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Original Article

Expressions and clinical significance of Bcl-2, Bcl-xL and c-IAP1 protein in cervical cancer

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Abstract: *Background and aim:* Cervical cancer is a common gynecologic tumor which has high mortality and seriously threatens the health of women. This study aimed to investigate the expressions of B-cell lymphoma 2 (Bcl-2), B-cell lymphoma xL (Bcl-xL) and cellular inhibitor of apoptosis protein 1 (c-IAP1) protein in cervical cancer and normal cervical tissue and their correlation in cervical cancer tissue. *Methods:* A total of 45 cases of cervical cancer specimens and 21 cases of normal cervical tissue specimens were confirmed by pathological diagnosis. The expressions of Bcl-2, Bcl-xL and c-IAP1 protein in cervical cancer and normal cervical tissue were determined by immunohistochemistry. Correlations of Bcl-2, Bcl-xL and c-IAP1 protein expression in cervical cancer tissues were analyzed. *Results:* There were significant differences in positive rates of Bcl-xL and c-IAP1 protein between cervical cancer and normal cervical tissues, respectively (all $P < 0.001$). The expression of Bcl-2 protein had significant difference in different clinical stages of cervical cancer ($P < 0.05$). There were significant correlation of Bcl-xL and c-IAP1 protein expression with lymph node metastasis, tumor size, differentiation grade, and clinical stage of cervical cancer ($P < 0.05$). In cervical cancer tissue, the expressions of Bcl-2 and Bcl-xL protein were negatively correlated ($r = -0.287$, $P = 0.048$); the expression of Bcl-2 and c-IAP1 were negatively correlated ($r = -0.342$, $P = 0.008$); the expression of Bcl-xL and c-IAPl were positively correlated ($r = 0.482$, $P = 0.001$). *Conclusion:* Compared with normal cervical tissue, Bcl-xL and c-IAP1 proteins are highly expressed in cervical cancer tissue, and Bcl-2 is lowly expressed in cervical cancer tissue.

Keywords: Cervical cancer, Bcl-2, Bcl-xL, c-IAP1, expression

Introduction

Cervical cancer is the fourth commonest cancer across the globe, which is a serious threat to the health of women [1]. In recent years, the relationships of tumor formation with anti-apoptotic genes and pro-apoptotic genes have been confirmed. The apoptosis plays an important role in eliminating the body aging and the potential abnormal growth of cells and maintaining the stability of the body [2, 3]. A variety of protein families are involved in the process of apoptosis, such as B-cell lymphoma 2 (Bcl-2), B-cell lymphoma xL (Bcl-xL) and cellular inhibitor of apoptosis protein 1 (c-IAP1).

Bcl-2 is an important regulator of apoptosis. The regulation of apoptosis by Bcl-2 is implemented through the mitochondrial pathway [4]. Bcl-XL is widely distributed on the surface of hematopoietic stem cells, which is also a key regulator of apoptosis [5]. c-IAP1 is a kind of protein with anti-apoptotic activity. The key part of the anti-apoptotic effect is the baculoviral inhibitor of apoptosis repeat domain. The mechanism of inhibition of apoptosis by c-IAPl is its direct inhibition on the activity of the Caspase family members in the process of protease cascade. The increased expression of c-IAP1 inhibits the activity of Caspase, which inhibits the apoptosis [6]. This study investigated the expressions of Bcl-2, Bcl-xL and c-IAP1 protein in cervical cancer and normal cervical tissue and the correlation of Bcl-2, Bcl-xL and c-IAP1 protein expression in cervical cancer tissue. The objective was to provide a theoretical basis for the further exploration of cervical cancer occurrence and development mechanism

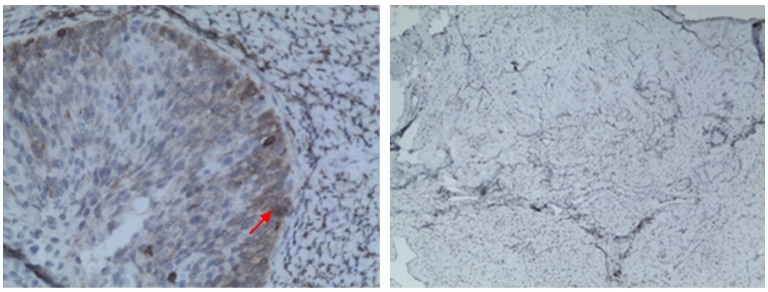

Figure 1. Expressions of Bcl-2 protein in cervical cancer (arrow) and normal cervical tissue (× 400). Bcl-2, B-cell lymphoma 2.

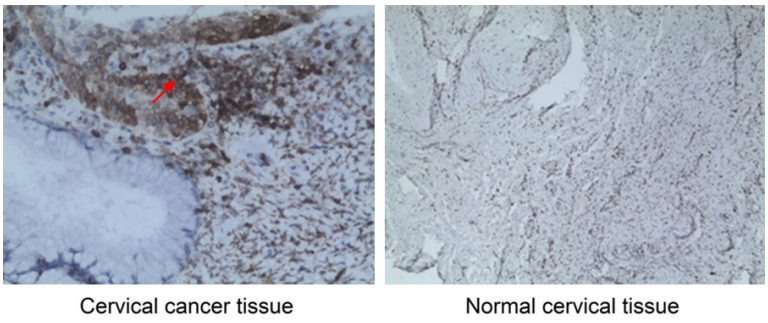

Figure 2. Expressions of Bcl-xL protein in cervical cancer (arrow) and normal cervical tissue (× 400). Bcl-xL, B-cell lymphoma xL.

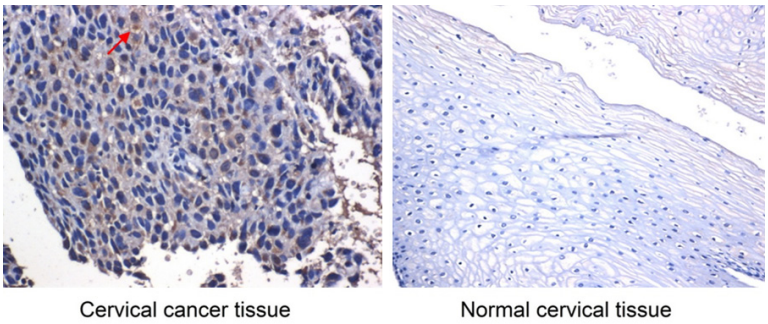

Figure 3. Expressions of c-IAP1 protein in cervical cancer (arrow) and normal cervical tissue (× 400). c-IAP1, cellular inhibitor of apoptosis protein 1.

and prediction and diagnosis of cervical cancer.

Subject and methods

Subjects

Forty-five patients with cervical cancer treated in the People's Hospital of Xinjiang Uyghur Autonomous Region from September 2012 to February 2013 were enrolled in this study. A total of 45 cases of cervical cancer specimens were obtained from the patients by biopsy or surgical resection. In addition, 21 cases of normal cervical tissue specimens (uterine fibroids) were used as control. The average age of 45 patients with cervical cancer was 46.4±5.1 years (27-65 years). The inclusion criteria were as follows: i) the patients were pathologically confirmed with cervical cancer by preoperative biopsy; ii) all patients had not received chemotherapy or radiotherapy; iii) all patients had no cervical cancer or other malignant tumor at the past. According to the WHO classification standard, the cervical cancer was classified into high differentiation, moderate differentiation and poor differentiation, with 9, 20 and 16 cases, respectively. According to the International Federation of Obstetrics and gynecology (FIGO) standard, the clinical stage of cervical cancer was divided into stage I, stage II and stage III, with 11, 17 and 17 cases, respectively. This study was approved by the ethics committee of the People's Hospital of Xinjiang Uyghur Autonomous Region. Written informed consent was obtained from all participants.

Pathological diagnosis of cervical cancer

The samples of cervical cancer tissue and normal cervical tissue were fixed using 10% formalin, followed by conventional dehydration and paraffin embedding. The 4 μm-thick slices were obtained. The routine HE staining was performed. The pathological diagnosis of cervical cancer was conducted according the reported standard [7]. After pathological diagnosis, all samples were divided into cervical cancer group (45 cases) and normal cervical tissue group (21 cases).

Table 1. Expressions of Bcl-2, Bcl-xL and c-IAP1 protein in cervical cancer and normal cervical tissue

Group	Positive rate of protein expression (%)		
	Bcl-2	Bcl-xL	c-IAP1
Cervical cancer	44.4 (20/45)	67.5 (27/45)	71.1% (32/45)
Normal cervical tissue	57.1 (12/21)	5 (1/21)	19% (4/21)
χ^2	0.924	14.327	17.886
P	0.243	< 0.001	< 0.001

Bcl-2, B-cell lymphoma 2; Bcl-xL, B-cell lymphoma xL; c-IAP1, cellular inhibitor of apoptosis protein 1.

Determination of Bcl-2, Bcl-xL and c-IAP1 protein expression

The immunohistochemistry (HRP-Envision™) method was used to determine the expressions of Bcl-2, Bcl-xL and c-IAP1 proteins in cervical cancer and normal cervical tissue. The known positive normal amygdala specimens, positive spleen specimen and positive prostate cancer specimen were selected as the positive control for Bcl-2, Bcl-xL and c-IAP1 protein, respectively. The primary antibodies such as monoclonal mouse anti-human Bcl-2 antibody (dilution 1:100), monoclonal mouse anti-human Bcl-xL antibody (dilution 1:200) and monoclonal mouse anti-human c-IAP1 antibody (dilution 1:100) were purchased from Fuzhou Maixin Biotechnology Development Co., Ltd. (Fuzhou, China). Phosphate buffer saline (Sigma-Aldrich Corp., MO, USA) instead of primary antibody was used as the negative control.

Determination of staining outcome

The criteria to determine the positive cells were as follows: the positive Bcl-2 and Bcl-xL proteins locate in the cytoplasm, with light yellow or brown yellow. The positive c-IAP1 protein presents light yellow or brownish yellow, and located in the cytoplasm or nucleus. According to the proportion of positive cells to all tumor cells, the positive intensity was divided into no positive cells (-), positive cells < 25% (+), 25%-75% positive cells (++) and positive cells > 75% (+++).

Statistical analysis

All statistical analysis was carried out using SPSS17.0 software (SPSS Inc., Chicago, IL, USA). The enumeration data were presented as number and rate, and were compared using χ^2 test. The correlation of two indexes was analyzed using Spearman correlation analysis. $P < 0.05$ was considered as statistically significant.

Results

Expressions of Bcl-2, Bcl-xL and c-IAP1 protein in cervical cancer and normal cervical tissues

Immunohistochemical staining showed that, the staining of Bcl-2 was in the cytoplasm, which presented brown yellow. The Bcl-xL staining was obvious in the cytoplasm. The c-IAP1 staining was obvious in cytoplasm or nucleus. There was obviously positive expression of Bcl-2 protein in both normal cervical tissues and cervical cancer tissues. In normal cervical tissues, the Bcl-2 positive cells were mainly distributed in the basal layer, while in cervical cancer tissue, the distribution of Bcl-2 positive cells was irregular, with patchy, nested or foci-like shape (**Figure 1**). The positive expressions of Bcl-xL and c-IAP1 protein in cervical cancer tissues were more obvious than those in normal cervical tissues (**Figures 2** and **3**).

The positive rates of Bcl-2 protein expression in cervical cancer and normal cervical tissues were 44.4% (20/45) and 57.1% (12/21), respectively. There was no significant difference between them ($P > 0.05$). The positive expression rates of Bcl-xL protein in cervical cancer and normal cervical tissues were 67.5% (27/45) and 5% (1/21), respectively, and those of c-IAP1 protein in cervical cancer and normal cervical tissues were 71.1% (32/45) and 19% (4/21), respectively. There were significant differences in the positive rate of Bcl-xL and c-IAP1 protein between cervical cancer and normal cervical tissues, respectively (all $P < 0.001$) (**Table 1**).

Expressions of Bcl-2 protein with different clinical pathological features in cervical cancer

There was no significant relationship between Bcl-2 protein expression and lymph node metastasis, tumor size or differentiation grade of cervical cancer ($P > 0.05$). In 11, 17 and 17 cases of clinical stage I, stage II and stage III cervical cancer, the positive rates of Bcl-2 protein expression were 90.9% (10/11), 47.1%

Table 2. Relationship between Bcl-2 protein expression and clinical pathological features of cervical cancer

Group	Case	Positive rate of Bcl2 protein expression (%)	χ^2	P
Lymph node metastasis			0.744	0.388
Yes	26	65.4 (17/26)		
No	19	52.6 (10/19)		
Tumor size			0.002	0.967
< 4 cm	24	38.0 (8/21)		
≥ 4 cm	21	37.5 (9/24)		
Differentiation grade			3.043	0.218
High differentiated	16	55.6 (5/9)		
Moderate differentiated	20	30.0 (6/20)		
Poor differentiated	9	56.2 (9/16)		
Clinical stage			10.288	0.001
I	11	90.9 (10/11)		
II	17	47.1 (8/17)		
III	17	29.4 (5/17)		

Bcl-2, B-cell lymphoma 2.

Table 3. Relationship between Bcl-xL protein expression and clinical pathological features of cervical cancer

Group	Case	Positive rate of Bcl-xL protein expression (%)	χ^2	P
Lymph node metastasis			5.662	0.017
Yes	26	76.9 (20/26)		
No	19	42.1 (8/19)		
Tumor size			7.872	0.005
< 4 cm	24	60.0 (12/24)		
≥ 4 cm	21	79.2 (19/24)		
Differentiation grade			13.918	0.001
High differentiated	16	55.6 (5/9)		
Moderate differentiated	20	10.0 (2/20)		
Poor differentiated	9	68.8 (11/16)		
Clinical stage			7.468	0.024
I	11	81.8 (9/11)		
II	17	35.3 (6/17)		
III	17	70.6 (12/17)		

Bcl-xL, B-cell lymphoma xL.

(8/17) and 29.4% (5/17), respectively. The expression of Bcl-2 protein had significant difference in different clinical stages of cervical cancer ($P < 0.05$, **Table 2**).

Expressions of Bcl-xL protein with different clinical pathological features in cervical cancer

As shown in **Table 3**, the positive rates of Bcl-xL protein expression in patients with and without lymph node metastasis were 76.9% (20/26) and 42.1% (8/19), respectively. The positive rates in patients with tumor size < 4 cm and ≥ 4 cm were 60.0% (12/24) and 79.2% (19/24), respectively. The positive rates in patients with high, moderate and poor differentiated tumor were 55.6% (5/9), 10.0% (2/20) and 68.8% (11/16), respectively. The positive rates in patients with clinical stage-I, stage-II and stage-III were 81.8% (9/11), 35.3% (6/17) and 70.6% (12/17), respectively. There was significant relationship of Bcl-xL protein expression with lymph node metastasis, tumor size, differentiation grade, and clinical stage of cervical cancer, respectively ($P < 0.05$ or $P < 0.01$).

Expressions of c-IAP1 protein with different clinical pathological features in cervical cancer

Table 4 showed that, the positive rates of c-IAP1 protein expression in patients with and without lymph node metastasis were 69.2% (18/26) and 26.3% (5/19), respectively. The positive rates in patients with tumor size < 4 cm and ≥ 4 cm were 60% (12/24) and 90.5% (19/21), respectively. The positive rates in patients with high, moderate and poor differentiated tumor were 37.5% (6/16), 80.0% (16/20) and 33.3% (3/9), respectively. The positive rates in patients with clinical stage-I, stage-II and stage-III were 36.4% (4/11), 76.5% (13/17) and 88.2% (15/17), respectively. There was significant relationship of c-IAP1 protein expression with lymph node metastasis, tumor size, differentiation grade, and clinical stage of cervical cancer, respectively ($P < 0.05$ or $P < 0.01$).

Table 4. Relationship between c-IAP1 protein expression and clinical pathological features of cervical cancer

Group	Case	Positive rate of c-IAP1 protein expression %	χ^2	P
Lymph node metastasis			8.091	0.004
Yes	26	69.2 (18/26)		
No	19	26.3 (5/19)		
Tumor size			8.562	0.003
< 4 cm	24	60.0 (12/24)		
≥ 4 cm	21	90.5 (19/21)		
Differentiation grade			9.183	0.010
High differentiated	16	37.5 (6/16)		
Moderate differentiated	20	80.0 (16/20)		
Poor differentiated	9	33.3 (3/9)		
Clinical stage			8.818	0.012
I	11	36.4 (4/11)		
II	17	76.5 (13/17)		
III	17	88.2 (15/17)		

c-IAP1, cellular inhibitor of apoptosis protein 1.

Table 5. Correction of Bcl-2 and Bcl-xL protein expressions in cervical cancer tissue

Bcl-2	Bcl-xL				r	P
	-	+	++	+++		
-	8	3	1	9	-0.287	0.048
+	1	3	4	3		
++	1	2	3	2		
+++	7	4	3	3		

Bcl-2, B-cell lymphoma 2; Bcl-xL, B-cell lymphoma xL.

Table 6. Correction of Bcl-2 and c-IAP1 protein expressions in cervical cancer tissue

Bcl-2	c-IAP1				r	P
	-	+	++	+++		
-	5	2	2	9	-0.342	0.008
+	2	4	5	4		
++	1	2	3	2		
+++	12	4	3	3		

Bcl-2, B-cell lymphoma 2; c-IAP1, cellular inhibitor of apoptosis protein 1.

Correlation of Bcl-2, Bcl-xL and c-IAP1 protein expression in cervical cancer tissues

The correlation analysis showed that, in cervical cancer tissue the expressions of Bcl-2 and Bcl-xL protein were negatively correlated (r = -0.287, P = 0.048); the expression of Bcl-2 and c-IAP1 protein were negatively correlated (r = -0.342, P = 0.008); the expression of Bcl-xL and c-IAPl protein were positively correlated (r = 0.482, P = 0.001) (**Tables 5**-**7**).

Discussion

Inhibition of apoptosis and excessive proliferation are the basis of the occurrence of tumor. The occurrence of cervical cancer is not only related to the mutation of oncogene and the inactivation of tumor suppressor genes, but also closely related to the imbalance of cell proliferation and apoptosis. Apoptosis blockage or the proliferation out of control is involved in the formation of tumor [8]. Bcl-2 protein plays an important role in cell apoptosis. The main biological function of Bcl-2 protein is its prolonging the cell life and increasing the resistance to many kinds of apoptosis stimulating factors [9]. The possible mechanism is that, Bcl-2 protein inhibits the increase of intracellular calcium concentration and oxidation damage by blocking cell nuclear transfer. Bcl-xL can inhibit apoptosis by underpinning the way of Bcl-2, which can inhibit apoptosis of many kinds of apoptosis inducing factors. Bcl-xL plays a key role in the process of cell transformation in the final part of apoptosis regulation [10]. The expression of inhibitor of apoptosis protein c-IAP1 in cervical cancer is still relatively low, but it exists extensively in other human tumors [11].

This study has investigated the expressions of Bcl-2, Bcl-xL and c-IAP1 protein in cervical cancer and normal cervical tissue and the correlation of Bcl-2, Bcl-xL and c-IAP1 protein expression in cervical cancer tissue. Results showed that, there were significant differences of positive rate of Bcl-xL and c-IAP1 protein between cervical cancer and normal cervical tissues, respectively (all P < 0.001) (**Table 1**; **Figures 2** and **3**). This indicates that, the high expressions of Bcl-xL and c-IAP1 protein are closely related to the incidence of cervical cancer. The excessive expression of c-IAP1 may be related to the imbalance of cell proliferation and apoptosis in Bcl-xL protein. In the course of the

Table 7. Correction of Bcl-xL and c-IAP1 protein expressions in cervical cancer tissue

Bcl-xL	c-IAP1				r	P
	-	+	++	+++		
-	11	5	1	1	-0.482	0.001
+	3	3	5	2		
++	1	2	2	3		
+++	0	3	2	2		

Bcl-xL, B-cell lymphoma xL; c-IAP1, cellular inhibitor of apoptosis protein 1.

development of cervical cancer, the expressions of Bcl-xL and c-IAP1 protein have a synergistic effect. c-IAP1 is the main pathway to inhibit apoptosis and promote the occurrence of tumors by enhancing the expression of Bcl-xL, but it is not the only one. c-IAP1 may be regulated by the positive regulation of Bcl-xl. It is found that, c-IAP1 can be combined with Caspase-3 and inhibit the occurrence of apoptosis in Bcl-2 and Bcl-xL over-expressed cells [12]. Whereas in normal cells, due to Smac release and combing with c-IAP1, caspase-3 is released, thus the apoptosis can be continued [13]. Therefore, it is indicated that Bcl-2 and Bcl-xL can indirectly promote the apoptosis inhibitory activity of c-IAP1 through SMAC-dependent manner. The expression levels of c-IAPl in the early and late stages of cervical cancer have significant difference. The expression level at late stage is significantly higher than that at early stage.

In this study, the expression of Bcl-2 is lower in cervical cancer, compared with normal cervical tissue. This may be related to the majority of specimens for advanced cervical cancer. For the relationship between Bcl-2 and the prognosis of cervical cancer, Ozalp *et al*. [14] and Jain *et al*. [15] have found that, Bcl-2, as a single variable, has no effect on the survival rate of patients with cervical cancer. However, it is believed that, the patients with high positive Bcl-2 protein expression have low degree of malignancy, high survival rate and good prognosis [16]. This study has not investigated the correlation of Bcl-2 protein expression and prognosis of cervical cancer, which should be further studied. Although the role of Bcl-2 in the development of cervical cancer is not as good as Bcl-xL, the expression of Bcl-2 protein is higher in the early stage of cervical cancer. This indicates that, the high expression of Bcl-2 protein may be related to better prognosis.

In conclusion, compared with normal cervical tissues, Bcl-xL and c-IAP1 proteins were highly expressed in cervical cancer tissues, and Bcl-2 was lowly expressed in cervical cancer tissues. The expression of Bcl-2 protein had significant difference in different clinical stages of cervical cancer. There were significant relationships of Bcl-xL and c-IAP1 protein expression with lymph node metastasis, tumor size, differentiation grade, and clinical stage of cervical cancer. The high expressions of Bcl-xL and c-IAP1 protein may play an important role in the anti-apoptotic mechanism of cervical cancer. These genes can be used in the susceptibility prediction, early diagnosis and disease monitoring of cervical cancer, with important significance for the development of molecular targeted therapy. Of course, the sample size of this study is relatively small, and there is no follow-up data. This is the limitation of this study. In further studies, the sample size should be increased, and the follow-up should be performed, for obtaining more convincing outcomes.

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Disclosure of conflict of interest

None.

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