



Expression levels of survivin, Bcl-2, and KAI1 proteins in cervical cancer and their correlation with metastasis

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ABSTRACT. Cervical cancer is associated with abnormal expression of multiple genes. Survivin and Bcl-2 proteins are apoptosis inhibitors. The tumor suppressor gene *CD82*, which encodes the protein KAI1, is downregulated in cervical cancer, and is associated with differentiation degree. We investigated the expression levels of three proteins and their correlation with metastasis in cervical cancer by comparing them in different cervical lesions. Immunohistochemistry was used to detect their three protein expression levels in the normal cervix, chronic cervicitis, cervical intraepithelial neoplasia (CIN) lesions, and cervical cancer. The relationships between the protein expression levels and tumor type, clinical stage, tissue differentiation, invasion, and metastasis were analyzed. Survivin and Bcl-2 expression levels in cervical cancer were significantly higher than in the normal cervix, chronic cervicitis, or CIN ($P < 0.05$). KAI1 expression was markedly lower in cervical cancer than in the normal cervix, chronic cervicitis, or CIN ($P < 0.05$). There was no statistical difference between the expression levels of the three proteins in CIN and

chronic cervicitis, but there were differences in expression between CIN and normal cervical tissues ($P < 0.05$). Bcl-2 and survivin levels were positively correlated while KAI1 expression was negatively correlated with clinical stage. Survivin and KAI1 expression levels were associated with lymph node metastasis ($P < 0.05$), and KAI1 expression was positively related with differentiation degree ($P < 0.05$). Survivin, Bcl-2, and KAI1 are metastasis-related factors in cervical cancer. Overexpression of survivin and Bcl-2, and low expression of KAI1 promotes cervical cancer progress and metastasis.

Key words: Cervical cancer; Bcl-2, Survivin; KAI1; Metastasis

INTRODUCTION

Cervical cancer is a common malignant tumor of the female reproductive organs. In recent years, the incidence of cervical cancer has increased annually as a result of environmental and life stresses. Furthermore, there is a trend toward earlier onset. Distant metastasis is a major cause of death. Patients with advanced cervical cancer present a poor prognosis. Early diagnosis and treatment represent the key to increasing cervical cancer survival rates and improving quality of life in patients. Investigations have focused on the mechanisms associated with cervical cancer invasion and metastasis, which are important for the improvement of patient prognoses (Ozden et al., 2014; Winer et al., 2015). Tumorigenesis is associated with multiple genes and the interaction between several factors. The pathological process of cervical cancer is related to apoptosis suppression, which is regulated by tumor-suppressor gene inactivation, oncogene activation or mutation, and anti-apoptosis gene overexpression (Ouyang et al., 2008a,b). Survivin and Bcl-2 are anti-apoptosis proteins (Adefolaju et al., 2014; Liu et al., 2014). *BCL2*, which has long been recognized as an apoptosis regulation gene, has received in-depth study, and its rate of expression increases in cervical cancer tissue. The *BIRC5* gene, which encodes the protein survivin, strongly inhibits apoptosis, and its expression level is elevated following a decrease in cancer differentiation. The tumor suppressor gene *CD82*, which encodes the protein KAI1, can suppress metastasis in a variety of tumors, such as lung, prostate, and colon cancers. However, the relationship between KAI1 and cervical cancer is controversial. KAI1 is a cell surface glycoprotein that participates in cell adhesion regulation and impedes tumor cell separation, thereby inhibiting tumor metastasis. *CD82* gene expression is downregulated in the early stages of cervical cancer (Wang et al., 2001; Singh et al., 2004). In this study, we investigated the relationship between the expression levels of three proteins and the various clinicopathologic characteristics of cervical cancer by comparing them at different stages of the cancer: normal tissue, chronic cervicitis, cervical intraepithelial neoplasia (CIN) lesions, and cervical cancer.

MATERIAL AND METHODS

Clinical information

Tissue specimens were selected from 25 cases of normal cervical tissue, 25 cases of chronic cervicitis, 30 cases of CIN, and 45 cases of cervical cancer (41 squamous cell carcinomas

and 4 adenocarcinomas). All hematoxylin and eosin (H&E)-stained slices were confirmed by two pathologists. The mean age of the 45 cervical cancer patients was 36.5 ± 4.2 (26-51) years. There were 14 cases with high differentiation, 28 cases with moderate differentiation, and 3 cases with poor differentiation. Furthermore, 4 cases were at stage I, 38 cases were at stage Ib-IIa, and 3 cases were at stage IIb-III. Lymph node metastases were present in 29 cases and absent in 16 cases. No patients received chemotherapy or radiotherapy before surgery. The patients who did not undergo surgery were diagnosed by magnetic resonance imaging, while those who did were diagnosed by pathology.

The mean age of the 30 patients with CIN was 37.1 ± 3.4 (25-50) years. There were 10 cases at CIN level I, 12 cases at CIN level II, and 8 cases at CIN level III. The mean age of the 25 normal controls was 36.8 ± 3.6 (25-52) years, and the patients with chronic cervicitis were 37.3 ± 3.33 (26-52) years old. There was no significant difference among the different groups ($P > 0.05$) (Tables 1 and 2).

Table 1. General clinical data for patients with different cervical lesions.

| Group | N | Mean age (y) | Differentiation (No.) | | | Lymph node metastasis (No.) | |
|--------------------|----|----------------|-----------------------|----------|------|-----------------------------|---------|
| | | | Good | Moderate | Poor | With | Without |
| Normal control | 25 | 36.8 ± 3.6 | - | - | - | - | - |
| Chronic cervicitis | 25 | 37.3 ± 3.3 | - | - | - | - | - |
| CIN | 30 | 37.1 ± 3.4 | - | - | - | - | - |
| Cervical cancer | 45 | 36.5 ± 4.2 | 14 | 28 | 3 | 29 | 1 |

CIN = cervical intraepithelial neoplasia.

Table 2. Clinical staging of patients with different cervical lesions.

| Group | N | Clinical staging (No.) | | |
|--------------------|----|------------------------|----|-----|
| | | I | II | III |
| Normal control | 25 | - | - | - |
| Chronic cervicitis | 25 | - | - | - |
| CIN | 30 | 10 | 12 | 8 |
| Cervical cancer | 45 | 4 | 38 | 3 |

CIN = cervical intraepithelial neoplasia.

The study protocol was approved by the Research Ethics Committee of our hospital, and all patients gave their informed consent before study commencement.

Methods

Immunohistochemistry was used to determine survivin, Bcl-2, and KAI1 protein expression levels in the different cervical tissues according to the manufacturer instructions supplied by the Beijing Zhongshan Biotechnology Co., Ltd (Beijing, China). Cervical tissue specimens were continuously resected into 4- μ m sections and treated with Bcl-2 monoclonal antibody (1:50), survivin polyclonal antibody (1:100), or KAI1 polyclonal antibody (1:200). The slices were observed following paraffin dewaxing, microwave antigen repair, 3,3'-diaminobenzidine staining, hematoxylin re-dyeing, making transparent, and sealing. Phosphate-buffered saline was used instead of antibody as the negative control, and breast biopsy was adopted as a positive control.

The relationship between survivin, Bcl-2, and KAI1 expression levels and cervical cancer invasion metastasis was analyzed.

Analysis of positive expression

The slices were reviewed by two pathologists using the double blind method. Cells that expressed survivin, Bcl-2, or KAI1 appeared as pale yellow or tan particles. The positive cell number and cellular staining intensity were observed under high magnification (400X) for semi-quantitative analysis. Staining intensity was scored as follows: 0 represented no coloring, 1 represented dyeing to pale yellow, 2 represented dyeing to yellow, and 3 represented dyeing to tan. Five visions of each section were randomly selected for observation and the percentage of positive cells in 500 cells was evaluated for scoring: 0 represented less than 10% positive cells, 1 represented 10-40%, 2 represented 40-70%, and 3 represented 70% or higher. The two scores were added together to provide a measure of positive expression: positive (+), ≥ 2 ; negative (-), 0-1.

Statistical analysis

All statistical analyses were performed using SPSS18.0 software (Chicago, IL). The Pearson χ^2 test and the Fisher's exact *t*-test were used to assess the differences between the enumeration data. Spearman rank correlation analyses were performed for correlation. P values of less than 0.05 were considered significant.

RESULTS

Bcl-2, survivin, and KAI1 expression levels in different cervical tissues

Table 3 shows that the expression levels of survivin and Bcl-2 in cervical cancer tissue (66.7 and 68.9%, respectively) were significantly higher than in normal cervical tissue (0.0 and 4.0%, respectively), chronic cervicitis (16.0 and 12.0%, respectively), and CIN (36.7 and 33.3%, respectively) ($P < 0.05$), while KAI1 expression in cervical cancer tissue (40.0%) was markedly lower than in normal cervical tissue (96.0%), chronic cervicitis (92.0%), and CIN (73.7%) ($P < 0.05$). The expression levels of survivin, Bcl-2, and KAI1 in CIN were not statistically different when compared with those for chronic cervicitis tissues, but were statistically different from normal cervical tissue ($P < 0.05$). Survivin and KAI1 expression levels were similar between normal cervical tissue and chronic cervicitis, while Bcl-2 expression was different between normal cervical tissues and chronic cervicitis ($P < 0.05$) (Table 3).

Table 3. Bcl-2, survivin, and KAI1 expression levels (N, %) in different cervical tissues.

| Group | N | Bcl-2 | Survivin | KAI1 |
|--------------------|----|-------------|-------------|-------------|
| Normal control | 25 | 1 (4.0)* | 0 (0)* | 24 (96.0)* |
| Chronic cervicitis | 25 | 3 (12.0)* | 4 (16.0)** | 23 (92.0)* |
| CIN | 30 | 10 (33.3)** | 11 (36.7)** | 22 (73.7)** |
| Cervical cancer | 45 | 31 (68.9)* | 30 (66.7)* | 18 (40.0)* |
| χ^2 | - | 38.5802 | 36.7766 | 32.9956 |
| P value | - | 0.00 | 0.00 | 0.00 |

CIN = cervical intraepithelial neoplasia. * $P < 0.05$ compared with normal control; ** $P < 0.05$ compared with cervical cancer.

Bcl-2 was mainly expressed in the cytoplasm, while survivin was mainly expressed in the cytoplasm and cell membrane, and their expression levels increased in increments from cervicitis to CIN and cervical cancer. KAI1 was mainly expressed in the cell membrane, and its expression declined from cervicitis to CIN and cervical cancer (Figure 1).

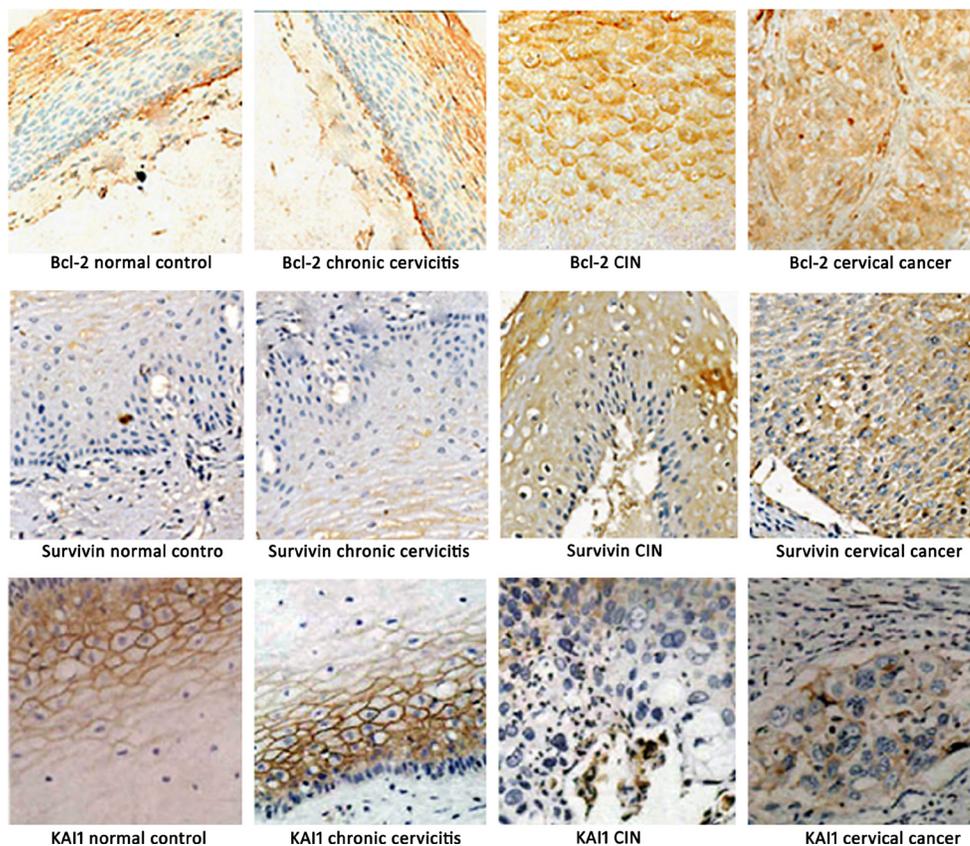


Figure 1. Bcl-2, survivin, and KAI1 expression in different cervical tissues.

Relationship between Bcl-2, survivin, and KAI1 expression levels and clinicopathological characteristics in cervical cancer

There were no statistically significant differences in the expression levels of the three proteins between young (<35 years) and older (≥ 35 years) patients ($P > 0.05$). Bcl-2 expression was associated with clinical stage ($P < 0.05$), but not with tissue type, tumor type, differentiation, or lymph node metastasis ($P > 0.05$). Survivin expression was positively correlated with clinical stage, and was associated with lymph node metastasis ($P < 0.05$), but not with tumor type, tissue type, or differentiation ($P > 0.05$). KAI1 expression was associated with lymph node metastasis, differentiation, and clinical stage ($P < 0.05$), but not with tumor type or tissue type ($P > 0.05$) (Table 4).

Table 4. Relationship between Bcl-2, survivin, and KAI1 expression levels and clinicopathological characteristics in cervical cancer (N, %).

| Factors | N | Bcl-2 | P value | Survivin | P value | KAI1 | P value |
|-------------------------|----|-----------|---------|------------|---------|------------|---------|
| Age (years) | | | | | | | |
| <35 | 20 | 14 (70.0) | 0.88 | 14 (70.0) | 0.46 | 8 (40.0) | 0.75 |
| ≥35 | 25 | 17 (68.0) | | 16 (64.0) | | 10 (40.0) | |
| Tumor type | | | | | | | |
| Exophytic | 24 | 16 (66.7) | 0.91 | 16 (66.7) | 0.95 | 9 (37.5) | 0.86 |
| Endophytic | 13 | 9 (69.2) | | 9 (69.2) | | 6 (46.2) | |
| Ulcerative | 8 | 6 (75.0) | | 5 (62.5) | | 3 (37.5) | |
| Tissue type | | | | | | | |
| Squamous cell carcinoma | 41 | 28 (68.3) | 0.78 | 28 (68.29) | 0.85 | 17 (41.4) | 0.91 |
| Adenocarcinoma | 4 | 3 (75.0) | | 2 (50.0) | | 1 (25.0) | |
| Clinical stage | | | | | | | |
| Ia | 4 | 1 (25.0) | 0.03 | 1 (25.0) | 0.04 | 4 (100.0) | 0.03 |
| Ib-IIa | 38 | 27 (71.1) | | 26 (68.4) | | 13 (34.2) | |
| Ib-IIb-III | 3 | 3 (100.0) | | 3 (100.0) | | 1 (33.3) | |
| Differentiation | | | | | | | |
| Good | 14 | 9 (64.3) | 0.47 | 8 (64.2) | 0.35 | 10 (71.4) | 0.02 |
| Moderate | 28 | 19 (67.9) | | 19 (67.9) | | 8 (28.6) | |
| Poor | 3 | 3 (100.0) | | 3 (100.0) | | 0 (0.0) | |
| Lymph node metastasis | | | | | | | |
| With | 29 | 19 (65.5) | 0.51 | 24 (82.7) | 0.002 | 7 (24.1) | 0.01 |
| Without | 16 | 12 (75.0) | | 6 (37.5) | | 11 (68.75) | |

Correlation analysis of Bcl-2, survivin, and KAI1 expression levels in cervical cancer

Among the 30 cases of survivin-positive cervical cancer tissue, 26 cases presented positive Bcl-2 expression, and 8 cases presented positive KAI1 expression. Of the 15 cases of survivin-negative cervical cancer tissue, 5 showed positive Bcl-2 expression and 10 showed positive KAI1 expression. Survivin expression was positively correlated with Bcl-2 ($r = 0.576$, $P < 0.05$), but not with KAI1 expression ($r = 0.096$, $P > 0.05$). In the 31 cases of Bcl-2-positive cervical cancer tissue, 11 cases showed positive KAI1 expression, and in the 14 cases of Bcl-2-negative cervical cancer tissue, 7 cases showed positive KAI1 expression. No significant correlation between Bcl-2 and KAI1 was observed ($r = 0.094$, $P > 0.05$).

DISCUSSION

The pathological process of cervical cancer is related to tumor-suppressor gene inactivation and proto-oncogene activation. Apoptosis is one of the basic functions of the cell. A dynamic balance is maintained between apoptosis and proliferation under normal conditions. Apoptosis disruption may lead to many diseases. The *BCL2* gene belongs to the anti-apoptotic genes in the *BCL2* gene family and a translocation between chromosome 14 and 18 results in the overexpression of the *BCL2* gene. As a membrane protein, Bcl-2 is overexpressed in cervical cancer tissue. It can prevent apoptosis and prolong the cell life cycle by inhibiting Ca^{2+} increases in the cell, closing cell nuclear transportation, and acting as an antioxidant (Saitoh et al., 1999; Eijsink et al., 2010). In this study, the expression rate of Bcl-2 in cervical cancer was significantly higher than in the normal cervix, chronic cervicitis, or CIN tissues. Bcl-2 protein, mainly located in the rough endoplasmic reticulum and the mitochondrial membrane, can enhance resistance to apoptosis factors. Bcl-2 overexpression can inhibit cell apoptosis, and cervical cancer can develop under the regulation of growth suppressor and proliferation genes (Han et al., 2012). Bcl-2 is expressed in normal

epithelial tissue. This study showed that Bcl-2 expression increased with an increase in the degree of cervical tissue lesions. Bcl-2 expression was positively correlated with clinical stage, but not with pathologic stage or lymph node metastasis. Following the increase of cervical cancer clinical stage, the significant elevation in the expression level of Bcl-2 suggested that it is closely related to cervical cancer development, and its expression is associated with cervical cancer infiltration (Lu et al., 2012). The anti-apoptotic mechanism of Bcl-2 is related to mitochondrial redox state changes, cell membrane potential control, the apoptosis protein precursor APAF-1, cytochrome C release, caspase-9 activation, and blocking of the caspase pathway (Wu et al., 2012). It has been suggested that Bcl-2 affects the early stages of cervical cancer, while its effect is not significant in the late stages. Cervical tissue cancerization may continue to activate other disease-causing genes, which could inhibit Bcl-2 expression to a certain extent. The pathological process of cervical lesions is a result of multiple gene interactions (Manusirivithaya et al., 2006; Wu et al., 2012). Bcl-2 is an important protein in cervical cancer cell apoptosis, and it can regulate cell apoptosis and proliferation (Manusirivithaya et al., 2006). Multiple studies have reported that the 5-year survival rate in cervical cancer patients is positively correlated with Bcl-2 expression, which may suggest that Bcl-2 controls cell apoptosis but fails to promote cell proliferation. Researchers have not found a correlation between Bcl-2 expression and the prognosis of patients with recurrent cervical cancer (Xue et al., 2011; Guo and Li, 2012). The *BIRC5* gene, which encodes the protein survivin and has the locus 17q25, can influence the apoptosis pathway (by acting on caspases and promoting cell division). Survivin may inhibit apoptosis through two pathways: promoting CDK4 (cyclin-dependent kinases) and releasing p21; and inhibiting caspase-7 and caspase-3 activity (Sukpan et al., 2011; Kogo et al., 2015). Survivin distribution is different from that of Bcl-2 and shows strong tissue selectivity. It is not expressed in most healthy tissues but is highly expressed in fetal tissues. In addition to the gonads and thymus, it is overexpressed in most tumor tissues, such as cancerous lung, colon, and cervical tissues. Survivin can also be expressed in precancerous tissue. Our study results showed that survivin expression increased following an increase in the degree of cervical lesions. Survivin expression was associated with clinical stage and lymph node metastasis; its expression level increased with the increase in clinical stage. Survivin expression increased with a decrease in the degree of cervical cancer tissue differentiation. Survivin overexpression can promote cervical squamous carcinoma. Patients with lymph node metastasis present significantly higher survivin expression than patients without lymphatic metastasis. This suggests that survivin plays a role in inhibiting apoptosis and promoting proliferation in cervical cancer development, which might be reflected in tumor invasiveness and poor prognosis. No difference was found in survivin expression between cervical adenocarcinoma and squamous carcinoma in this study. This may have been due to the small sample size of the collected cervical adenocarcinoma. The question of whether survivin can predict cervical cancer prognosis requires further investigation owing to the lack of survival time follow-up data.

The *CD82* gene, which encodes the KAI1 protein, is a tumor metastasis suppressor gene and has the chromosomal locus 11p11.2. KAI1 is mainly located on the cell membrane and is downregulated in colon, pancreatic, and cervical cancers. It can inhibit tumor metastasis without affecting tumor formation. Its expression in cervical cancer tissue is reduced or even absent, and its relationship with clinical features has not yet been definitively determined. It is thought that a decrease in KAI1 expression is associated with the early stages of cervical cancer (Xiong et al., 2005; Liu et al., 2014). In our research, KAI1 expression levels in cervical cancer tissue decreased with the increasing degree of cervical tissue pathological changes. KAI1 expression was associated

with lymph node metastasis, differentiation, and clinical stage. This suggests that KAI1 expression was downregulated with cervical lesion development and tissue differentiation decrease, as its expression in poorly differentiated cervical cancer tissue was significantly lower than in highly differentiated tissue. KAI1 expression was downregulated in the late clinical stages. The patient's prognosis worsens with increase in clinical stage. This suggests that KAI1 decline might be an early event in the process of cervical cancer. The level of KAI1 protein may be related to patient prognosis. However, the relationship between the level of KAI1 and invasion and metastasis in cervical cancer remains controversial (Schindl et al., 2001; Liu et al., 2003; Xiong et al., 2005). Our results showed that KAI1 expression was associated with lymph node metastasis. The KAI1 protein participates in reactions between cells or between the extracellular matrix and cells, and affects cancer cell invasion and metastasis. The downregulated expression of KAI1 is related to cervical cancer prognosis. Tumor metastasis is the main cause of death in the majority of malignant tumor patients. Our study suggested that patients with downregulated KAI1 expression, late clinical stage, worse tissue type, and the presence of lymph node metastasis might have a higher risk of recurrence. Lymph node metastasis, clinical stage, and KAI1 protein expression were relative prognosis factors for cervical cancer patients.

Correlation analyses of survivin, Bcl-2, and KAI1 expression levels in 45 cases of cervical cancer were performed. Survivin expression was positively correlated with Bcl-2 ($r = 0.576$, $P < 0.05$), which may be related to *BIRC5* gene chromosome instability. The loci of the *BIRC5* gene are involved in *BCL2* gene locus t (14, 18) translocation and *BCL2* gene activation. In addition, *BIRC5* and *BCL2* genes are regulated by similar promoter sequences, which suggests that they may have similar mechanisms for regulating cell transcription activity (Schindl et al., 2001). The *BCL2* gene regulates apoptosis by preventing cytochrome C release by mitochondria, which is upstream in the caspase cascade. *BIRC5* may block the apoptosis pathway (by affecting caspases and promoting the cell division pathway). Two anti-apoptotic pathways may work together in cervical cancer. Survivin and Bcl-2 both showed no significant correlation with KAI1 expression ($r = 0.096$, $P > 0.05$; $r = 0.094$, $P > 0.05$, respectively). *BIRC5* and *BCL2* are both anti-apoptotic genes, and they participate in cervical cancer lesions through regulating cell apoptosis. *CD82* is a tumor metastasis suppressor gene and works by interacting with CD51 and CD9 (Miranti, 2009). To summarize, survivin, Bcl-2, and KAI1 are expressed abnormally in cervical cancer tissue, and their expression levels have a certain correlation with cervical cancer occurrence and development. KAI1 expression is negatively correlated with cervical cancer metastasis. Survivin, Bcl-2, and KAI1 are cervical cancer recurrence- and prognosis-related factors, although their role in cervical cancer prognosis requires confirmation.

Conflicts of interest

The authors declare no conflict of interest.

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