Research Progress on Malignant Transformation Mechanism of Precancerous Diseases of Breast Cancer

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Abstract: Breast cancer occurs in the epithelial tissue of breast, which is one of the most common female cancers in the world. In recent years, with the improvement of people's living standards, the incidence of breast cancer is also growing rapidly, so the prevention of breast cancer is very significant. At present, the etiology and pathogenesis of breast cancer are still unknown. Precancerous diseases are benign breast lesions with potential canceration, which may develop into breast cancer if they have not cured for a long time. This paper summarizes the latest research progress on the mechanism for malignant transformation of breast precancerous diseases in recent years, hoping to provide theoretical reference for basic research and early clinical diagnosis of breast cancer.

1. Introduction

Breast cancer is a malignant tumor that occurs in the epithelial tissue of the breast. The incidence of breast cancer ranks first among female malignant tumors, which seriously endangers the women's physical and mental health[1]. In modern society, with the change of people's life style and the increase of women's work and life pressure, the incidence of breast cancer is getting higher. According to statistics from relevant departments, in China, there were about 269,000 cases of breast cancer and 70,000 died in 2015, accounting for 15% and 7% of women's morbidity and death respectively[2], which seriously threatened women's physical and mental health. At present, the etiology of breast cancer are still unclear. The interaction of heredity, hormones, immunity and various environmental factors may participate in the occurrence and development of breast cancer. Precancerous lesion is an important stage in occurrence and development of breast cancer, detection and intervention in the early stage are essential methods to prevent and control breast cancer. Precancerous lesion of breast cancer is a multistage process, including epithelial hyperplasia (EH), atypical hyperplasia (AH), lobular carcinoma in situ (LCIS) and ductal carcinoma in situ (DCIS). Most precancerous lesions are in an unstable state, and malignant changes can occur under the continuous action of pathogenic factors, however, once the carcinogenic factors are relieved, they may remain stable, degenerate or reverse, and may return to normal state. This article reviews and summarizes the research progress on the mechanism for malignant transformation of breast precancerous lesions in recent years.
2. Tumor Angiogenesis
The growth and metastasis of tumors are closely related to angiogenesis, the expression of angiogenic factors can promote neovascularization and create conditions for the growth, invasion and metastasis of tumors. Angiogenesis has been found in the process of atypical hyperplasia of breast and it increases with the severity of atypical hyperplasia. Therefore, angiogenesis plays an important role in the occurrence, development and metastasis of precancerous diseases of breast cancer, and anti-angiogenesis has become a target in treating breast cancer. Lots of studies have shown that signaling pathways are involved in tumor angiogenesis, such as VEGF, CXCL16 and Leptin.

As a growth factor in vascular endothelial cells, VEGF can induce mitosis, promote the migration and proliferation of vascular endothelial cells, increase the permeability and integrity of blood vessels, which is essential for angiogenesis. Moreover, VEGF can promote angiogenesis, provide oxygen and nutrients needed for tumorigenesis, and increase the permeability of blood vessels and lymphatics to promote the growth and metastasis of breast tumors. Chemokine CXCL16 interacts with various kinds of cells in tumor cells and tumor microenvironment, which plays multiple roles in tumor cell proliferation, migration, apoptosis and angiogenesis. It was found that the expression of CXCL16 in breast cancer tissues and metastatic lymph nodes was significantly higher than that in normal tissues, and was positively correlated with the malignancy of the tumors. Adding S-CXCL16 into the cell line in vitro could enhance the proliferation, migration and invasion of the tumors. Overexpression of TM-CXCL16 in breast cancer cells by transfection can significantly inhibit cell migration and invasion. Binding with the leptin receptor (OBR) on breast cancer cells can activate multiple signaling pathways, promote the proliferation of cancer cells, inhibit apoptosis induce angiogenesis, and then promote the occurrence and development of breast cancer. With the strategy of blocking the angiogenesis of tumors, the development of angiogenesis inhibitors may provide a new method to inhibit the growth and metastasis of breast cancer cells.

3. Proto-oncogenes and TumorSuppressor Genes
With the development of cell biology and molecular biology, it has been recognized that the occurrence and development of breast cancer is the result of the interaction of a variety of abnormal genes. From the gene level, the occurrence of breast cancer is mainly due to the activation of proto-oncogene and the inactivation of tumor suppressor gene, which makes the cells lose normal regulation and differentiation out of control, infinite proliferation, and ultimately leads to the occurrence of cancer. In atypical breast hyperplasia, many oncogene proteins have expressed, such as microRNAs, HER-2, Cyclin, C-erbB-2, BRCA1, P53, PTEN etc.

It had been found that the miRNA-126 in breast cancer tissue was low expression and negatively correlated with the expression of vascular VEGF. Upregulation of miRNA-126 could reduce the expression of vascular endothelial growth factor and inhibit the proliferation and migration of breast cancer cells. The microRNA-126 knocked out the increased phosphorylation of ERK and AKT induced by vascular endothelial growth factor (VEGF) in cancer cells suggesting that microRNA-126 could inhibit tumor growth by targeting vascular VEGF to regulate the signal pathway of VEGF/Pi3K/AKT. Guo explored the expression and correlation of breast cancer susceptibility gene 1 (BRCA1) riboprotein and p53 protein in breast invasive ductal carcinoma (BIDC). The results showed that both BRCA1 and p53 were expressed in the nucleus, and the positive rates were 85.9% and 34% respectively. what's more, the expression of BRCA1 was closely related to lymph node metastasis and TNM stage, suggesting the interaction between BRCA1 and p53 affected the occurrence and development of BIDC.

Experiments have shown that the positive expression rates of BRCA1 and NM23-H1 in breast cancer are significantly lower than those in benign breast tumors; the expressions of BRCA1 and NM23-H1 gradually decrease with the increase of clinical stages and lymph node metastasis, suggesting that the coordinated decline of BRCA1 and NM23-H1 in the development of breast cancer may lead to tumor invasion and metastasis; BRCA1 is positively correlated with NM23-H1 expression in breast cancer, which may play a role in the occurrence and development of breast cancer.
a key participant in the ubiquitination of histone H2A, histone H2A affects gene expression patterns involved in proliferation, growth, DNA repair, apoptosis and aging of cells. In breast cancer, the decrease of BMI protein level leads to proliferation, apoptosis and aging of cells. Therefore, inhibiting BMI1 expression in breast cancer stem cells may be a potential strategy to eliminate cancer and prevent recurrence of cancer [9]. The mutation and amplification and overexpression of C-erbB-2 can cause tumorigenesis, which is common in breast cancer, ovarian cancer and gastrointestinal tumors. The oncogene C-erbB-2 and epidermal growth factor receptor EGFR had homology and can activate tyrosine kinase and participate in many kinds of intracellular signal transduction [10]. By detecting the expression of AQP-1 and AQP-4 in atypical breast hyperplasia, ductal carcinoma in situ and invasive ductal carcinoma, it was found that the positive expression rates of AQP-1 and AQP-4 decreased with the progression and expansion of breast lesions, which negatively correlated with the occurrence and development of breast cancer, suggesting that AQP-1 and AQP-4 may played an anti-oncogene role in the precancerous diseases of breast cancer, has important value in the diagnosis of breast cancer [11].

4. Hormone Receptor

The occurrence and development of breast cancer is the result of multi-factor and multi-step mutation. Breast is the main target organ of sex hormones, the growth and development of breast is regulated by various hormones, especially estrogen and progesterone. They mainly interact with receptors ER and PR in breast tissue cells. ER is a member of steroid nuclear receptor superfamily, it binds to estrogen and stimulate the signal transduction pathway of estrogen receptor, affecting the proliferation, differentiation and apoptosis of mammary epithelial cells. ERα and ERβ are the key factors to test the effectiveness of endocrine therapy [12]. Studies had shown that the positive expression rates of ER in normal breast tissues, benign lesions, atypical hyperplasia and early breast cancer were 25.00%, 34.29%, 63.16% and 60.00%, respectively. The positive expression rates of PR in the above groups were 37.50%, 42.86%, 68.42% and 76.67%, respectively, the differences were statistically significant. (P < 0.05). The results showed that the expression of ER and PR increased with time in atypical occurrence and carcinogenesis of breast, which was an essential factor to promote malignant transformation of precancerous diseases and provides an important basis for the prevention and early diagnosis of breast cancer [13].

5. Proliferation and Apoptosis of Cell

Cell proliferation and apoptosis in normal breast tissue are always keep in balance. The occurrence of breast cancer is closely related to uncontrolled cell proliferation and decreased apoptosis, CDCA7, p53 and Bcl-2 are the main genes related to cell apoptosis. The expressions of BAG-1, Bcl-2 and Bax were detected in FEA, DCIS, IDC and normal breast tissues. The positive expression rates of Bax and BAG-1 in normal breast tissues were significantly lower than those in IDC and DCIS groups. The positive expression rates of BAG-1 in breast cancer tissues were correlated with the positive expression rates of Bax, suggesting that BAG-1 and Bcl-2 promoted each other in the process of atypical breast hyperplasia transforming into breast cancer [14].

Tri-negative breast cancer (TNBC) is the most aggressive subtype of breast cancer with high proliferation and metastasis phenotype. CDCA7 is a new member of the cell division cycle related gene family, which is involved in embryonic development and disordered in various types of human cancer. It was found that CDCA7 was preferentially expressed in TNBC cell lines and tissues. CDCA7 silencing TNBC cell lines could effectively inhibit cell proliferation, invasion and migration. it's important that the depletion of CDCA7 greatly reduces the tumorigenicity and distant colonization of TNBC cells in vivo. In addition, EZH2 is a marker of malignant transformation of breast cancer, CDCA7 can increase the expression of EZH2 by enhancing the transcriptional activity of its promoter, at the same time, the increase of EZH2 expression is an important factor in the progression of TNBC mediated by CDCA7. These results suggest that CDCA7 up-regulates EZH2 through transcription, which may be a potential prognostic factor and therapeutic target for TNBC [15]. Therefore, to study the
pathological mechanism of the deterioration and excavate potential targets of breast precancerous diseases are particularly important for the accurate diagnosis and treatment of breast cancer.

6. Exosomes

Exosomes are nano-vesicle-like bodies secreted by autologous cells, which participate in material transport and signal transmission between cells and internal environment. Studies had shown that exosomes could carry genetic information of tumors, influence the formation of tumor microenvironment, promote tumor angiogenesis, enhance the ability of invasion and metastasis of tumor cells, mediate tumor immune suppression and participate in resistance to radiotherapy and chemotherapy, thereby promoting the occurrence and development of tumors\(^{[16]}\). Recent studies have found that the stimulated breast cancer cells could secrete certain types of exosomes. Nucleic acids and proteins transported by exosomes played an important role in the occurrence, metastasis and treatment of breast cancer. At the same time, exosomes could also transport antineoplastic drugs out of breast cancer cells, which leaded to drug resistance. However, exosomes, as cancer drug carriers, exhibited very low immunogenicity and biological toxicity, and were expected to become a new biological marker for early breast cancer screening\(^{[17]}\). Exo-BCa transformed adipose mesenchymal stem cells into myofibroblasts via the Smad pathway, participating in the reconstruction of tumor blood vessels and tumor cell metastasis. The miR-210 in the exosome entered vascular endothelial cells and acted on the target gene tyrosine protein kinase A3, which could activate endothelial cells so as to induce angiogenesis factors, thereby promoting angiogenesis\(^{[18]}\).

In conclusion, the development and deterioration of breast precancerous diseases are closely related to angiogenesis, oncogene expression, estrogen and progesterone, abnormal cell proliferation, apoptosis and exosomes. These factors play different roles in the process from atypical breast hyperplasia to carcinogenesis through independent action or interaction. Since the occurrence of cancer is the result of a combination of multiple factors, the current research on the mechanism of precancerous lesions of breast cancer is mostly from a single level, angle and factor. Therefore, the mechanism of precancerous lesions of breast cancer should be studied from multiple level, angle and factors in the future research. In short, we should strengthen the research on the mechanism of malignant transformation of breast precancerous lesions, and “do not treat the disease, but preventive treatment of disease”, to provide new ideas, ways and means for the intervention and treatment of breast precancerous lesions. The effective ways to prevent and control breast cancer is to strangle it in germination stage.

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