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Expression of p73 and c-Abl Proteins in Human Ovarian Carcinomas

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Abstract

The p73, a homologue of the p53 tumor suppressor protein, has a pro-apoptotic activity which is induced by the c-Abl, a protein tyrosine kinase appearing in the nucleus and cytoplasm of proliferating cells. However, the role of p73 and c-Abl in ovarian cancer is not well-defined. We investigated immunohistochemical expressions of p73 and c-Abl in 64 ovarian carcinomas, 13 borderline and 14 benign ovarian tumors to elucidate their clinicopathological relevances. Of the malignant, borderline, and benign ovarian tumors, respectively, 33 (51%), 10 (77%) and 13 (93%) had negative or low p73 expression, 31 (48%), 3 (23%) and 1 (7%) had high p73 expression, 23 (36%), 5 (38%) and 10 (71%) had negative or low c-Abl expression, and 41 (64%), 8 (61%) and 4 (29%) had high c-Abl expression. A high p73 or c-Abl expression was significantly associated with ovarian carcinomas as compared to benign tumors ($p = 0.003$ and $p = 0.03$ respectively). In addition, a significant correlation was found between the high p73 expression and disease stage ($p = 0.04$) and patient's survival ($p = 0.02$). No correlation was found with c-Abl expression. These results reveal an association of p73 overexpression with advanced ovarian carcinomas which may suggest the p73 overexpression as an indicator of poor prognosis. (J Nippon Med Sch 2003; 70: 234–242)

Key words: ovarian tumor, p 73, c-Abl, immunohistochemistry, disease stage, survival

Introduction

Among gynecological malignancies, ovarian carcinoma has the highest mortality rate. At the time of diagnosis, about two-thirds of patients have already advanced disease, yet the molecular mechanisms of ovarian cancer development remain obscure. Detection of biological molecules that in association with established clinicopathologic parameters predict which patients are at high risk for the development of tumor progression contributes greatly to better treatment strategies and longer survival benefit for patients with ovarian carcinoma. One approach to this task is the characterization of potential molecules involved in the development of ovarian cancer and detection of their relations with clinicopathological and prognostic factors of the disease.

The p73, a novel family member of the p53 tumor suppressor protein, has recently been identified and found to induce apoptosis[1,2]. The p73 gene was also

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Table 1 Expression of p73 and c-Abl in human ovarian tumors

Variable	No.	p73 expression		c-Abl expression	
		Neg/Low	High	Neg/Low	High
Adenocarcinoma	64	19/33	31	8/23	41
Serous	29	9/15	14	4/13	16
Mucinous	12	4/8	4	2/3	9
Endometrioid	5	2/3	2	1/3	2
Clear cell	18	4/7	11	1/4	14
Borderline tumor	13	6/10	3	3/5	8
Serous	2	1/1	1	0/0	2
Mucinous	11	5/9	2	3/5	6
Benign cystadenoma	14	10/13	1	8/10	4
Serous	5	4/5	0	2/3	2
Mucinous	9	6/8	1	6/7	2

Adenocarcinoma versus borderline tumors: p73 ($p = 0.08$) and c-Abl ($p = 0.14$).
Adenocarcinoma versus benign tumors: p73 ($p = 0.003$) and c-Abl ($p = 0.03$).

considered as a candidate of the imprinted tumor suppressor gene, as it was mapped on 1 p36, a chromosomal region frequently found to be deleted in many types of cancer[1,3]. Overexpression of p73 was found in several cancers such as lung, bladder, prostate, and colorectal carcinomas[4-7]. In lung cancer, the expression of p73 was increased independent of p53 gene mutation[8]. By contrast, these data suggested an oncogenic role for p73 expression[9].

The c-Abl proto-oncogene has been identifed as the normal cellular homologue of the transforming gene of Abelson murine leukemia retrovirus and has been mapped on chromosome 9q34 in humans[10]. The protein encoded by c-Abl is a ubiquitous cytoplasmic tyrosine kinase that contains three nuclear localization signals and a nuclear export signal[11]. Activated transforming c-Abl proteins are localized mainly in the cytoplasm bound to F-actin, suggesting that the cytoplasmic retention of c-Abl may normally participate in signal transduction pathways that stimulate mitogenesis. In contrast, nuclear c-Abl appears to be regulated in a cell cycle-dependent manner, and it has been implicated in the regulation of gene transcription[12]. Nuclear c-Abl may also have an apoptosis inhibitory role[13].

In ovarian cancer, genetic aberrations involving ras, c-erb-B2, Bcl-2, and p53 genes have been identified. However, the role of p73 and c-Abl expressions in the development of this disease is not well-defined. Since p73 and c-Abl have been implicated in the pathogenesis of several types of cancer, they may also be involved in the development and/or progression of ovarian cancer. We have, therefore, studied the expression of p73 and c-Abl in 91 ovarian tumors and correlated the results with the established clinicopathologic factors of the disease.

Materials and methods

Patients

Serial 4-μm sections from the representative paraffin-embedded tissue specimens of 64 consecutive ovarian carcinomas, 13 borderline and 14 benign ovarian tumors were used (**Table 1**). The study was approved by the Institutional Review Board of Nippon Medical School. The ages of ovarian carcinoma patients ranged from 21 to 88 years (median: 54 years). A section from each tissue was stained with hematoxylin and eosin to confirm the diagnosis. Histological types and grades were determined using the World Health Organizatin Criteria[14], and the stage of tumors was assessed according to the International Federation of Gynecology and Obstetrics staging system[15]. All carcinoma patients in this study received postoperative chemotherapy for a high-risk early stage (stage I, grade 3; stage IC; any stage II) or advanced diseases (stages III and IV).

The clinicopathologic characteristics of ovarian carcinoma patients are shown in **Table 2**. Tumor sizes ranged from 5 to 30 cm in greater diameter (median: 12 cm). Of the 64 ovarian carcinoma patients, 43 were alive with no evidence of the disease, 6 were alive with disease, and 15 were dead of the disease at the time of analysis. The median follow-up for all patients (n = 64) was 31 months (range, 3 to 120), and for surviving patients (n = 49) was 40.5 months (range, 16 to 120).

Antibodies

Affinity-purified goat polyclonal antibody raised against a peptide mapping at the carboxy terminus of p73β of human origin (differs from corresponding p73α sequence by two amino acids) and rabbit polyclonal antibody raised against a peptide mapping within the kinase domain of c-Abl of human origin were used (Santa Cruz Biotechnology, Inc, Santa Cruz, CA). The anti-p73 antibody reacts with both p73α and p73β of human origin and is non cross-reactive with other p73 isoforms. The anti-c-Abl antibody reacts with c-Abl p120 and chimeric Bcr/Abl proteins of mouse, rat, and human origin, and does not inhibit c-Abl tyrosine kinase activity.

Immunohistochemistry

Immunostaining for p73 and c-Abl was performed using the avidin-biotin-peroxidase complex method. Endogenous peroxidase was blocked in deparaffinized tissue sections by 3% hydrogen peroxide in methanol for 30 min. After washing with phosphate buffer saline (PBS), pH 7.4, tissue nonspecific binding sites were blocked by 10% normal rabbit serum for 10 minutes at room temperature. The sections were then incubated with affinity-purified goat polyclonal anti-human p73 at 1: 150 dilution or rabbit polyclonal anti-human c-Abl at 1: 400 dilution for 60 min. After washes with PBS, biotinylated anti-goat or rabbit IgG (Vector Laboratories, Burlingame, CA) was applied followed by washing and detection using the avidin-biotin-proxidase complex (Dako Co., Japan). Diaminobenzidine was used as chromogen. The sections were counterstained briefly with Mayer's hematoxylin, dehydrated, and mounted. Negative controls included the use of a nonspesific goat or rabbit immunoglobulin as the primary antibody. As positive controls, we used sections from an adenocarcinoma of the lung previously found to be positive for p73 and c-Abl expression.

All interpretations were made without any knowledge of the clininal status of the patients. The stainings were assessed semiquantitatively by the percentage of the stained tumor cells derived from the enumeration of more than 500 tumor cells in comparable areas in serial sections at 400 x magnification and classified as: score 0, ＜5%；score 1, 5～25%; score 2, 26～50%; score 3, 51～75%; and score 4, ＞75% of positive cells.

Western blot analysis

Proteins were extracted from the representative samples with positive (n = 9) or negative (n = 3) expression for p73 or c-Abl. Equal amounts of protein (50 μg/lane) were size fractionated on a 12.5 %SDS-polyacrylamide gel, blotted onto Immobilon polyvinylidene difluoride (PVDF) membranes (Bio-Rad Laboratories, Hercules, CA) in transfer buffer containing 192 mM glycine, 25 mM Tris-HCL, pH 8.3, 20% v/v methanol, and 0.02% SDS), and incubated with blocking buffer (5% nonfat dry milk, 50 mM Tris-HCl, pH 7.5, 150 mM NaCl, 0.1% Tween-20) overnight at 4℃. The membranes were then incubated with goat anti-p73 or rabbit anti-c-Abl antibodies at 1: 1,000 dilutions at room temperature for 2 hr. After washes with TBST (50 mM Tris-HCl, pH 7.5, 150 mM NaCl, 0.1% Tween-20) buffer and treatment with corresponding alkaline phosphatase-conjugated secondary antibodies, the reactions were developed with the ProtoBlor NBT and BICP Color Developmet System (Promega, Madison, WI).

Statistical analysis

The expressions of p73 and c-Abl in relation to various clinicopathologic factors were assessed using the chi-square test or Fisher's exact test. Correlation between p 73 expression and c-Abl was examined by Spearman rank correlation test. Cumulative survival probablities of the patients were calculated by the Kaplan-Meier method and log-rank test. The results were analyzed for the endpoint of overall survival. Survival times of patients still alive were censored with the last follow-up date. All statistical analyses were done by the SPSS statistical software system (SPSS Inc.,

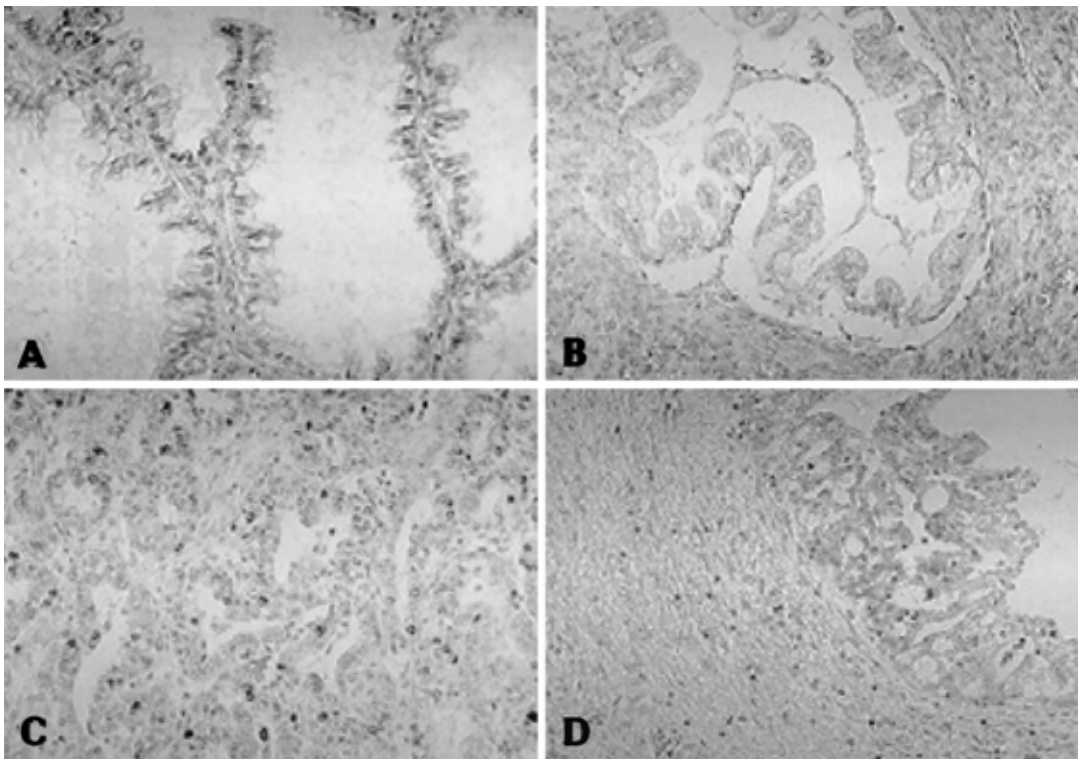

Fig. 1 Immunohistochemical expression of p73 and cAbl in benign and malignant ovarian tumors. Benign ovarian epithelial cells in mucinous cystadenomas showed no or trace staining for p73 (A) and c-Abl (B). Ovarian carcinoma cells (serous type) showed moderate to strong staining for p73 (C) or c-Abl (D). Original magnification ×200.

Chicago, IL). The degree of significance was set at $P < 0.05$.

Results

Immunohistochemistry

Fig. 1 depicts the representative immunostainings for p73 and c-Abl in benign and malignant ovarian tumors. The p73 was mainly expressed in the nucleus, while c-Abl was mostly observed in the cytoplasm. In benign ovarian tumors and associated normal ovarian surface epithelium, no appreciable expression of p73 or c-Abl was observed. In contrast, ovarian carcinoma cells showed moderate to strong stainings for p73 or c-Abl in a considerable number of cases. No staining for p73 or c-Abl was seen in the negative control sections.

The median semi-quantitative score for p73 and c-Abl was a score of 2.0, which was set to divide the cases into two groups of low (≦2.0) and high (>2.0) expressions for statistical comparisions. The inter-observor variability was less than 7%. Of the malignant, borderline, and benign ovarian tumors, respectively, 33 (51%), 10 (77%) and 13 (93%) had negative or low expressions, and 31 (48%), 3 (23%) and 1 (7%) showed high expressions for p73, and 23 (36%), 5 (38%) and 10 (71%) had negative or low expressions, and 41 (64%), 8 (61%) and 4 (29%) showed high expressions for c-Abl (**Table 1**). Of the 31 and 38 ovarian carcinomas with high expressions for p73 and c-Abl respectively, 22 showed coexpression.

Western blot

The immunostaining results were confirmed by western blot and the peptide competitions in western blot assays in a group of ovarian tumors with positive (n=7) or negative (n=3) expression each for p73 or c-Abl (**Fig. 2**). In the group with positive immunostatings, the protein bands of 73 kD and 120 kD respectively for p73 and c-Abl were detected, while negative immunostaining group showed no bands. The peptide competetion assays

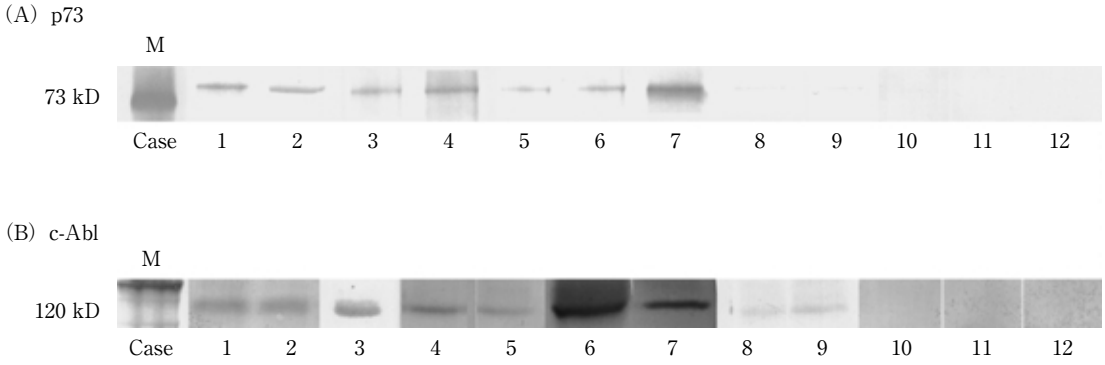

Fig. 2 Western blot analysis showed the protein bands of 73 kD and 120 kD respectively for p73 (A) and c-Abl (B) in tumor tissues from 7 cases (lanes 1 to 7) with positive and 3 cases (lanes 10 to 12) with negative reactions each for p73 (A) and c-Abl (B). Lanes 8 and 9 show weak bands after peptide competetion assays for cases 1 and 2 in each category. M: marker.

Table 2 Clinicopathologic characteristics versus p73 and c-Abl expressions in human ovarian carcinomas

Variable	No.	p73 expression		p	c-Abl expression		p
		Neg/Low	High		Neg/Low	High	
Age							
= 60 yrs	42	13/23	19	0.47	6/18	24	0.61
> 60 yrs	22	6/10	12		2/7	15	
Tumor size							
= 10 cm	20	8/11	9	0.71	3/10	10	0.11
> 10 cm	44	11/22	22		5/13	31	
Histologic type							
Serous	29	9/15	14	0.49	4/13	16	0.22
Mucinous	12	4/8	4		2/3	9	
Endometrioid	5	2/3	2		1/3	2	
Clear cell	18	4/7	11		1/4	14	
Histologic grade							
Low (1—2)	46	12/24	22	0.87	8/18	28	0.39
High (3)	18	7/9	9		0/5	13	
Disease stage							
Low (Ⅰ—Ⅱ)	37	12/23	14	0.04	3/11	26	0.22
High (Ⅲ—Ⅳ)	27	7/10	17		5/12	15	
Chemoresponse							
CR	40	15/22	18	0.60	4/15	25	0.27
NR	17	3/7	10		3/4	13	
NA	7	1/4	3		1/4	3	
Patient outcome							
Alive with no evidence of disease	43	12/25	18	0.13	4/13	30	0.17
Died or alive with disease	21	7/8	13		4/10	11	

CR, complete response; NR, no response; NA, not available.

for two cases each with positive p73 or c-Abl expression showed a decreased band density.

Clinicopathologic correlations of p73 and c-Abl expressions

A high expression of p73 or c-Abl was significantly correlated with ovarian carcinomas as compared to benign tumors ($p = 0.003$ and $p = 0.03$ respectively; **Table 1**). Comparisons with borderline tumors revealed a near significant association with p73 expression only ($p = 0.08$). A significant correlation was found between the p73 expression and disease stage ($p = 0.04$; **Table 2**). However, other

Table 3 Survival analyses in relation to the clinicopathologic factors and expressions of p73 and c-Abl in human ovarian carcinomas

Variable	No.	No. of events	p
Age			
= 60 yrs	42	6	0.06
> 60 yrs	22	9	
Tumor size			
= 10 cm	20	6	0.55
> 10 cm	44	9	
Histologic type			
Serous	29	6	0.96
Mucinous	12	3	
Endometrioid	5	2	
Clear cell	18	4	
Histologic grade			
Low (1—2)	46	8	0.13
High (3)	18	7	
Disease stage			
Low (Ⅰ—Ⅱ)	37	3	0.008
High (Ⅲ—Ⅳ)	27	12	
Chemoresponse			
CR	40	5	0.10
NR	17	6	
NA	7	4	
p73			
Neg/Low	33	3	0.02
High	31	12	
c-Abl			
Neg/Low	23	7	0.48
High	41	8	

CR, complete response; NR, no response; NA, not available

factors such as patient's age, tumor size, histologic type, histologic grade, response to chemotherapy, and patient's outcome did not show a significant correlation with either p73 or c-Abl expression. In addition, the p73 and c-Abl expressions correlated with each other (Spearman rank correlation coefficients: $r = 0.2536$, $p = 0.04$).

To investigate whether p73 or c-Abl expression correlates with survival of ovarian carcinoma patients, cumulative survival curves for the 64 patients were constructed according to the Kaplan-Meier method, and differences in survival were assessed with the log-rank test. The overall 5-year survival probability of the patients in our series was 66.4%. The survival rates of patients with high disease stage (survivors, $n = 15$) or high p73 expression in the tumor (survivors, $n = 19$) were significantly worse than those of patients with low disease stage (survivors, $n = 34$; $p = 0.008$) or a negative and low p73 expression (survivors, $n = 30$; $p = 0.02$; **Table 3** and **Figs. 3 and 4**). Further survival analysis of low stage patients ($n = 37$) in relation to p73 or c-Abl expression did not show a significant difference. A high or low c-Abl expression did not correlate with the survival time of patients (**Table 3**). Finally, comparison of combined expression of p73/c-Abl did not show a significant correlation with the clinicopathological factors.

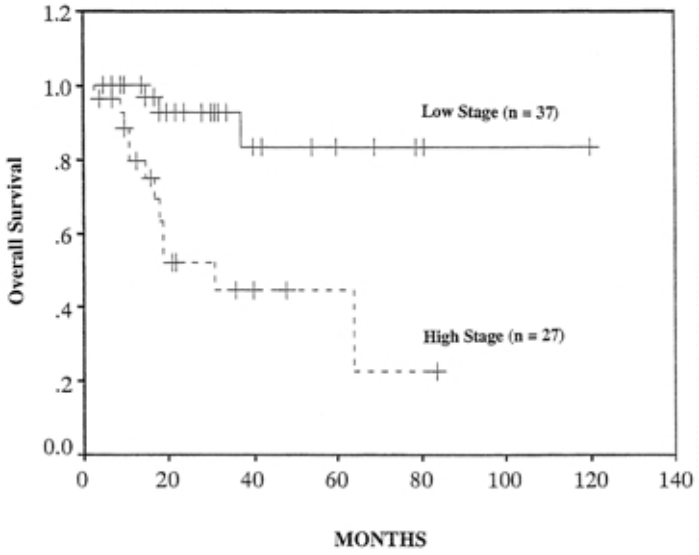

Fig. 3 Survival curves of ovarian carcinoma patients grouped according to low (I-II) and high (III-IV) disease stages showing a significant difference ($p = 0.0004$).

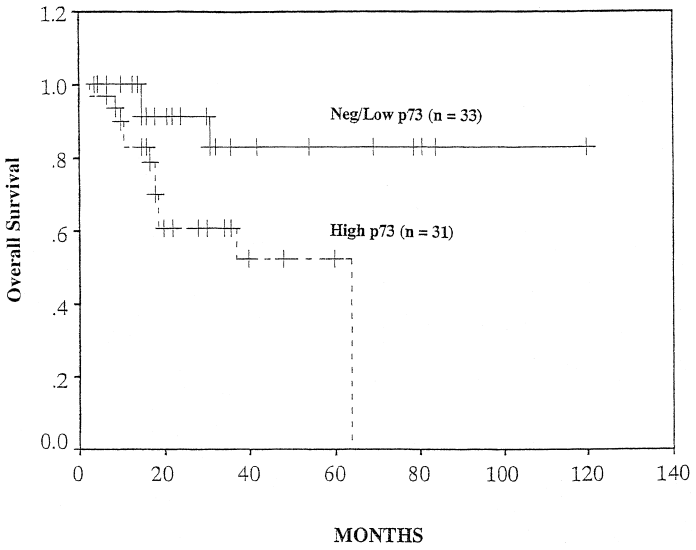

Fig. 4 Survival curves of ovarian carcinoma patients grouped according to negative/low versus high p73 expression showing a significant difference ($p = 0.008$).

Discussion

The results of our retrospective study showed that p73 and c-Abl were infrequently detectable in benign ovarian tumors, whereas their overexpressions were significantly associated with ovarian carcinoma. Overall, a high expression of p73 or c-Abl was observed, repectively, in 7% or 29% of benign cystadenomas, 23% or 61% of borderline tumors, and 48% or 64% of carcinomas. In addition, a significant correlation was found between the high p73 expression and a high disease stage or poor survival time. These findings suggested that p73 overexpression may play an important role in advanced ovarian cancer.

The p73 gene is a novel family member of the p53 tumour-suppressor gene[1] which has several alternatively spliced variants including α, β, γ, δ, ε, and ζ, each encoding a corresponding protein isoform. The α and β variants of p73 have been shown to be universally present in both normal tissues and cancers, whereas the other variants γ, δ, ε, and ζ are smaller and expressed in certain normal tissues[16].

The role of p73 as a true tumor-suppressor gene is still undetermined. A classical feature of a tumor suppressor gene would be an association of tumor development with the loss of the gene's function. However, accumulated data have failed to show an association between tumor development and loss of p73 function[9,17]. In ovarian cancer, loss of heterozygosity at p73 locus was found in 50% of 44 invasive tumors but in none of the 19 borderline tumors[18], and no detectable mutations in the functionally important domains of p73 were observed. Moreover, 71% of the invasive and 92% of the borderline tumors demonstrated overexpression of p73 transcript. Another study showed that only 2 out of 51 ovarian cancers had loss of heterozygosity at the p73 gene locus and there were no differences in allelic expression[19].

Several molecular studies on p73 expression suggested that the levels of p73 mRNA were higher in a variety of cancers than in the corresponding normal tissues[3,5,20]. In addition, epithelial ovarian carcinomas expressed higher levels of p73 mRNA and protein than ovarian adenomas[18]. Concordant with these results, we also found a significantly higher expression of p73 in ovarian carcinomas than in benign ovarian tumors. Other studies have correlated the p73 expression with cancer prognosis. In a study on 92 patients with colorectal carcinomas, a high p73 expression indicated a shorter survival period, and a correlation was found with disease recurrence[21]. Likewise, in 70 breast carcinomas, p73

mRNA overexpression showed significant association with lymph node metastasis, vascular invasion and higher pathologic stage[22]. The expression of p73 in the advanced ovarian cancer was found to be 2～10 times higher than that in the normal ovarian tissue[23]. Additionally, our own study revealed a significant correlation of p73 expression with disease stage and patient's survival. Taken together, the above data support the view that overexpression of p73 may play an important role in advanced ovarian carcinoma.

The c-Abl protein is a ubiquitous cytoplasmic tyrosine kinase that contains three nuclear localization signals and a nuclear export signal[11]. The cytoplasmic c-Abl is regulated by cell adhesion through its interaction with the F-actin in the cytoskeleton[24,25], suggesting that it may have a role in signal transduction pathways that stimulate mitogenesis in normal cells. In contrast, nuclear c-Abl appears to be cell cycle-regulated and it has been implicated in the regulation of gene transcription[11].

In our study, c-Abl expression was mostly observed in the cytoplasm of cancer cells. In proliferating cells, c-Abl is actively transported between the nucleus and the cytoplasm[26,27], The cytoplasmic chimeric Bcr-Abl tyrosine kinase might activate a number of signalling pathways to promote cell proliferation and to inhibit apoptosis[13,28], while the nuclear Bcr-Abl activated apoptosis[29,30]. The c-Abl might stabilize the p73 and activate its pro-apoptotic function[31－33]. Alternative splicing of p73 led to expression of p73 proteins with or without an N-terminal transactivating (TA) domain[17]. TA-positive p73 proteins upregulated p53-responsive genes and induced apoptosis[2]. TA-negative p73 proteins blocked the expression of p53-responsive genes and inhibited apoptosis[27,34]. TA-negative p73 proteins are expressed in adult neurons and appear to be essential for the survival response to nerve growth factors[34]. Expression of a dominant negative p73 protein inhibited apoptosis induced by the nuclear Bcr-Abl tyrosine kinase[27]. These observations together with the recent finding that p73 could compete with p53 and reduce its potential activity[35], add support to an apoptosis inhibitory role for p73 overexpression. In this respect, the anti-p73 antibody used in our series detected p73 α and β splice variant proteins (both 73 kDs) which may include both TA-negative and TA-positive p73 proteins. However, the significant correlations found between the p73 overexpression and a high disease stage and a poor prognosis may point to a TA-negative p73 protein involvement.

In our study, a significant correlation was found between the expression of p73 and c-Abl in ovarian carcinomas. The majority of carcinomas with high p73 expression, also had high c-Abl expression. Since, both p73 and c-Abl may, under certain conditions, induce or conversely inhibit apoptosis, we also sought to determine the relationship between a combined expression of p73 and c-Abl and the clinicopathological factors, but found no significant correlation.

In conclusion, our study revealed an association between p73 overexpression and advanced ovarian carcinomas which may suggest the p73 overexpression as an indicator of poor prognosis.

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