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Full Length Research Paper

The expression of tumor metastasis suppressor gene KAI1 and matrix metalloproteinase 2 in breast cancer tissues

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The objective of this study is to investigate the expression of tumor metastasis suppressor gene KAI1 protein and matrix metalloproteinase 2 (MMP-2) in breast carcinoma. We retrospectively analyzed 60 cases of patients from June, 2005 to June, 2011 treated with radical mastectomy for invasive ductal breast cancer in our department. The carcinoma tissue was stained for KAI1 and MMP2 with immunohistochemistry. In breast cancer group, the positive expression rate of KAI1 was 41.7%, which was significantly lower than control (83.3%) (χ^2 = 17.328, P < 0.05); the positive expression rate of MMP-2 was 80.0%, which was significantly higher than control group (16.7%) (χ^2 = 41.637, P < 0.05). Within the breast cancer patients, the group with lymph node metastasis showed higher positive rate of KAI1 and MMP2 expression than those without lymph node metastasis (P < 0.05). The patients with tumor diameter more than 5 cm showed lower positive rate of KAI1 but higher positive rate of MMP-2 expression than patient group with tumor diameter less than 5 cm. Additionally, tumor-nodes-metastasis III (TNM III) grade patients showed lower positive rate of KAI1 but higher positive rate of MMP-2 expression than patient group in I and II grades. KAI1 and MMP-2 were highly expressed in breast cancer tissues. The positive expression of KAI1 and MMP-2 were associated with tumor metastasis, tumor size, TNM grades etc.

Key words: Breast cancer, KAI1, matrix metalloproteinase 2 (MMP-2), immunohistochemistry.

INTRODUCTION

Breast cancer is one of the most common malignant cancers in woman, with increasing incidences in recent decades. The causes of mortality by breast cancer mainly include the lymph node and blood metastasis (Budach, 2011; Ruiterkamp and Ernst, 2011). Therefore, the investigation of the underlying molecular mechanisms controlling tumor metastasis is critical in breast cancer control and treatment.

KAI1 is a newly identified inhibitory gene for tumor metastasis, while its role in breast cancer metastasis has not been fully investigated (Dong et al., 1995; Ueda et al., 1996; Yang et al., 1997). Additionally, matrix metalloproteinase-2 (MMP-2) has also been known for its roles in tumor invasion and metastasis due to its degrading function of the basal membrane and the extracellular matrix (ECM) components (Cockett et al., 1998; Bachmeier et al., 2005; Jezierska and Motyl, 2009). However, whether these two factors jointly involved in tumor/breast cancer metastasis is unknown. The present study investigated the changes of KAI1 and MMP-2 in breast cancer patients and correlated the results with clinical pathological characteristics.

MATERIALS AND METHODS

Clinical data

Sixty (60) cases of patients (24 to 70 years old with a mean of 43.6 ± 11.5 years old, median age 45 years old) from June, 2005 to

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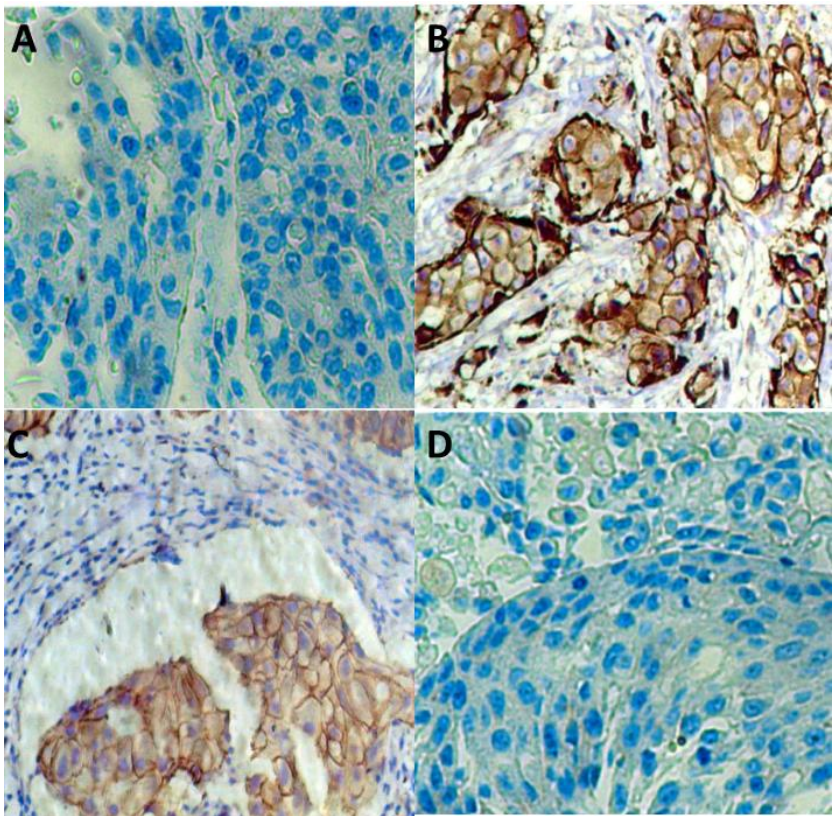

Figure 1. A, In invasive ductal carcinoma tissue KAI1 is lowly expressed in cell membrane and cytoplasm (×200); B, In benign breast tissue, KAI1 is highly expressed in cell membrane and cytoplasm (×200); C, In invasive ductal carcinoma tissue MMP-2 is positively expressed in cell membrane and cytoplasm (×200); D, In benign breast tissue MMP-2 is lowly expressed in cell membrane and cytoplasm (X×200).

June, 2011 treated with radical mastectomy for invasive ductal breast cancer in our department was retrospectively recruited in this study. The diagnoses were confirmed with pathological sample dissected from the surgery, and all patients were without pre-chemotherapy. The patients were divided according to tumor-nodes-metastasis (TNM) grades: 14 cases of stage I, 29 cases of stage II, and 17 cases of stage III, or by histological grades: 29 cases of stage I, 17 cases of stage II, and 14 cases of stage III. Twenty-seven (27) cases of patients showed tumor size more than 5 cm. Twenty-one (21) cases of patients showed lymph node metastasis. Fifteen (15) patients have post-menopausal.

Thirty (30) cases of subjects (25 to 70 years old, averaged at 44.8 ± 9.7 years old) with benign breast cancer tissue samples were recruited as control group. There were no differences in the age composition of the two groups (P>0.05). The study has been approved by Local Ethic Committee of human research and has the informed written consent of all patients.

Immunohistochemistry

The samples obtained during surgery were fixed in 10% neutral formalin solution, and processed for 5 μm paraffin sections. The mouse-anti human KAI1 and MMP-2 monoclonal antibody (1:200, Jinqiao, Beijing) were incubated overnight at 4°C and finally the reaction was visualized with 3,3'-diaminobenzidine (DAB) approach. Then sections were examined under microscope and 5 areas per section were randomly selected for counting of positive cells. The positive cell rate were recorded as negative (–) for < 5%, positive (+) for 5 to 25%, ++ for 25 to 50%, and +++ for >50%.

Statistics

All data were represented as mean ± standard deviation (SD) and analyzed with SPSS 13.0 software (Chicago, US). The χ^2 test was used to examine the relationship between the expression of KAI1/MMP-2 and the clinical characteristics; the correlationship was examined with Pearson test; P<0.05 was determined as statistically significant.

RESULTS

The expression of KAI1 and MMP-2 in breast cancer and control groups

The staining results are shown in Figure 1. In breast cancer, the positive expression rate of KAI1 was 41.7%, which was significantly lower than control (83.3%) (χ^2 =17.328, P<0.05); the positive expression rate of MMP-2 was 80.0%, which was significantly higher than control group (16.7%) (χ^2=41.637, P<0.05) (Table 1).

Table 1. The expression of KAI1 and MMP-2 in breast cancer and control groups.

Group	n	KAI1			MMP-2		
		Positive (cases)	Negative (cases)	Positive rate (%)	Positive (cases)	Negative (cases)	Positive rate (%)
Breast cancer	60	25	35	41.7*	48	12	80.0*
Control	30	25	5	83.3	5	25	16.7
x^2				5.328			12.777
P				0.000			0.000

*, P<0.05 in comparism with control group.

Table 2. The expression of KAI1 and MMP-2 in breast cancer patients with different clinical features.

Clinical parameter		n	KAI1		*t*	P	MMP-2		*t*	P
			Positive (cases)	Positive rate (%)			Positive (cases)	Positive rate (%)		
Age	<50years	41	17	41.5	2.708	>0.05	32	78.0	2.877	>0.05
	≥50 old	19	8	42.1			16	84.2		
Lymph node metastasis	Yes	21	3	14.3	10.530	<0.05	20	95.2	3.537	<0.05
	No	39	22	56.4			28	71.8		
Tumor size	≥5 cm	27	9	33.3	3.879	<0.05	26	96.3	3.852	<0.05
	<5 cm	33	16	48.5			22	66.7		
TNM stage	Stage I - II	43	22	51.2	7.731	<0.05	32	74.4	3.373	<0.05
	Stage III	17	3	17.6			16	94.1		
Histological stages	Stage I	29	18	62.1	13.176	<0.05	21	72.4	3.007	<0.05
	Stage II	17	6	35.3			14	82.4		
	Stage III	14	1	7.1			13	92.9		
Menstruation	Normal	45	19	42.2	2.815	>0.05	37	82.2	2.690	>0.05
	Paused	15	6	40.0			11	73.3		

The expression of KAI1 and MMP-2 in breast cancer patients with different clinical features

Within the breast cancer patients, the group with lymph node metastasis showed higher positive rate of KAI1 and MMP2 expression than those without lymph node metastasis (P<0.05). The patients with tumor diameter more than 5 cm showed lower positive rate of KAI1 but higher positive rate of MMP-2 expression than patient group with tumor diameter less than 5 cm. Additionally, TNM III grade patients showed lower positive rate of KAI1 but higher positive rate of MMP-2 expression than patient group in I and II grades (Table 2).

DISCUSSION

KAI1 was firstly identified as tumor metastasis gene from human prostate cancer hybrid cell in 1995 (Dong et al., 1995, 1997; Ueda et al., 1996).

KAI1 could mediate the interactions between cells or cells and the ECM to change the ability of cell adhesion and migration (Yoshida et al., 1998). It has been shown that low differentiation of the cancer cells was associated with lower expression of KAI1 (Chen et al., 2011). This is in consistent with the present results: the KAI1 expression was down-regulated in breast cancer tissues, and the patients with lymph node metastasis showed lower KAI1 expression than those without. These data suggested that decreased KAI1 expression is closely related to the tumor progression and metastasis.

MMPs were considered as one of the most important proteolytic enzymes involving in tumor growth and invasion (Cockett et al., 1998). MMP-2 has been shown to be involved in breast cancer metastasis, by degradation of the ECM and induction of angiogenesis (Jezierska and Motyl, 2009). The present study showed that in breast cancer group, the MMP-2 was highly expressed; within the cancer group, MMP-2 expression is positively correlated with tumor metastasis, but not with age and menopause factors.

Taken together, our studies proved that changes of KAI1 and MMP-2 were associated with the development and progression of breast cancer in our population. These provided rational bases for molecule-based diagnosis of breast cancer and prognosis. Future studies are still required to recruit more patients to verify these results.

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