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Co-expression of Survivin and Bcl-2 in Primary Brain Tumors : Their Potential Effect on Anti-apoptosis

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Objective : Survivin is an inhibitor of apoptosis protein(IAP), which inhibits apoptosis through a pathway distinct from the Bcl-2 family members. Overexpression of survivin and Bcl-2 have been commonly reported in human neoplasms. The authors investigate whether there is a synergistic effect on the anti-apoptosis rate of primary brain tumors "in situ" based on the co-expression of survivin and Bcl-2.

Methods : One hundred and two brain tumor patients who had been resected were included in this study. Survivin and Bcl-2 were detected by Western blotting analysis, while apoptosis was examined by DNA fragmentation analysis. An anti-apoptotic rate was assessed in these brain tumor samples based on the expression of survivin and Bcl-2 or co-expression of both.

Results : Survivin and Bcl-2 were expressed in 57(55.9%) and 53(52.0%) of 102 brain tumor samples studied respectively, and co-expressed in 31(30.4%). The percentage of astrocytic and meningeal tumors expressing survivin was significantly correlated with histological grades; however, Bcl-2 was not correlated (p=0.106). The anti-apoptotic rate in primary brain tumors with survivin, Bcl-2, and both was detected in 49(86.0%) of 57 samples, 42(79.9%) of 53 samples, and 27(87.1%) of 31 samples, respectively. Their difference in the frequency of anti-apoptosis was not significant.

Conclusion : Survivin or Bcl-2 is involved in the anti-apoptosis. However, it suggests that co-expression of survivin and Bcl-2, together, have no synergistic effect on the anti-apoptotic properties of the primary brain tumors.

KEY WORDS : Survivin · Bcl-2 · Apoptosis · Brain neoplasm · Co-expression.

Introduction

Apoptosis or programmed cell death plays an important role to preserve normal homeostasis and developmental morphogenesis[27]. It is also an essential protective mechanism against mutation, malignant transformation, and neoplastic progression[6]. Many factors and oncogenes are involved in regulation of apoptosis. The *bcl-2* gene, first described at a translocation breakpoint in B-cell lymphoma, has been shown to prevent apoptosis caused by a variety of physiologic, pathologic, and pharmacologic stimuli[25]. Furthermore, high levels of Bcl-2 have been associated with poor therapeutic response in at least some groups of patients with lymphoma, leukemia, and prostate cancer.

On the other hand, survivin is a recently characterized inhibitor of apoptosis protein(IAP) that can bind specifically to the terminal effector cell proteases, caspase-3 and -7, and inhibit caspase activity and apoptosis in cells exposed to diverse apoptotic stimuli[22]. It is abundantly expressed during developmental stage and in common neoplasms, but undetectable in normal adult tissue[2]. Survivin has been also shown to be expressed in cancers of breast, lung, ovary, prostate, and kidney or leukemia, lymphoma, melanoma[22]. The expression of survivin was significantly associated with Bcl-2 expression and reduced apoptotic indices, which were strongly correlated with poor prognosis after surgery in both gastric and colorectal cancers[10,16,20].

In the current study, we assessed the expression of survivin and Bcl-2 in the primary brain tumors and investigated whether there was a synergistic effect on the frequency of tumor cell apoptosis when co-expressed.

Materials and Methods

Patients and samples

We studied a total of 102 patients with primary brain tumors. Their specimens have been prospectively collected from conse-

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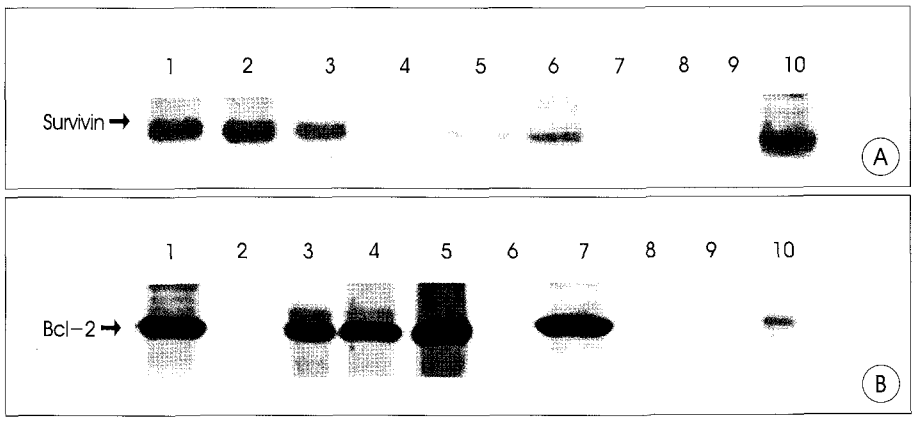

Fig. 1. A : Expression of survivin protein by Western blot analysis using monoclonal anti-survivin (Novus, Littleton, CO, USA). Positive expression noted in the lane1-3, 5-6, and 10. B : Expression of Bcl-2 by Western blot analysis using monoclonal anti-Bcl-2 (Zymed, San Francisco, CA, USA). Note Bcl-2 expression in the lane 1, 3-5, 7, and 10. Lanes 1-2, astrocytomas; lanes 3-5, meningiomas; lanes 6-7, glioblastomas; lane 8, oligodendroglioma; lane 9, pituitary adenoma; lane 10, acoustic neurinoma.

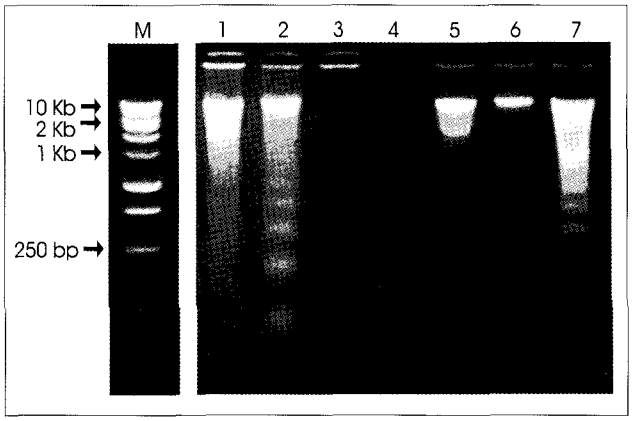

Fig. 2. DNA fragmentation in agarose gel. Fragmented DNA was isolated and electrophoresed in a 2.0% agarose gel containing 50ng/ml ethidium bromide. Typical laddering pattern represents in the lane 2 and 7. M : molecular marker.

cutive patients who had undergone curative resection between July 2000 and December 2002. Pathological types were categorized by World Health Organization(WHO) criteria. Clinical data were reviewed for each medical record. Each specimen was snap frozen in liquid nitrogen after surgical removal and stored at -80°C until use.

Western blot analysis

Frozen tissues were washed in phosphate-buffered saline(PBS) and lysed by using a homogenization buffer containing 0.1M sodium phosphate buffer, pH 6.1, 1mM EDTA, 1mM DTT, 0.1mM PMSF, and 1mM benzamidine. After protein quantification performed by using the DC Protein Assay (Bio-Rad, Hercules, CA, USA), 15$\mu\ell$ of proteins were loaded on each lane and subjected to SDS-PAGE on 10% acrylamide gel. Proteins were then transferred overnight onto polyvinylidene difluoride(PVDF) membranes (Bio-Rad, Hercules, CA, USA). Membranes were saturated for 1 hour using 5% dry milk in TBS-T (10mM Tris-buffer pH 7.5, 100mM NaCl, 0.1% Tween 20) and incubated for overnight with 1$\mu\ell$/ml monoclonal anti-survivin (Novus, Littleton, CO, USA) or monoclonal anti-Bcl-2 (Zymed, San Francisco, CA, USA) at 4°C The membranes were then incubated for 1 hour with anti-mouse IgG conjugated to alkaline phosphatase (Zymed, San Francisco, CA, USA). Blots were washed, and bands were visualized by ECL detection kit (Amersham, Arlington Heights, IL, USA) according to the manufacturer's protocol (Fig. 1).

DNA fragmentation analysis

Tissues were washed with PBS (pH 7.4) 3 times and homogenized with lysis buffer (10mM Tris-HCl, 100mM EDTA, 0.5% SDS, pH of 8.0). Homogenized samples were centrifuged at 1500rpm for 5 min. Supernatants were moved to new tubes. For time course of experiments, experimental and control cells were terminated at the same time. Samples were dissolved in 20$\mu\ell$ of sample buffer (50mM Tris-HCl, 0.05% SDS, 10mM EDTA, pH 8.0) and incubated with 10 mg/ml heat-treated RNAse A (Sigma Chemical Co., St. Louis, MO, USA) at 56°C for 1 hour. Proteinase K (10mg/ml) (Promega, Madison, WI, USA) was added to each sample and incubated for 1 hour at 37°C The reaction was stopped by increasing the temperature to 70°C for 10 min. Five microliters of loading buffer (20% glycerol, 20mM EDTA, 0.15% bromphenol blue) was added and samples were analyzed on 2% agarose gels in Tris/boric acid/EDTA buffer (89mM Tris base, 89mM boric acid, 2.5mM EDTA, pH 8.0)containing 50ng/mL ethidium bromide. Electrophoresis was performed at 100 V for 50 min and DNA fragmentation were visualized by ultraviolet transillumination (Fig. 2). Anti-apoptotic rate was defined as the percentage of tumor numbers without apoptosis to all tumors.

Statistical analysis

Statistical analysis was performed using the SPSS 10 software package for Windows (SPSS, Inc., Chicago, IL, USA). Difference of survivin and Bcl-2 expression according to histological types of brain tumors were analyzed by the Kruskal-Wallis test. To determine if a relationship exist between anti-apoptosis and survivin or Bcl-2 expression, or between the co-expression of Bcl-2 and survivin, the two-tailed Fisher's exact test was used. Nonparametric test was performed to compare the difference of anti-apoptotic rate among survivin, Bcl-2 or both expre-

Table 1. Expression of survivin, Bcl-2 protein, and apoptosis in 102 patients with primary brain tumors

Pathological diagnosis	Expression rate (%)		No. of patients
	Survivin	Bcl-2	with apoptosis(%)
Glioma (n=41)	23(56.1)	20(48.8)	10(24.4)
Astrocytoma (n=12)	5(41.7)	7(58.3)	2(16.7)
Anaplastic astrocytoma (n=3)	2(66.7)	0(0)	1(33.3)
Glioblastoma (n=15)	11(73.3)*	6(40.0)	6(40.0)
Oligodendroglioma (n=2)	2(100)	2(100)	0(0)
Ependymoma (n=4)	2(50.0)	3(75.0)	1(25.0)
Anaplastic ependymoma (n=3)	1(33.3)	2(66.7)	0(0)
Mixed glioma (n=2)	0(0)	0(0)	0(0)
Acoustic neurinoma (n=20)	12(60.0)	11(55.0)	5(25.0)
Meningioma (n=26)	15(57.7)	14(53.8)	7(26.9)
Benign (n=19)	14(73.7)†	10(52.6)	5(26.3)
Atypical (n=5)	1(20.0)	3(60.0)	2(40.0)
Malignant (n=2)	0(0)	1(50.0)	0(0)
Pituitary adenoma (n=15)	7(46.7)	8(53.3)	2(13.3)
Total 102	57(55.9)	53(52.0)	24(23.5)

* Survivin expression in glioblastoma was significantly higher than astrocytoma and anaplastic astrocytoma (p=0.001). †Survivin expression in benign meningiomas was higher than atyical or malignant meningiomas (p=0.026)

Table 2. Relationship between apoptosis, survivin, and Bcl-2 expression in 102 patients with brain tumors

	Apoptosis (%)		p-value*
	Yes	No	
Survivin (n=57)	8(14.0)	49(86.0)	0.004
Bcl-2 (n=53)	11(20.1)	42(79.9)	0.003
Survivin and Bcl-2 (n=31)	4(12.9)	27(87.1)	$p<0.001$

* by Fisher's exact test

ssed groups. A value of $p < 0.05$ was considered statistically significant.

Results

Demographic data and Tumor pathology

The patient groups were 37 males and 65 females (sex ratio, 1.8:1). At the time of surgery, the patients ranged in age from 13 to 72 years, with a median age of 46 years. The specimens consisted of 41 gliomas, 20 acoustic neurinomas, 26 meningiomas, and 15 pituitary adenomas (Table 1).

Expression of survivin, Bcl-2, and Apoptosis

Survivin and Bcl-2 expression were analysed by Western blotting in 102 brain tumor specimens. As illustrated in figure 1 for representative examples, survivin and Bcl-2 were detected in specimen from most tumor types. Positive expression of survivin was shown in 57 (55.9%) of 102 patients. High expression frequency of survivin was found in glioblastomas. The percentage of tumors expressing survivin was significantly correlated to the histological grade of glioma (p=0.001). There was significant difference in survivin expression according to the histological grade of meningiomas (p=0.026) (Table 1). However, the frequency of survivin expression was not different among all types of tumor tissues statistically (p=0.426).

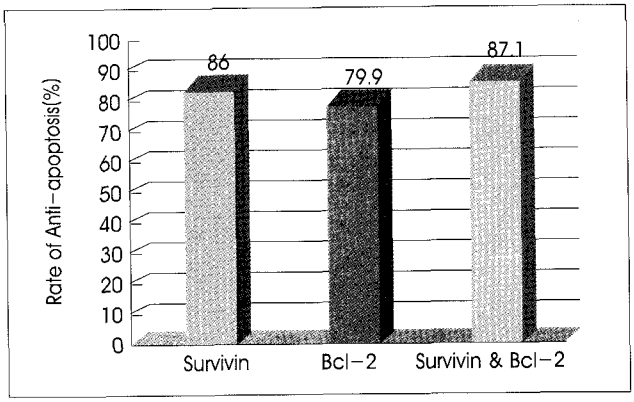

Fig. 3. Bar graph displaying the anti-apoptotic rate of tumors expressing survivin, Bcl-2, or both in 102 patients (p>0.05).

Bcl-2 protein expression was positive in 53 (52.0%) of 102 patients. Its expression was not correlated to histological grade (p=0.106). Co-expression of survivin and Bcl-2 was shown in 31 (30.4%) patients. Apoptosis in tumor specimens was investigated by DNA fragmentation. A typical laddering pattern of DNA fragmentation was depicted (Fig. 2). Apoptosis in brain tumors was demonstrated in 24 (23.5%) of 102 patients (Table 1).

Relationship between Bcl-2, survivin expression, and Anti-apoptosis

To investigate the anti-apoptotic rate as it relates to survivin and/or Bcl-2 expression in brain tumor specimens, we compared the anti-apoptotic rate between survivin-positive, Bcl-2-positive, and both positive groups, each others. Anti-apoptosis for survivin-positive or Bcl-2-positive tumors was found to be in 49 (86.0%) of 57 patients and 42 (79.9%) of 53 respectively. A correlation of anti-apoptosis to survivin or Bcl-2 expression was statistically significant (p=0.004 and 0.003, respectively). In survivin and Bcl-2-positive tumors, anti-apoptosis was demonstrated in 27 (87.1%) of 31 (Table 2). Their differences in the frequency of the anti-apoptosis among tumors expressing survivin, Bcl-2, or both were not significant although survivin or Bcl-2 expression affect on apoptosis (p= 0.075)(Fig. 3).

Discussion

The main result of this study suggested that the expression of survivin or Bcl-2 in primary brain tumors related to the anti-apoptosis of tumor "in situ". However, the co-expression of Bcl-2 and survivin could not have a synergistic effect on anti-apoptosis of brain tumors. Our results imply that pro-

teins involved in the inhibition of apoptosis are actively expressed in primary brain tumors. Proteins such as survivin and Bcl-2 may promote the brain tumor growth.

In the recent years, novel anti-apoptotic proteins that signal through caspase-dependent and independent mechanisms have been characterized. In humans, six members of this IAP family have been introduced : HIA1, HIAP2, XIAP, NIAP, SURVIVIN, and LIVIN[4]. Survivin was an IAP that directly inhibited caspase-3 and -7 activity, and regulated the G2/M phase of the cell cycle[22]. Its gene was encoded at chromosome 17q25 and survivin associated with microtubules of the mitotic spindle[3,15,18]. Disruption of survivin-microtubule interactions resulted in the loss of its anti-apoptotic function and increased caspase-3 activity during mitosis. The overexpression of survivin in cancer may obliterate apoptotic checkpoint and allow aberrant progression of transformed cells through mitosis[15].

Survivin was normally expressed during development, but completely down-regulated and undetectable in normal adult tissues, and then prominently reexpressed in the most human carcinomas[2]. However, the timing of its reexpression during carcinogenesis was still unknown. Survivin expression has been reported in many human neoplasms including the lung, stomach, colon, pancreas, breast, and prostate cancers, as well as neuroblastomas, melanomas, and lymphomas[1,2,10,16,23]. Survivin was also expressed in the majority of primary brain tumors, particularly in glioblastomas, meningiomas, and schwannomas[12,13,21]. Our results also confirmed that survivin was expressed at high levels in glioblastomas and benign meningiomas. Survivin expression in human neoplasms was associated with a more aggressive and invasive clinical phenotype[1], and correlated with the reduction of apoptosis[10]. IAPs may have greater potential for apoptosis inhibition than any other family of apoptotic inhibitors, Bcl-2[14].

Expression of survivin was significantly associated with malignant grade of astrocytic tumors and shorter overall survival times[26]. Quantifying the levels of survivin and its splice variants was also useful for the prediction of the cell biological malignancy of gliomas[29]. In addition, it may play a role in enhancing the malignant behavior of glial cell tumor[5]. In the current study, the relationship between survivin expression and histological malignancy of astrocytic tumors was confirmed and also, the difference of survivin expression according to the histological grade of meningiomas was also significant. These findings were coincident to previously published findings[9,11].

Bcl-2 has been implicated in counteracting the upstream initiation of the caspase activation cascade by interfering with cytochrome C release from mitocondria[28]. Bcl-2 and survivin have potent anti-apoptotic properties[12]. However, it appeared that survivin and Bcl-2 may mediate non-overlapping, anti-apoptotic mechanisms. Expression of Bcl-2 was positively correlated with expression of survivin gene in epithelial ovarian cancer[30], but survivin expression was not correlated with Bcl-2 in astrocytic tumors[9]. As stated earlier, survivin reportedly affects caspase-3 or -7 in various pathways of the Bcl-2 family[22]. Although the anti-apoptotic effect of survivin has been controversial and not clearly understood, low survivin expression in tumor cells was associated with a high median apoptotic index and correlated to the level of Bcl-2[18]. Furthermore, the presence of survivin in bladder tumor specimens did not seem to be associated with high levels of Bcl-2. This did not seem surprising, due to the fact that survivin and Bcl-2 did not completely share common mechanisms of transcriptional activation[4]. Nevertheless, the expression of survivin and Bcl-2 in melanomas may provide two independent mechanisms of apoptosis inhibition leading to growth advantage for tumor cells[8].

The significant co-association of survivin and Bcl-2 in breast cancer cells implied a strong mechanism of apoptosis inhibition, which potentially contributed to tumor progression and multidrug resistance[7]. The expression of survivin was significantly associated with Bcl-2 expression and reduced apoptotic indices, which were strongly correlated with poor prognosis after surgery in both gastric and colorectal cancers[10,16]. Expression of survivin gene alone or survivin gene plus other anti-apoptotic genes like *bcl-2* may cause more pronounced anti-apoptotic effects in breast carcinomas[23]. But, this study showed that there was no synergistic anti-apoptotic effect in co-expressed group with primary brain tumors.

Recent studies suggested that survivin was a viable therapeutic target in cancer, either directly or by affecting endothelial cell viability[19,24]. Survivin antisense treatment has already been demonstrated to cause regression in vascular capillary formation[17]. The presence of anti-angiogenic effects, in addition to anti-tumor cell effects, might be particularly attractive if survivin antisense therapy can be directed toward glioblastomas, anaplastic oligodendrogliomas, or other highly vascular gliomas.

We studied heterogenous pathology of brain tumors and the number of cases with same pathology so limited. The limitation of this study is also that anti-apoptosis in the same pathology of brain tumors was not evaluated and quantitative measurements of apoptosis by immunohistochemistry was not performed. Another larger study using the same pathology of brain tumors and immunohistochemistry must be undertaken to define the definite relationship between apoptosis, Bcl-2, and survivin expression.

Conclusion

Although it has been no synergistic effect of anti-apoptosis in co-expressing tumors of survivin and Bcl-2, our results propose that survivin or Bcl-2 has potent anti-apoptotic

properties in the primary brain tumors. Therapeutic inhibition of survivin or Bcl-2 function may be an attractive strategy to induce apoptosis in the management of primary brain tumors.

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Commentary

This article is an interesting contribution to the neuro-oncological literature on inhibitors of apoptosis in patients with brain tumor. The authors examined the expression of survivin, Bcl-2, and apoptosis. They found that proteins involved in the inhibition of apoptosis are actively expressed in primary brain tumors (surviving expression in 55.9% of brain tumors and Bcl-2 expression in 52% of brain tumors). They also reported on the significant correlation between survivin expression and histological grades in astrocytic or meningeal tumors. High grade gliomas show more expression than low grade gliomas. Interestingly, the expression pattern is reverse in meningiomas : Survivin expression is higher in benign meningiomas than in malignant meningiomas. The coexpression of survivin and Bcl-2 does not show synergistic effect on the anti-apoptotic properties of the primary brain tumors.

One of the most important factors in carcinogenesis is apoptosis. The ability of tumor cell populations to expand in number is determined not only by the rate of cell proliferation but also by the rate of cell attrition. To achieve complete tumor regression, anticancer treatment should be not cytostatic but cytocidal. Cytocidal anticancer strategy can be achieved using stimulators for pro-apoptotic process or inhibitors for anti-apoptotic event. Before therapeutic application of apoptotic agent, the understanding of the biological profile of apoptosis in brain tumors is the major premise.

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