr [52].

Therefore, the involvement of PTEN in cellular regulation may be in the form of dephosphorylation. It has been shown that PTEN gene can be mutated, missing or inactivated up to 46% in human breast cancer tissues and cell lines, and that PTEN expression is significantly downregulated in breast cancer [53]. Taken together, it is clear that PTEN may promote the metastatic and malignant progression of breast cancer by mediating the PI3K/AKT/mTOR signaling pathway.

mir-19a-3p Promotes Breast Cancer Progression by Targeting PTEN-Mediated PI3K/AKT/Mtor Signaling Pathway

Combining the above recent advances at home and abroad, we found that in breast cancer, PTEN has been reported to be a target gene of some miRNAs. miR-19a-3p promotes the proliferation and migration of breast cancer cells by inhibiting the translation and expression of PTEN, while participating in the regulation of PI3K/AKT signaling pathway [54,55]. Therefore, miR-19a-3p, PTEN

gene and PI3K/AKT/mTOR signaling pathway all play important regulatory roles in breast cancer metastasis. miR-19a-3p may promote breast cancer progression by targeting PTEN-mediated PI3K/AKT/mTOR signaling pathway.

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Author Contributions

Chao Niu and Xiaogang Li conducted statistical analysis and drafted the manuscript. Bo Li and Ruofei Sun participated in the statistical analysis and the writing of the manuscript. Xiaodong He and Youcheng Zhang conceived the research, participated in the research design and coordination, and provided suggestions on the writing of the manuscript. All authors read and approved the final manuscript.

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