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EXPRESSION OF THE SURVIVIN GENE IN PROSTATE CANCER: CORRELATION WITH CLINICOPATHOLOGICAL CHARACTERISTICS, PROLIFERATIVE ACTIVITY AND APOPTOSIS

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ABSTRACT

Purpose: Although survivin expression has been reported in prostate cancer, the clinical significance of survivin expression remains unclear. To clarify the clinical significance of survivin in prostate cancer we examined survivin mRNA levels in prostate cancer tissues, and correlated these levels with parameters including the clinicopathological characteristics of patients and proliferation and apoptosis levels within prostate cancer tissues.

Materials and Methods: Cancer and matched control tissues were obtained from the prostates of 150 patients who were treated with radical prostatectomy between July 1998 and December 2002. Of the 150 samples, RNA could be extracted and pathological confirmation obtained from 82 prostate cancer and 80 normal prostate samples. Polymerase chain reaction studies were performed using primers for the survivin gene with the G3PDH gene serving as control. Preoperative prostate specific antigen doubling time (PSA-DT) could be calculated for 50 patients by linear regression analysis. Immunohistochemical staining was used to study expression of proliferating cell nuclear antigen as an index of proliferative activity and single stranded DNA as an index of apoptosis.

Results: Of 82 prostate cancer samples 68 (82.9%) and 47 (58.8%) of 80 control samples exhibited detectable levels of survivin mRNA. In the 65 cases in which RNA could be extracted from prostate cancer and matched control samples, the mean level of survivin expression ± SE in prostate cancer was significantly higher than that found in control tissues (0.079 ± 0.017 vs 0.025 ± 0.005, $p = 0.003$). The survivin expression in cancers with a short PSA-DT (less than 2 years) was significantly higher than those with a moderate PSA-DT (2 to 4 years, $p < 0.05$) or long PSA-DT (greater than 4 years, $p < 0.05$). In the 82 cases with prostate cancer, survivin expression was significantly higher in cancers with a high pathological T stage ($p < 0.05$), positive lymph node metastasis ($p = 0.002$), positive vessel invasion ($p = 0.03$), positive surgical margin ($p = 0.02$) and high Gleason score ($p < 0.05$). A positive correlation was present between survivin expression and proliferative activity ($p = 0.005$). A nonsignificant inverse association was found between survivin expression and apoptosis of prostate cancer cells ($p = 0.06$).

Conclusions: These results suggest that the degree of survivin expression is related to the progression and aggressiveness of prostate cancer.

KEY WORDS: prostatic neoplasms, apoptosis, proliferating cell nuclear antigen; DNA, single-stranded

Survivin, a new member of the inhibitor of apoptosis (IAP) family is expressed predominantly in fetal tissue but is also found in many common human cancers.[1] It inhibits the processing of caspase-3 and caspase-7, terminal effectors of apoptosis, and also inhibits the induction of apoptosis by Fas, Bax and caspases.[2] Moreover, survivin expression correlated with poor survival among patients with various tumors, including neuroblastoma,[3] nonsmall-cell lung cancer,[4] breast carcinoma,[5] esophageal cancer,[6] gastric carcinoma,[7] rectal cancer,[8] recurrent colorectal carcinoma[9] and bladder cancer.[10] Therefore, survivin expression is thought to be an important prognostic marker in cancers.

Although expression of survivin in prostate cancer tissue[1] or cell lines such as LNCap, PC3 and DU145[11] has been reported, the clinical significance of survivin expression and correlation with the biological aggressiveness of prostate cancer remain unclear. To clarify the clinical significance of survivin in prostate cancer tissue, we investigated survivin mRNA expression in normal and prostate cancer specimens. In addition, we correlated expression of survivin with clinicopathological characteristics of the patients. We examined the immunohistochemical expression of proliferating cell nuclear antigen (PCNA) and single stranded DNA (ssDNA) to investigate the relationship between survivin expression and proliferative activity or apoptosis of prostate cancer cells.

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MATERIALS AND METHODS

Patients. A total of 150 patients (median age 69 years, range 49 to 80) who underwent radical prostatectomy for localized prostate cancer at Shimane University Hospital from July 1998 to December 2002 were studied. These patients had not received any therapy before surgery. Of the 150 samples, RNA could be extracted and pathological confirmation was obtained from 82 prostate cancer tissues and 80 normal control prostate tissues. A total of 68 prostate cancer tissues were excluded from study. RNA extraction failed in 47 tissues while 21 specimens were assessed as inadequate since pathological examination indicated that they contained limited cancer tissue.

To investigate prostate specific antigen (PSA) biochemical

failure and patient prognosis, 54 of 82 cancer cases that had not received any adjuvant therapy such as radiotherapy or hormonal therapy after radical prostatectomy were studied. The median followup for these 54 cases was 24 months (range 4 to 57). PSA biochemical failure was defined as PSA higher than 0.2 ng/ml and 3 consecutive increases in the serum PSA value in this study. Preoperative PSA doubling time (PSA-DT) was calculated by linear regression analysis for the 50 patients who had a minimum of 3 PSA measurements and a minimum of 2 months of preoperative followup.

Pathological staging and histological grade were evaluated according to 1997 TNM and Gleason grading system,[12] respectively. Pathological T staging of 82 cases of prostate cancer was identified as pT2a in 20 cases, pT2b in 24, pT3a in 28, pT3b in 7 and pT4 in 3. The dissection of pelvic lymph node was performed in 53 cases with radical retroperitoneal prostatectomy and the pathological N staging of these 53 cases was pN0 in 45 and pN1 in 8 cases. The other 29 patients preoperatively diagnosed with low risk for lymph node metastasis by Partin nomogram[13] underwent a radical perineal prostatectomy that did not routinely involve the dissection of pelvic lymph nodes. These 29 cases were identified as pNx.

Samples. Fresh surgical specimens were obtained from all patients, and cancer and matched control prostate tissues were prepared for investigation under a dissecting microscope to remove inappropriate tissue components. In addition, after pathological confirmation inadequate specimens such as those containing limited cancer tissue were excluded from study. The tissue samples were stored at −80C until analysis.

Reverse transcriptase-polymerase chain reaction (RT-PCR) of survivin and G3PDH. Total RNA was extracted from the tissue samples by the acid guanidinium-phenol-chloroform method using ISOGEN (Nippon Gene, Tokyo, Japan). RT-PCR for survivin gene expression was performed as previously described[6] with a slight modification. Complementary DNA was synthesized by random priming using less than 1 μg total RNA as template (ReverTra Ace-α, Toyobo Co., Ltd., Osaka, Japan). The primer pair used for survivin gene amplification was forward primer 5′-GCA TGG GTG CCC CGA CGT TG-3′ (corresponding to position 48–67 of the survivin mRNA [Genbank accession NM 001168]) and reverse primer 5′-GCT CCG GCC AGA GGC CTC AA-3′ (position 475–494) which produced a polymerase chain reaction (PCR) product of 431 bp. As an internal standard a fragment of human G3PDH was amplified by PCR using forward primer 5′-ACC ACA GTC CAT GCC ATC AC-3′ and reverse primer 5′-TCC ACC ACC CTG TTG CTG TA-3′ which gave a PCR product of 450 bp.

The PCR amplification was performed in a final volume of 20 μl which comprised 1 μl of the reverse transcriptase reaction mix, 3 pmol each of 5′ and 3′ primers for the survivin or G3PDH genes, 160 μM of deoxynucleotide triphosphate, 1 mM MgSO4 and 0.3 units of Taq DNA polymerase in reaction buffer (KOD-Plus, Toyobo Co. Ltd.). PCR was performed using a thermal cycler (TaKaRa PCR Thermal Cycler MP, Takara Bio Inc., Shiga, Japan) with an initial denaturation step at 94C for 2 minutes followed by 32 cycles of 20 seconds at 94C for denaturation, 30 seconds at 68C for annealing and 45 seconds at 72C for extension. The final extension step was prolonged to 5 minutes at 72C. PCR products were separated on 2% agarose gels by electrophoresis. To determine the appropriate number of PCR cycles for quantification, PCR was performed in 24 to 40 cycles in increments of 2 cycles.

The expression ratios of survivin to G3PDH were reasonably constant between 30 to 40 cycles so that 32 PCR cycles were used in subsequent experiments. The values at 32 PCR cycles were defined as the expression levels of the target genes with the mean value from at least 3 independent experiments used to determine the level of survivin gene expression. Signal intensities were quantified using the software package NIH image (National Institutes of Health, Bethesda, Maryland). The level of survivin gene expression was quantified as the ratio of the survivin signal intensity to that of G3PDH and expressed as the mean plus or minus standard error of mean.

Immunohistochemical staining method. Immunohistochemistry was performed on formalin fixed, paraffin embedded tissue sections using the peroxidase labeled dextran polymer method. One representative paraffin block from each patient containing viable cancer tissue was used for this study. Four micrometer thick sections were dewaxed in xylene, dehydrated in ethanol and then incubated with 3% hydrogen peroxide for 15 minutes. Sections were washed 3 times in Tris-HCl and incubated overnight with a mouse monoclonal antibody against PCNA (PC10, Dako Japan Co., Kyoto, Japan) at 1:50 dilution, or a rabbit polyclonal antibody against ssDNA (Dako Japan Co.) at a 1:400 dilution.[14] After washing the slides with Tris-HCl, anti-mouse Envision+ for PCNA (Dako Japan Co.) or anti-rabbit Envision+ for ssDNA was applied for 60 minutes. The reaction products were visualized with diaminobenzidine and tissue sections were counterstained with hematoxylin.

Determination of PCNA labeling index and apoptotic index. PCNA or ssDNA positive cells were counted in at least 20 nonoverlapping microscopic fields of each sample with a minimum of 1,000 cancer cells counted. Results were expressed as the PCNA labeling index (PCNA-LI) and apoptotic index (AI).

Statistical analysis. The data were analyzed using the StatView V statistical package (SAS Institute Inc., Cary, North Carolina). The difference in survivin gene expression intensity between cancer and control tissue was examined by the Mann-Whitney U test or the Wilcoxon signed rank test. Correlations between survivin gene expression and various clinicopathological factors were examined by the Mann-Whitney U test or the Kruskal-Wallis rank test followed by the Tukey-Kramer test. Correlations between survivin gene expression and PCNA-LI or AI were examined by simple regression analysis, with $p < 0.05$ considered statistically significant.

RESULTS

RT-PCR and survivin gene expression. The expected survivin product of 431 bp was amplified (fig. 1). Of 82 cancer samples 68 (82.9%) and of 80 control tissues 47 (58.8%) had detectable levels of survivin mRNA. Mean survivin expression ± SE was significantly higher in prostate cancer compared to control tissue (0.076 ± 0.014 vs 0.024 ± 0.004, $p < 0.001$). In the 65 cases in which RNA could be extracted from prostate cancer and matched control samples, the level of survivin expression was also significantly higher in prostate cancer (0.079 ± 0.017 vs 0.025 ± 0.005, $p = 0.003$, fig. 2).

Correlation between survivin mRNA expression and clinical characteristics. There was no significant correlation between the level of survivin expression and patient age at surgery or preoperative serum PSA (table 1). There were 54 of 82 cases without adjuvant therapy after radical prostatectomy. Pathological staging of these 54 cases was identified as pT2a in 20 cases, pT2b in 24 and pT3a in 10, and all 54 cases were identified as pN0 or pNx. Only 3 of 54 cases exhibited PSA biochemical failure and none exhibited clinical recurrence or death secondary to cancer. There was no significant correlation between the levels of survivin expression and PSA biochemical failure. Of the 82 cancer cases PSA-DT could be calculated for 50 cases that had a minimum of 3 PSA measurements and a minimum of 2 months of preoperative followup. In cases with a short PSA-DT (less than 2 years) mean survivin expression ± SE was 0.134 ± 0.054. This level was significantly higher than the levels of survivin expres-

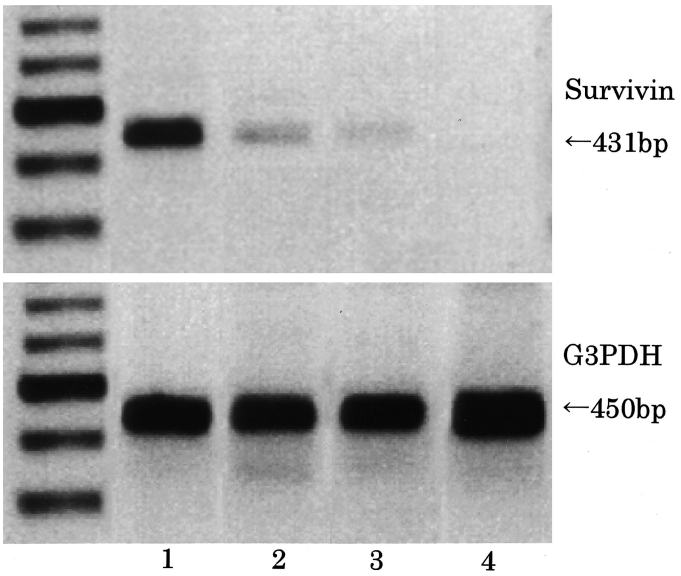

FIG. 1. RT-PCR products of prostate cancer specimens. High (lane 1), moderate (lane 2), low (lane 3) and negative (lane 4) expression of survivin were demonstrated. G3PDH was amplified as internal control.

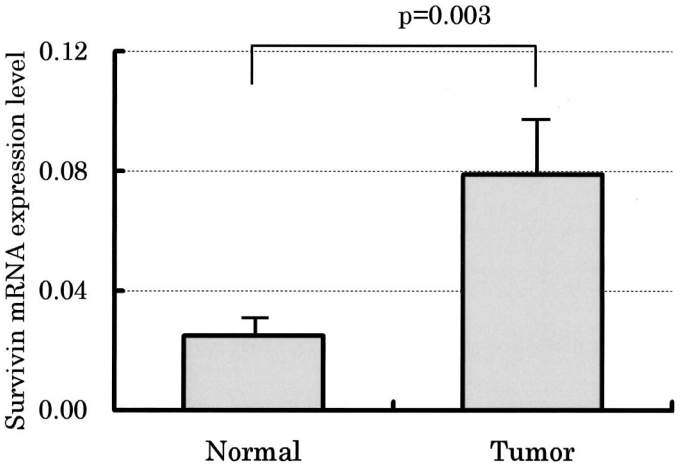

FIG. 2. Level of survivin expression was significantly higher in prostate cancer compared to matched control tissue (0.079 ± 0.017 vs 0.025 ± 0.005, Wilcoxon signed rank test p = 0.003) in 65 cases in which RNA could be extracted from prostate cancer and matched control samples.

sion in cancers with a moderate PSA-DT (2 to 4 years, 0.043 ± 0.016, p <0.05) or long PSA-DT (greater than 4 years, 0.034 ± 0.010, p <0.05, table 1).

Correlation between survivin mRNA expression and pathological characteristics. Prostate cancer specimens from cancers greater than stage pT3b had significantly higher survivin expression than those cancers less than stage pT2b (table 2, p <0.05). In cancers with a high Gleason score (8 to 10), mean survivin expression was 0.184 ± 0.057, which was significantly higher than those with a low Gleason score (6 or less, 0.049 ± 0.012, p <0.05). In addition, survivin expression was significantly higher in cancers with positive lymph node metastasis, positive vessel invasion or positive surgical margin compared to negative counterparts (p = 0.002, p = 0.03, p = 0.02, respectively, table 2). However, no significant correlation was found between survivin expression and number of cancer in prostate or cancer size. Also, although survivin expression was higher in cancers with positive lymphatic invasion, positive perineural infiltration, positive capsular invasion, positive seminal vesicle invasion or positive urethral invasion, the differences were not statistically significant (table 2).

Immunohistochemical staining of PCNA and ssDNA. Mean PCNA-LI ± SE was 182 ± 35 (range 5 to 580, fig. 3) and mean AI was 5.53 ± 2.1 (range 0 to 55, mean ± SE, fig. 4). Survivin expression was positively correlated with PCNA-LI (regression line Y = 0.00033X + 0.052, r = 0.44, p = 0.005, fig. 5). Although not quite statistically significant, an inverse correlation was found between survivin expression and the AI (regression line Y = −0.0024X + 0.135, r = 0.21, p = 0.06, fig. 5).

DISCUSSION

Apoptosis and various apoptosis regulatory molecules such as members of the bcl-2 family have an important role in the accumulation of prostate cancer cells.[15] Recently, the IAP family has been demonstrated to be of similar significance in prostate cancer cell lines.[11] Survivin, a new member of the IAP family, is expressed in many cancers and inhibits apoptosis. It has been reported that survivin blocks downstream part of both apoptotic pathways by directly inhibiting the terminal effector caspase-3 and caspase-7, and interfering with caspase-9 activity/processing.[16] In addition, survivin counteracts pro-apoptotic stimuli induced by interleukin-3, Fas, Bax, tumor necrosis factor, anticancer drugs and X-irradiation.[2,16] As previously described survivin expression is inversely correlated with apoptosis during tumorigenesis, and positively correlated with proliferation and angiogenesis with the inhibition of apoptosis by survivin, predicting poor prognosis and shorter survival in human cancers.[16]

In this study we investigated mRNA expression of survivin in normal and cancer tissues of the prostate. We found that 82.9% of cancer samples and 58.8% of normal prostate tissue had detectable levels of survivin mRNA on RT-PCR. In addition we demonstrated that the level of survivin expression in cancer tissue was significantly higher than that in normal tissue. Recent publications have demonstrated survivin expression in all the most common human cancers.[16] However, it has been reported that survivin expression is not detected in normal adult tissues with immunohistochemical survivin expression being absent in normal tissues.[5,10,16] However, in this study 58.8% of normal prostate tissues exhibited detectable survivin expression by RT-PCR. Using the more sensitive RT-PCR method, survivin expression has been detected in many kinds of normal tissues although the levels of survivin expression in normal tissues were lower than paired malignant tissues in every report.[4,6,9,16] Although the role of survivin in cancer tissues is being steadily elucidated, some reports demonstrate that survivin has a crucial role during malignant transformation.[17] Ultimately the significance of survivin expression in normal tissues, particularly the correlation with malignant potential, remains unclear. Therefore, further studies are required to address the role of survivin in normal tissue such as whether survivin in normal tissue relates to tumorigenesis and whether patients with positive survivin expression in some normal tissues have an increased potential risk for the development of cancer.

We used preoperative PSA-DT to assess the relationship between survivin expression and tumor aggressiveness. PSA-DT is a unique parameter peculiar to prostatic neoplasms and can be used to evaluate biological and clinical characteristics, and predict patient prognosis.[18] In addition, prostate cancers with a shorter PSA-DT appear to be more aggressive, with PSA-DT correlating with risk of progression.[18] Our data indicate significantly higher survivin expression in cancers with a short PSA-DT (less than 2 years). This finding suggests that survivin expression may be related to tumor aggressiveness, the consequent risk of progression and patient prognosis.

TABLE 1. *Correlation between survivin expression of prostate cancer and clinical factors*

Clinical Factors	No. Pts	Mean Survivin Expression ± SE	p Value
Pt age:*			
69 or Younger	48	0.085 ± 0.019	0.49
70 or Older	34	0.065 ± 0.021	
Ng/ml PSA:*			
Less than 4.0	13	0.058 ± 0.026	
4.0–10.0	29	0.074 ± 0.027	0.80
Greater than 10.0	40	0.085 ± 0.020	
PSA biochemical failure:*			
Yes	3	0.018 ± 0.006	
No	51	0.054 ± 0.015	0.61
X	28		
Yrs PSA-DT:†			
Less than 2	14	0.134 ± 0.054	
2–4	10	0.043 ± 0.016	<0.05 (statistically significant)
Greater than 4	15	0.034 ± 0.010	<0.05 (statistically significant)
No change	11	0.038 ± 0.020	
Impossible to calculate	32		

* Examined by the Mann-Whitney U test.
† Examined by the Kruskal-Wallis rank test followed by the Tukey-Kramer test.

TABLE 2. *Correlation between survivin expression of prostate cancer and pathological factors*

Pathological Factors	No. Pts	Mean Survivin Expression ± SE	p Value
No. tumors:*			
1	31	0.078 ± 0.022	
2–3	30	0.075 ± 0.029	0.59
4 or More	21	0.098 ± 0.033	
Tumor size (cm^2):*			
Less than 1.0	28	0.061 ± 0.021	
1.0–5.0	30	0.053 ± 0.018	0.10
Greater than 5.0	24	0.126 ± 0.034	
pT stage:*			
pT2b or lower	44	0.047 ± 0.011	
pT3a	28	0.095 ± 0.026	<0.05 (statistically significant)
pT3b or higher	10	0.160 ± 0.075	
Gleason score:*			
6 or Less	50	0.049 ± 0.012	
7	19	0.078 ± 0.036	<0.05 (statistically significant)
8–10	13	0.184 ± 0.057	
pN stage:†			
0	45	0.055 ± 0.011	
1	8	0.277 ± 0.081	0.002 (statistically significant)
X	29		
Lymphatic invasion:†			
Neg	52	0.047 ± 0.011	
Pos	30	0.130 ± 0.032	0.07
X	0		
Vessel invasion:			
Neg	48	0.044 ± 0.010	
Pos	30	0.131 ± 0.031	0.03 (statistically significant)
X	4		
Surgical margin:†			
Neg	48	0.041 ± 0.010	
Pos	32	0.125 ± 0.029	0.02 (statistically significant)
X	2		
Perineural infiltration:†			
Neg	27	0.053 ± 0.019	
Pos	45	0.089 ± 0.019	0.25
X	10		
Capsular invasion:†			
Neg	45	0.048 ± 0.011	
Pos	35	0.115 ± 0.028	0.16
X	2		
Seminal vesicle invasion:†			
Neg	68	0.066 ± 0.012	
Pos	9	0.170 ± 0.082	0.23
X	5		
Urethral invasion:†,‡			
Neg	60	0.084 ± 0.017	
Pos	8	0.098 ± 0.066	0.79
X	14		

* Examined by the Kruskal-Wallis rank test followed by the Tukey-Kramer test.
† Examined by the Mann-Whitney U test.
‡ Urethral invasion negative indicates that cancer tissue does not reach the prostatic urethral mucosa, while positive indicates that cancer tissue tightly contacts or penetrates the mucosa of the prostatic urethra.

In addition, we also examined the relationship between survivin expression and a variety of pathological factors. Although some pathological factors did not exhibit a statistically significant correlation with survivin expression, we found that survivin expression was higher in more advanced or aggressive cancers. Previous reports have demonstrated

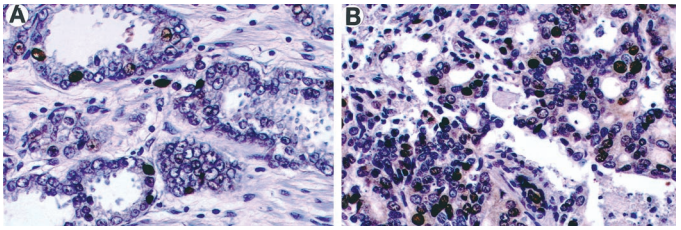

FIG. 3. Positive immunohistochemical staining of PCNA was demonstrated (reduced from × 200). *A*, PCNA-LI was 181. *B*, PCNA-LI was 580.

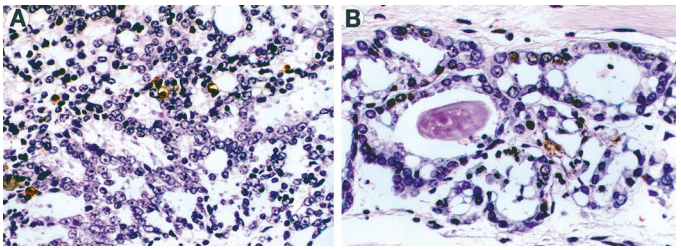

FIG. 4. Positive immunohistochemical staining of ssDNA was demonstrated (reduced from × 200). *A*, AI was 5. *B*, AI was 55.

that increased survivin expression correlated with advanced grade of endometrial carcinoma[19] and laryngeal squamous cell carcinoma.[20] In this study we demonstrated that the expression of survivin was significantly increased in tumors with a high Gleason score compared to those with a low score. Since prostate cancer with a high Gleason score has more malignant potential, it has been suggested that an increased level of survivin expression in prostate cancer may be related to the aggressiveness of prostate cancer cells and may be involved in promoting tumor growth.

Together with other pathological factors, survivin expression was significantly higher in tumors with a high pathological T stage, positive lymph node metastasis, positive vessel invasion and positive surgical margin. These results also suggest that survivin expression is related to tumor progression in prostate cancer. A similar relationship between survivin expression and cancer progression has been reported in many cancers such as neuroblastoma,[3] esophageal cancer[6] and laryngeal squamous cell carcinoma.[20] Furthermore, survivin expression was significantly associated with clinical stage, histological grade, clinical outcome and survival rate in patients with endometrial carcinoma.[19]

Previous work has suggested that survivin expression may have a role in cell proliferation.[17,21] In this study we demonstrated that survivin expression is positively related to tumor proliferative activity measured by the PCNA labeling index. In ovarian tumorigenesis Sui et al demonstrated that survivin expression was closely associated with an increased PCNA index, and concluded that survivin may promote cell proliferation and contribute to the development of ovarian tumors.[17]

Yamamoto and Tanigawa have reviewed the relationship between survivin expression and tumor cell apoptosis, and have revealed a significant inverse correlation between these 2 factors in gastric, colorectal and breast cancers.[16] In this study, although it did not quite reach statistical significance, our data demonstrated a tendency for survivin expression to be inversely related with apoptosis evaluated by immunohistochemical staining of ssDNA. Staining of ssDNA has been used to detect cells at an early stage of apoptosis preceding cell detachment and DNA fragmentation with the results of ssDNA staining correlating with conventional TUNEL staining.[14] As previously mentioned[2,16] survivin inhibits apoptosis via various mechanisms, and it is apparent that increased resistance to apoptosis would confer significant biological advantage to a rapidly growing tumor and facilitate tumor cell accumulation by decreasing the rate of cell loss.[5] Our data suggest that survivin expression within prostate cancer tissue, as with other cancers, may well be an important effector molecule acting to augment cell proliferation and inhibit apoptosis of cancer cells. This process is likely to represent the biological mechanism whereby the degree of survivin expression is associated with the progression and aggressiveness of prostate cancer.

It has been reported that survivin expression correlated with poor patient survival in colorectal cancer,[9] nonsmall cell lung cancer,[4] breast cancer,[5] neuroblastoma[3] and esophageal cancer.[6] In this study many patients with disease stage higher than pT3a and/or positive lymph node metastasis had received radiotherapy or hormonal therapy immediately after surgery. As a result we had no cases of clinical recurrence or death related to tumor progression, and therefore we could not assess the correlation between survivin expression and patient survival. In 54 of 82 cases studied for PSA biochemical failure, only 3 cases exhibited biochemical failure and the cancer specimens from these 3 cases exhibited positive expression of survivin. Although no significant correlation was evident between survivin expression and PSA biochemical failure, the small number of cases was insufficient for rigorous statistical analysis. Increased patient numbers and an

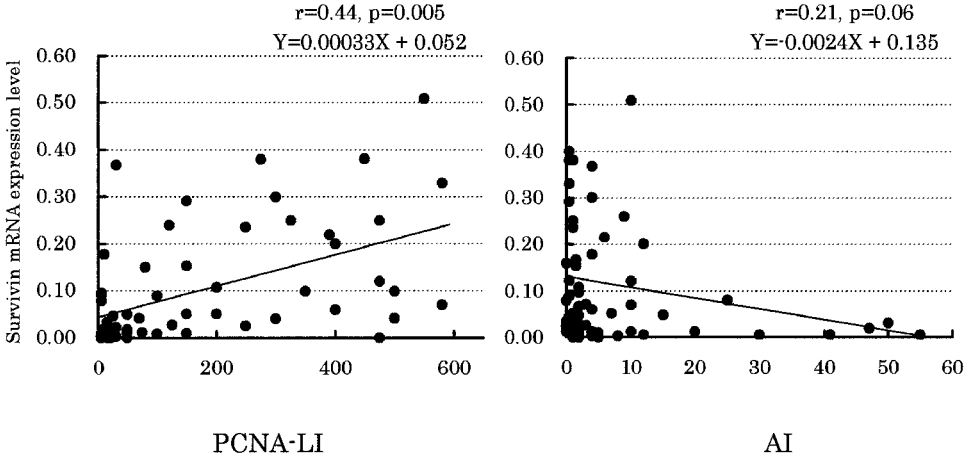

FIG. 5. Positive correlation was evident between survivin expression and PCNA-LI (Y = 0.00033X + 0.052, r = 0.44, p = 0.005 by simple regression analysis). Although not statistically significant, inverse correlation was evident between survivin expression and AI (Y = −0.0024X + 0.135, r = 0.21, p = 0.06 by simple regression analysis).

extended followup are necessary to evaluate these issues further. However, since more progressive and aggressive cases of prostate cancer exhibited high levels of survivin expression, survivin expression may well be related to poor prognosis in prostate cancer as in other tumors. Therefore, patients with prostate cancer exhibiting high expression of survivin may require closer followup for PSA biochemical failure or tumor recurrence.

CONCLUSIONS

In summary, although survivin expression may be a common event in many kinds of cancer tissues, this study demonstrates an increased level of survivin expression in prostate cancer. Expression of survivin was significantly increased in cancers with a short PSA-DT, advanced pathological stage and high Gleason score, and was positively correlated with PCNA-LI and inversely correlated with AI. These data suggest that the degree of survivin expression is associated with the progression and aggressiveness of prostate cancer. As many previous reports have described, survivin is thought to have an important role in tumor progression, and may provide useful clinical and prognostic insight in patients with prostate cancer.

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