RESEARCH PROGRESS OF METASTATIC GENES IN BREAST CANCER

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ABSTRACT

The metastasis of breast cancer is a complex process, which is involved by many genes and completed by many steps. The common sites of metastasis of breast cancer are bone, lung, liver, and brain. A 52-year-old woman with primary lobular carcinoma of the right breast in our hospital showed small bowel and colon metastases, which is a rare case. The regulation of metastasis related genes is the molecular basis of tumor metastasis. Metastasis related genes are a class of genes that can promote or block the potential of tumor metastasis without affecting the growth and proliferation of tumor cells. Transfer related genes can be divided into two categories: transfer promotion gene and transfer inhibition gene, which involves cell adhesion change, extracellular matrix degradation, cell migration and motor ability change and neovascularization. The elucidation of the mechanism of breast cancer metastasis related genes and downstream signal transduction pathways will lay a foundation for molecular diagnosis and individualized treatment of metastatic breast cancer.

Keywords: *Breast cancer, metastasis, oncogene, tumor suppressor gene.*

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Introduction

The organs of distant metastasis of advanced breast cancer are usually lung, liver, bone, and brain[1]. Bone metastasis occurred in about 40% of patients, followed by lung metastasis, accounting for about 22%[2]. Solitary gastrointestinal metastasis from breast cancer is extremely rare[3], and the specific site of metastasis is not specific and often occurs in lobular carcinoma of the breast[4]. A 51-year-old female patient was admitted to our hospital because of intermittent epigastric pain for more than 8 months. The patient underwent right primary lobular carcinoma eradication, followed by postoperative radiotherapy and chemotherapy and bilateral oophorectomy nine years ago. Eight months ago, the patient had upper abdominal pain, colic and paroxysmal, lasting from a few minutes to more than half an hour, accompanied by diarrhea and watery stools. Abdominal pain was slightly relieved after defecation, accompanied by nausea and vomiting. The vomitus was stomach contents. One month ago, CA153 and CEA values were found to be increased, and no obvious abnormality was found in PET-CT value. The patient had no significant recent changes in body weight. Colonoscopy revealed scattered congestion points in ileum mucosa, uplifted lesions from hepatic curvature of the colon to 75 cm from the ascending colon to the anal margin, mild stenosis of the lumen, nodular and paving stone-like changes

on the lesion surface, and partial congestion of the mucosa. Intestinal pathology (ascending colon) reveals chronic mucosal inflammation, lymphoid tissue hyperplasia, and multiple lymphoid follicles. Clinical consideration of Crohn's disease, intestinal tuberculosis and intestinal neoplastic lesions cannot be excluded. Pathological results showed a few metastatic cancer cells in the ascending colon, chronic inflammation of mucosa in the terminal ileum, hyperplasia of lymphoid tissue with extrusion, abundant small blood vessels with small round cell proliferation.

Immunohistochemistry revealed CK7(+), CK20(+), ER(+), PR(-), HER2(1+), GCDFP-15(+), Mammagolobin(-), CDX-2(-), and Ki-67 (10%). Immunohistochemical results suggested metastatic breast cancer. Metastasis of breast cancer is a continuous and complex process in which many genes participate, interact and interact with each other. The basic process includes the change of cell adhesion, including the decrease of epithelial cell adhesion, the increase of epithelial cell adhesion to stroma, the degradation of extracellular matrix, the change of cell migration and angiogenesis. This article will focus on the breast cancer genes and tumor suppressor genes involved in the above-mentioned metastasis steps.

Materials and methods

Promotion of breast cancer metastasis related proteins

Protooncogene (AKT2)

Akt, a primary oncogene, belongs to the serine-threonine protein kinase family and is activated by some growth factors and cytokines in a phospholipid 4-acylinositol-3 kinase dependent manner. Akt family has three members: AKT1 (protein kinase α), AKT2 (protein kinase β) and Akt3 (protein kinase γ). The phosphorylation sites of them were at 473 (AKT1), 474 (AKT2) and 472 (Akt3) and 308 (AKT1), 309 (AKT2) and 305 (Akt3) threonine residues.

The Akt signaling pathway of phosphoinositol-3 kinase (PI-3K) plays an important role in the regulation of cell migration, invasion and metastasis. AKT1 and AKT2 have the same substrate in vivo, but their functions are different. The activation levels of AKT1 and AKT2 in different cells are different, and their subcellular localization is also different. AKT2 accumulates in the cytoplasm during mitosis and enters the nucleus during muscle cell differentiation. The function of AKT1 has been widely proved to mediate cell growth and survival. In recent years, studies have found that only AKT2 can promote the invasion and metastasis of breast cancer[5]. The full-length AKT2 cDNA with my tag was transfected into five different breast cancer cells: metastatic breast cancer cell line (MDA-MB-435), highly metastatic breast cancer cell line (MDA-MB-231), and breast cancer cell lines (MCF7, T47D, and SKBR3). It was found that the cell lines with high expression of AKT2 could promote the morphological changes of cells, that is, the cells became larger, the nuclei increased, and the vacuoles in the cytoplasm gathered; it interferes with the formation of cell membrane.

AKT2 overexpression can enhance the binding of cells to collagen IV and promote the adhesion and invasion of breast cancer cells, which is achieved by increasing the expression of integrin β 1, a collagen IV binding receptor[6]. Integrin β1 has been reported to be involved in many cancer metastasis related genes, and its synthesis is regulated by AKT2, indicating that integrin β1 also plays an important role in cancer cell metastasis. With the progress of research, AKT2 may be used as an important clinical detection index to predict the metastasis of breast cancer.

COX-2

Cyclooxygenase (COX) is a membrane-bound protease, which is the rate limiting enzyme of prostaglandin (PG) biosynthesis. It can catalyze arachidonic acid to produce bioactive end products PGE2, PGD2, PGF2, PGI2 and thromboxane. Studies have shown that[7] COX-2 and its catalytic product PG not only widely participate in many processes such as inflammation, but also participate in the occurrence and development of many solid tumors through a variety of pathogenic mechanisms. High expression of COX-2 contributes to the proliferation and transformation of precancerous cells and inhibits apoptosis[8].

Its functions are reflected in the following aspects:

• The product PGE2 stimulates the proliferation of tumor cells. PGE2 can also act on the same or adjacent cells, bind to the endogenous pyrogen (EP) receptor of cell membrane, and promote cell growth through G2 protein coupling pathway or peroxisome proliferator-activated receptor (PPAR[9].

• COX-2 is involved in tumor cell adhesion: the expression of COX-2 is increased and the level of E-cadherin is decreased, resulting in the loss

of contact inhibition between tumor cells, thus promoting tumor metastasis; COX-2 also affects cell adhesion by up-regulating the expression of CD44.

• Involved in extracellular matrix degradation: high expression of COX-2 can increase the expression of matrix metalloproteinase-2 and 9, imbalance matrix metalloproteinase / matrix metalloproteinase inhibitor (MMPs / tmmps), and degrade extracellular matrix[10].

Endothelin-1(ET-1)

Endothelin-1 (ET-1) is distributed in many tissues and organs, and its biological function requires binding to ET-1 receptor. Endothelin receptor is a glycoprotein composed of a single peptide chain located on the cell membrane. There are mainly two subtypes (ETA and ETB), which are G protein-coupled receptors[11, 12].

Endothelin can activate different signaling pathways, including phospholipase C, inositol triphosphate (IP3, IP3, IP4) and diacylglycerol (DG). IP3 promotes the mobilization of intracellular calcium, IP4 promotes the opening of membrane calcium channels and the influx of extracellular calcium. IP3 and IP4 work together to increase intracellular calcium concentration[13, 14].

DAG activates PKC and changes the permeability of ion channels. The increase of intracellular calcium and the opening of ion channels can activate a variety of cellular information pathways, resulting in biological effects.

The molecular basis of endothelin-1 in tumor metastasis is to promote the formation of tumor blood vessels:

• Tumor cells secrete ET-1, which can stimulate the proliferation and migration of endothelial cells and directly induce the formation of blood vessels by paracrine ETB receptor acting on endothelial cells.

• ET-1 promotes the secretion of vascular endothelial growth factor (VEGF) by binding to the ETA receptor and stimulates the proliferation and angiogenesis of endothelial cells induced by VEGF[12, 15, 16]. In turn, VEGF promotes the expression of ET-1 mRNA and the secretion of ET-1 in endothelial cells, and positively regulates the angiogenesis of ET-1.

• ET-1 can also activate matrix metalloproteinase-2, which is beneficial to the degradation of extracellular matrix and the invasion and migration of endothelial cells. The results show that: MMP-2 is very important for the invasion of endothelial cells in angiogenesis[17].

Metastasis-associated gene (MTA1)

The candidate metastasis related gene MTA1 was screened and cloned from 13762NF rat breast cancer metastasis system by dif2ferential cDNA library screening. MTA1 is expressed in both non tumor cells and tumor cells[18, 19], but the expression level is different in different cell lines. MTA1 gene is a new highly conserved gene, and its gene product is a nuclear protein. By using indirect immunofluorescence, it can be seen that MTA1 Protein is located in the nucleus, but the nucleolus is negative. Toh et al.[20] used Northern blot hybridization to detect the expression of MTA1 gene in mouse and human breast cancer cell lines. The results showed that the expression level of MTA1 gene in mouse high metastatic breast cancer cell line MTLn3 was 4 times higher than that in non metastatic cell line mtc4, and that in human high metastatic breast cancer cell line MDA-MB-231 was 4 times higher than that in non metastatic cell line MDA2-MB-2468, The ratio of expression level in human non metastatic breast cancer cell line MCF27, invasive cell line MCF LCC1 and metastatic cell line MCF7 LCC2 was 1:2:4. These results suggest that the mRNA level of MTA1 gene in mouse and human breast cancer cell lines is related to their metastatic or invasive potential. MTA1 is a subunit of nucleosome histone deacetylation complex (NuRD), which contains histone deacetylase (HDAC).

MTA1 is closely bound to HDAC in this complex, which is positively related to histone deacetylation, and is a co activator of histone deacetylase (HDAC)[21]. Therefore, MTA1 promotes breast cancer metastasis and histone deacetylation. As a new tumor metastasis related gene, although its function is not completely clear, existing studies and data show that the MTA1 gene is closely related to many tumor invasion and metastasis[22-24], and plays a role in signal pathways[25, 26]. With the further research, the mechanism of MTA1 gene will be more clear, which will provide a useful tool for the control of tumor metastasis.

Inhibition of breast cancer metastasis related proteins

Nm23 gene

Nm23 gene was isolated from the cDNA library of mouse K1735 melanoma cell line by steeg in 1988(27,28). So far, nine members of the nm23 gene family (nm23-h1-nm23-h9) have been found in the human body. Among them, nm23-H1 gene is most

closely related to tumor invasion and metastasis. Nm23-H1 gene product has the activities of nucleoside diphosphate kinase (NDPK), histidine protein kinase and serine autophosphorylation. Murakami et al.[29] showed that nm23-H1 protein can regulate the structural components of cytoskeleton and change cell morphology, and its expression level is related to the invasion and metastasis of human tumors. In recent years, studies at home and abroad have shown that nm23-H1 is also closely related to tumor resistance to radiotherapy and chemotherapy[30].

The possible molecular basis of nm23-H1 gene in tumor invasion and metastasis includes:

• nm23-H1 gene can up-regulate the expression of metastasis related gene products such as β-catenin and E-cadherin. In addition, nm23-H1 gene can inhibit the metastasis of matrix MMP-2, CD44v6 and VEGF, and promote the expression of related gene products.

• nm23-H1 protein inhibits the activity of some important kinases in tumor metastasis related signal transduction pathways, including mitogen activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK), protein kinase A (PKA), Wnt, protein kinase C (PKC) pathways(31-33).

• nm23-H1 gene protein can regulate the assembly of tubulin: intracellular tubulin binds to GDP, which is conducive to microtubule polymerization and maintains normal cell morphology. Nm23-H1 gene product with nucleoside diphosphate kinase (NDPK) activity can convert GDP on tubulin into GTP, which is prone to microtubule depolymerization and cell movement, and then tumor cell invasion and metastasis[34, 35].

BRMS1 gene

Seraj et al.[36] labeled human normal chromosome 11 with neomycin and introduced it into human breast cancer cell line MDA-MB-435. The human breast cancer metastasis suppressor gene (BRMS1) was found by comparing the DNA of MDA-MB-435 cells with that of MDA-MB-435 cells transduced with neomycin labeled chromosome 11.

BRMS1 gene is located in chromosome 11q13.1-q13.2, and its cDNA is 1485kb. The largest open reading frame of BRMS1 is 741kb (nucleotide 122-862), and it encodes a protein of 246 amino acids (molecular weight about 28500). BRMS1 gene has multiple phosphorylation sites, which indicates that BRMS1 gene may inhibit metastasis by regulating transcription. Human BRMS1 gene and its coding protein share 85% and 95% homology with mice, respectively, indicating that the gene is highly conserved in biological evolution[36, 37]. Through sequence alignment, it was found that there were other sequences with high homology with BRMS1, indicating that there might be a BRMS1 family[38]. Cicek et al.[39] showed that the metastatic potential of BRMS1 transfected breast cancer cells decreased by 50% - 90%. Zhang et al.(40) showed that BRMS1 can also play an inhibitory role in the process of breast cancer metastasis to the brain.

The expression level of BRMS1 gene in patients with brain metastasis of breast cancer decreased significantly, suggesting that the decreased expression level is related to distant metastasis of breast cancer. Zhang et al.[14] found that BRMS1 expression in early ovarian cancer was significantly higher than that in the late stage, which affected the metastasis of cancer cells. The results showed that BRMS1 did not change the proliferation of HO-8910PM cells and the formation of tumor in vivo, but it significantly inhibited the adhesion and invasion of HO-8910PM cells. The results showed that the formation of lung metastasis was significantly reduced by injecting BRMS1 into nude mice. These studies show that BRMS1 gene has no effect on tumor growth, but has an inhibitory effect on tumor metastasis.

Zhang et al.[41] reported that BRMS1 mRNA expression was significantly increased in breast cancer patients with age >50 years, tumor <2 cm or pr (+) and HER-2 (-). Therefore, the detection of BRMS1 gene expression in breast cancer tissues may indicate the prognosis of patients. Patients with high BRMS1 mRNA expression have a better prognosis than those with low BRMS1 mRNA expression. BRMS1 mRNA expression is a reliable prognostic factor for disease-free survival of breast cancer, and it is speculated that the measurement of BRMS1 mRNA expression will help to identify those breast cancer patients with poor prognosis. Saunders et al.[42] showed that BRMS1 expression was (0.372±0.038) in axillary lymph node metastasis group and (0.475±0.041) in non metastasis group. These results suggest that decreased BRMS1 gene expression can promote axillary lymph node metastasis of breast cancer. BRMS1 may be used as an indicator of lymph node metastasis in breast cancer patients, and it is speculated that the decreased expression of BRMS1 may be the characteristic of some high metastatic potential breast cancer. Based on the above analysis, we infer that the expression level of BRMS1 in breast cancer is negatively correlated with distant metastasis

and clinical stage, but not with pathological type. Until now, the mechanism of BRMS1 inhibiting tumor metastasis is not clear. Saunders et al.[42] found that after BRMS1 gene was transfected, breast cancer cells restored homojunction, and the expression of connexin 43 was up-regulated, which improved the signal transduction of heterogeneous connexion between cancer cells and normal tissue cells, and inhibited the metastasis of cancer cells from the primary tumor. Dewald et al.[43] found that BRMS1 is related to the decrease of phosphatidylinositol signaling pathway in breast cancer cells, which can regulate the structure of mammalian cytoskeleton and inhibit the metastasis of cancer cells. Samant et al.[44] found that BRMS1 regulates OPN by controlling the activity of NF kappaB (osteopontin is a tumor metastasis activator, which is related to tumor progression and invasion). Inhibition of OPN may be one of the mechanisms of BRMS1 inhibiting tumor metastasis.

Currently, there are not many studies on BRMS1 in gastric cancer. A study had used immunohistochemistry to detect the expression of BRMS1 protein in 60 cases of gastric cancer tissues and 60 cases of corresponding adjacent tissues[45]. The expression difference in the adjacent tissues is statistically significant. At the same time, its research also shows that the differences in the degree of tissue differentiation, lymph node metastasis and clinical stage of BRM1 in patients with gastric cancer are also statistically significant. In summary, BRMS1 is as important as breast cancer in terms of metastasis and prognostic evaluation of gastric cancer patients.

E-cadherin

E-cadherin (E-Cad) is a calcium dependent adhesion molecule, which widely exists in all kinds of epithelial cells. A large number of data show that when the expression of E-cad is decreased, the adhesion between cells will be weakened, the cells are easy to fall off, and the adhesion between cells will be decreased, resulting in the cells easy to disperse and infiltrate outward.

The tumor thrombus is easier to attach to the capillary bed than the scattered cancer cells. The patients with decreased E-cad activity of breast cancer are prone to lung and bone metastasis. Studies have found that not only the abnormal expression of E-cad protein itself can cause changes in its adhesion function, which can promote tumor invasion and metastasis, but also the deletion and structural changes of catenin, a part of E-cad functional complex, can affect the normal adhesion function of E-cad[46, 47]. The intracellular segment of E-cad is connected to the cytoskeleton through catenin, which connects E-cad to other membrane binding proteins to maintain the adhesion between cells and maintain close contact between cells. For example, the dysfunction of cytoplasmic catenin can make e-cad-mediated cell adhesion unstable, and E-cad can not function if catenin is not expressed.

PTEN

Phosphatase and tensionhomolog deleted from chromosome 10 (PTEN), a tumor suppressor gene, was discovered in 1997. PTEN loss and mutation exist in a variety of human malignant tumors and hereditary tumor susceptibility gene syndrome. The occurrence of breast cancer is often accompanied by the loss or weakening of PTEN protein. It has been reported that the expression of PTEN protein is negative in 15% of breast cancer and weakened in 18% of breast cancer. If the expression of PTEN protein is absent or weakened, it can not antagonize the effect of protein kinase PI3K and lose the negative regulation of PI3K/PKB/Akt signal transduction pathway, resulting in abnormal function of this signal transduction pathway; such abnormality can make mammary gland acinar epithelial cells lose normal cell cycle regulation, cell proliferation is excessive and prone to malignant transformation[48].

It was found that PTEN was highly expressed in normal breast tissues. The expression rate of PTEN in breast cancer with axillary lymph node metastasis was 37.8%, which was significantly lower than that in breast cancer without lymph node metastasis. With the increase of histological grade and clinical stage, the expression of PTEN decreased. The low expression rate of PTEN protein in invasive breast cancer was higher than that in carcinoma in situ, and the low expression rate of PTEN protein was the highest in stage II and III tumors. Combined with clinicopathological parameters, PTEN may be an independent prognostic indicator. PTEN has abnormal expression in breast cancer, plays a certain role in the occurrence and development of breast cancer, and is one of the prognostic factors of breast cancer[49, 50].

CD cathepsin

CD is a glycoprotein that can be synthesized in normal tissues. It exists in low concentrations in all cells, mainly distributed in the cytoplasm, and can also be found on the cell membrane. CD

is stored in the lysosome in the cytoplasm. It is an aspartate endopeptidase and has a two-leaf structure like other aspartases such as renin, chymosin and pepsin (proto), But different from them: CD reaches the lysosome through intracellular pathways(51). In breast cancer research[52], CD has been shown to be a mitogen at work, which promotes cell growth through the inactive propeptide of the enzyme. CD showed mitogenic activity in breast cancer cell lines cultured in vitro. Blonde and colleagues[53] reported that the down-regulation of CD gene expression through the transfer of antisense genes can inhibit experimental lung metastasis in human MDA MB 231 breast cancer cells. The artificially synthesized peptide of CD precursor has no mitogenic effect, which indicates that the receptor of the precursor fragment is not involved. Furthermore, the mitogen activity of CD is not due to the inhibition of CD precursor and mannitol 6 phosphate. (M6P) The interaction of the receptor[52] is blocked. Excessive M6P partially inhibits the binding and intracellular uptake of CD precursors, which indicates that M6P related receptors that contribute to phagocytosis may be related to the mitogen activity of CD. These results indicate that CD is a protein Ligand exists and interacts with a mitogen receptor, but the mechanism of this mitogen activity is still unclear.

Through IH analysis of the distribution of CD in gastric tissue, it was found that this proteolytic enzyme is commonly present in various types of cells in normal gastric mucosa, and also in benign and malignant gastric diseases, but it is in the malignant invasion of gastric cancer. The specific role of the process is not clear[54]. The important difference between this proteolytic enzyme in normal gastric mucosa and inflammatory gastric diseases has not been clarified in the early stage, and these studies have not found any immune response to CD in intestinal metaplasia or well-differentiated gastric adenocarcinoma, but in Strong and diffuse CD staining can be observed in poorly differentiated gastric adenocarcinoma and signet ring cell carcinoma. It shows that the expression level of CD is related to the degree of differentiation of gastric cancer, but it has not clarified whether it plays a specific role in the progression of gastric cancer. However, clinical observations support the hypothesis that CD may play an important role in this process. Tumor cells become more aggressive. The CD in tumor cells was stained by IH and found that the strongest staining site was at the edge of tumor progression. This particular site was closely related to certain clinical parameters of gastric cancer progression, such as clinical staging and lymph node metastasis. Allgayer et al.[55] conducted a continuous study on 203 patients through IH and showed that the level of CD is closely related to overall survival and a short disease-free interval. Multivariate analysis believes that CD can be used as a response to disease-free interval. Independent parameters. The study of Goishi et al.[56] on 136 patients with infiltration into the submucosa and muscularis propria showed that the probability of lymphatic metastasis increases when CD expression is high. These observations are consistent with the findings of Ikeguchi et al.[57]. Their study on 160 patients with early gastric cancer showed that the expression level of CD is closely related to lymph node metastasis, and further studies on these patients found CD-positive cancer cells The percentage is higher in diffuse gastric cancer than intestinal gastric cancer. Moreover, Ikeguchi et al.[58] further reported that the expression level of CD in diffuse and intestinal gastric cancer is related to the depth of tumor invasion and the very low five-year survival rate. These results indicate that interstitial cell CD plays an active role in this type of tumor infiltration and can greatly affect the prognostic significance of this enzyme.

Although studies on CD that may induce the growth and spread of gastric cancer cannot fully clarify the mechanism, they can provide a basis for clinically using CD as a marker involving lymph node metastasis, and suggest that this proteolytic enzyme can be used as a clinical prognosis for patients with gastric cancer.

Conclusion

Breast cancer seriously affects women's health, and distant metastasis of breast cancer is closely related to the treatment and prognosis of breast cancer. The distant metastasis of breast cancer is a complex process of multiple factors and the interaction of multiple metastasis related proteins. In the treatment of breast cancer, in addition to the traditional surgical treatment, radiotherapy and chemotherapy, hormone therapy and molecular targeted therapy have also achieved a certain effect[59, 60].

Although there are a lot of studies on metastasis related genes of breast cancer, the exact mechanism of many related genes affecting metastasis is not very clear. With the continuous progress of research work in this area, new genes and related factors are constantly found, and their mechanism of action

is more and more in-depth study, which is of great significance to the comprehensive treatment and prognosis of breast cancer. It is helpful to provide new ideas for the early and postoperative adjuvant treatment of breast cancer, inhibit the metastasis of breast cancer early, and improve the quality of life of patients.

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