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CORRELATIONS OF BMI-1 EXPRESSION AND TELOMERASE ACTIVITY IN OVARIAN CANCER TISSUES

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Aim: **To investigate the correlation between oncoprotein Bmi-1 and telomerase activity in ovarian cancer tissues.** ***Methods*****: SP immunohistochemistry was adopted to detect the expression of Bmi-1 protein in tissues of 47 ovarian epithelial cancer cases. Modified telomeric repeat amplification protocol (TRAP, silver staining technique) was used to detect the telomerase activity.** ***Results:*** **While in 80.85% (38/47) of ovarian epithelial cancer cases Bmi-1 protein was overexpressed, 46.81% (22/47) had very strong expression level. Bmi-1 expression levels in ovarian carcinoma tissue differ depending on tissue grade (higher for G3 cancer cases — 93.10% than for grade G2 cases — 61.11%) and the stage of the disease (lower for phase II and phase III cases — 66.67% than for phase IV cases — 92.31%). In ovarian epithelial cancer tissues, 87.23% (41/47) demonstrated positive telomerase activity in contrast to zero activity in normal tissues. Majority (90.24%) of specimens with positive telomerase activity possessed high Bmi-1 expression levels. Spearman correlation analysis indicated that expression of Bmi-1 protein was positively correlated with the elevated telomerase activity.** ***Conclusions:*** **Bmi-1 protein is highly expressed in ovarian epithelial cancer tissues, and its expression level correlates with histological grade and clinical phase of the patients. Elevation of Bmi-1 expression is closely correlated to the increased telomerase activity.**
Key Words: **Bmi-1 expression, telomerase activity, ovarian cancer.**

Bmi-1 was first found in Netherlands Cancer Center in 1991 and it belongs to the polycomb group gene family (PcG) [1]. *Bmi-1* overexpression has been indicated in several malignant diseases such as leukemia [2], lymphoma [3], colon carcinoma, small cell lung cancer and breast cancer [4, 5]. More recently, it has been shown that Bmi-1 is strongly expressed in primary neuroblastomas [6, 7]. Since the identification of telomerase in 1985 by Greider and Blackburn [8], the biological functions of telomerase have been extensively studied. Telomerase activation is directly correlated with cell immortalization and tumorigenesis and more than 85% of malignant tumor tissues were found to have enhanced telomerase expression [9]. Bmi-1 protein has been suggested to be closely related to the telomerase activity [10].

Currently, the expression of Bmi-1 in ovarian cancer tissues has not been reported. In this study, the correlation of Bmi-1 expression, telomerase activity and effects of Bmi-1 on genesis and development of ovarian epithelial cancer were investigated.

MATERIALS AND METHODS

Patient samples. 47 patients' samples were randomly selected from the ovarian epithelial cancer cases admitted into the Department of Gynecology, Affiliated Oncology Hospital of Harbin Medical University from August 2006 to June 2007. All cases were confirmed as ovarian epithelial cancer by pathological examination. Ten cases of normal ovarian tissues were chosen as controls. Within 30 min after specimens were excised, portions of tissue were frozen at –70 °C. The rest were fixed using 10% formalin and embedded in paraffin. Of the 47 cancer cases, the age of the patients ranged from 30 to 72 y/o. Serous papillary adenocarcinoma was diagnosed in 28 cases, while the rest 19 cases had mucoid adenocarcinoma. According to the staging method of International Federation of Gynecology and Obstetrics (FIGO), 9 cases had cancer of phase II, 12 cases phase III and 26 cases phase IV.

Reagents. Mouse anti-human Bmi-1 monoclonal antibody was purchased from Upstate Company (USA). SP immunohistochemistry kit and antibody diluent were obtained from Beijing Zhongshan Company (China). Primers for *Bim-1* were the same as reported by Kim *et al* [4] and they were as following: Forward: 5'-AATCCGTCGAGCAGAGTT-3' and Reverse: 5'-CCCTTACCCTTACCCTTACCCTTAA-3'. Primers were synthesized by Shanghai Bioengineering Company (China).

SP immunohistochemical examination. Serial sections of 4 μm were taken from each paraffin block of the patients and controls. These sections were then dewaxed twice in dimethyl benzene for 10 min each. After dehydratation by ethanol gradient, the endogenous peroxydase was eliminated by 3% H_2O_2, and then tissues were reduced using EDTA (pH 8.0) solution. Then sections went through 5 min of intensive heating, 2 min room temperature (RT) cooling, 20 min medium and low heating to allow antigens to be fully exposed. After natural cooling at RT, solution A from the SP kit (Beijing Zhongshan, China) was added to the sections and incubated for 15 min at RT before the over night incubation with mouse anti-human Bmi-1 antibody at 4 °C. Sections were then flushed with 1×PBST (0.1% Tween in 1 x PBS) three times, 5 min each. After washing, solution B from the SP kit was added to the slides and incubated for 15 min at RT before three-time washing with 1× PBST, 5 min each. Solution C was then added and slides were incubated for 15 min at RT, followed by three-time flushing with 1 × PBST. Later, slides were developed with DAB for 10 min and restained with hematoxylin before

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Abbreviations used: hTERT – human telomerase reverse transcriptase; TRAP – telomeric repeat amplification protocol.

fixed with ethanol hydrochloride. Finally, slides were mounted and observed under a light microscope. Similar treatment without primary antibody was adopted as the negative control.

Modified TRAP-silver staining [11]. For protein isolation, pre-chilled lysis buffer 200 µl (10 mM Tris-HCl, pH7.5, 1 mM $MgCl_2$, 1 mM EGTA, 0.1 mM PMSF, 5 mM β-mercaptoethanol, 0.5% CHAPS, 10% glycerine) was added to 40–80 mg of tissues from each sample. Tissues were homogenized completely in an iced bath and sit on ice for 30 min before centrifugation for 20 min, at 16,000 rpm, 4 °C. Supernatants were transferred to new tubes and the protein concentrations were determined. Protein samples were aliquoted and stored at -70 °C. For the TRAP-PCR reaction, a 25 µl of total reaction was prepared, which included 20 mM Tris-HCl (pH 8.0), 1.5 mM $MgCl_2$, 63 mM KCl, 0.005% Tween-20, 1 mM EGTA, 50 µM dNTP, Forward and Reverse primers 0.1 µg, 1 unit *Taq* polimerase and 0.5–1 µl telomerase extract (5 µg total protein). Amplification conditions were as the following: 25 °C for 30 min, 94 °C for 2 s, followed by 30 cycles of 94 °C for 30 s, 50 °C for 30 s, 72 °C for 90 s and a final elongation step — 10 min at 72 °C. PCR products were separated in 12% native polyacrylamide gel, and silver stained. Cellular extract of cell line 293, which had constant positive telomerase activity, was adopted as positive control, and cell free lysis buffer was used as negative control for the TRAP assay.

Data assessment. Expression levels of Bmi-1 protein were visualized by observing the stained tissues under a light microscope. Positive expression of Bmi-1 was defined as the presence of brown or yellowish brown granules in the nuclei, though occasionally yellowish brown granules could also be seen in the cytoplasm. Four fields were randomly chosen under high power lens (400 ×) and cell numbers with positive Bmi-1 expression was counted and scored according to the percentage of positive cells. When positive cells were less than 10%, it was rated as 1 point; 10% to 50%, 2 points; 50% to 75%, 3 points and > 75%, 4 points. Meanwhile, the staining degree was also scored: negative, 1 point; weak staining, 2 points; medium staining, 3 points; and strong staining, 4 points. The two different scores of corresponding sample were then multiplied. Points equal or less than 4 was marked as (−); 4 points to 8 points was marked as (+); 8 points to 12 points, (++); and 12 points to 16 points, (+++). For statistical analysis, (−) and (+) were counted as negative and weak positive respectively, while (++) and (+++) were counted as strong positive. Results were observed and assessed by at least two pathologic doctors, without knowing the identity of the samples.

Statistical analysis. Statistical analysis was conducted with SPSS 13.0 (SPSS Inc., Chicago, IL, USA). Data were analyzed with χ^2 test and probabilities in four-fold table. Correlation analysis was performed for exact probability and enumeration (Spearman correlation analysis). $P < 0.05$ was set as the significance level.

RESULTS

Expression of Bmi-1 protein in ovarian epithelial cancer tissues. Immunohistochemical examination of the 47 ovarian epithelial cancer specimens revealed that the positive expression rate of Bmi-1 was 80.85% (38/47) and positive expression was mainly concentrated in the nuclei of tumor cells (Fig. 1). Strong positive rate of Bmi-1 expression was 46.81% (22/47).

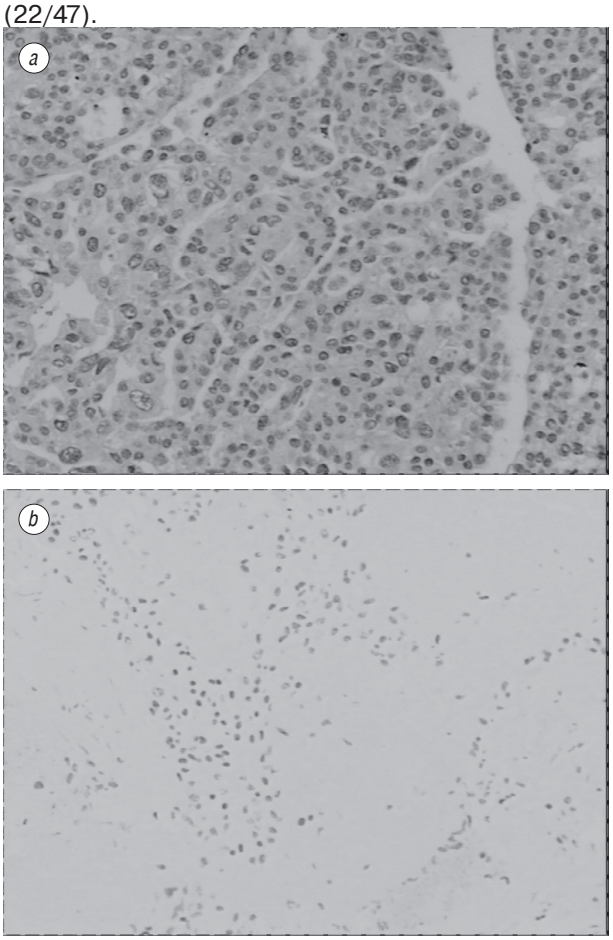

Fig. 1. Expression of Bmi-1 protein in tissues of ovarian epithelial cancer. *a*: A typical histochemical staining of the tissue with positive expression of Bmi-1. The yellowish brown to brown granules in the nuclei represent the location of Bmi-1 protein; *b*: A sample with negative expression of Bmi-1. (400 ×)

As summarized in Table 1, Bmi-1 expression of grade G3 was higher than that of grade G2, and the difference was significant ($\chi^2 = 7.3423$, $\chi^2_{0.01,\,1} = 6.63$, $P < 0.01$). Expression rate for clinical stage phase II and III was 66.67%, 92.31% for phase IV, and the difference was significant ($\chi^2 = 4.46$, $\chi^2_{0.05,\,1} = 3.84$, $P < 0.05$). No significant difference in Bmi-1 expression was found between serous and mucous tissues ($\chi^2 = 0.0747$, $\chi^2_{0.05,\,1} = 3.84$, $P > 0.05$).

Table 1. Expression of Bmi-1 protein in epithelial ovarian cancer of various clinopathological types

Clinicopathological types of tumors	Total	−	+	++	Positive, %	Strong positive, %
Pathological type:						
serous ovarian cancer	28	5	10	13	82.15	46.43
mucinous ovarian cancer	19	4	6	9	78.95	47.37
Histological grades:						
G2	18	7	6	5	61.11	27.78
G3	29	2	10	17	93.10	58.62
Clinical stage:						
II & III	21	7	8	6	66.67	28.57
IV	26	2	8	16	92.31	61.54

Detection of telomerase activity. A representative result of the modified TRAP-silver staining [11] of the specimens was shown on Fig. 2. Table 2 summarized data of telomerase activity in ovarian epithelial cancer and normal ovarian epithelia tissues. The positive rate of telomerase activity was 87.23% (41/47) for ovarian epithelial cancer samples, while no expression was observed in normal ovarian epithelial tissues. No significant differences was observed between serous and mucous tissues ($\chi^2 = 0.1437$), G2 and G3 grades ($\chi^2 = 0.0717$) or phases II–III and IV ($\chi^2 = 0.0787$) specimens ($\chi^2_{0.05,\,1} = 3.84$, $P > 0.05$).

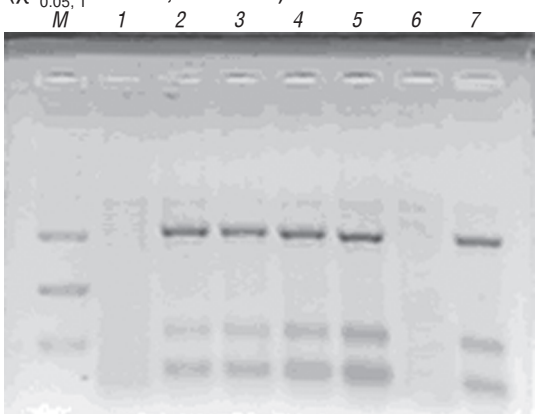

Fig. 2. Telomerase activities in tissues of ovarian epithelial cancer as examined by telomere repeat amplification protocol. Lane M, 293 cell used as positive control; Lane 1, tissue free sample used as negative control; Lanes 2–7, tissue samples from 6 selected cases

Table 2. Telomerase activity in epithelial ovarian cancer of various clinopathological types

Clinicopathological types of tumors	Total	Telomerase activity		
		–	+	Positive, %
pathological type:				
serous ovarian cancer	28	4	24	85.71
mucinous ovarian cancer	19	2	17	89.47
histological grades:				
G2	18	2	16	88.89
G3	29	4	25	86.21
clinical stage:				
II & III	21	3	18	85.71
IV	26	3	23	88.46
Total cases	47	6	41	87.23

Correlation analysis of telomerase activity and Bmi-1 protein expression. Results indicated significant difference in Bmi-1 protein expression levels in tissues of the patients with positive and negative telomerase activity ($\chi^2 = 18.3018$, $\chi^2_{0.01,\,1} = 6.63$, $P < 0.01$) (Table 3). In tissues with positive telomerase activity, the expression rate of Bmi-1 was remarkably high (90.24%, 37/41). In telomerase activity negative specimens, the expression rate of Bmi-1 protein was much lower (16.67%, 1/6). Spearman correlation analysis indicated that Bmi-1 expression and telomerase activity were positively correlated ($P < 0.05$).

Table 3. Correlation of telomerase activity and Bmi-1 expression

	Bmi-1 protein	
	+	–
Telomerase activity (+)	37/41 (90.24%)	4/41 (9.76%)
Telomerase activity (-)	1/6 (16.67%)	5/6 (83.33%)

DISCUSSION

Bmi-1 belongs to the polycomb gene family, which includes RAE28, Bmi-1, EZH2, etc. and controls gene activities during the body growth. Bmi-1 is an extensively expressed neucleoprotein and it can act as a transcription factor providing specific undisturbed inhibition of targeted gene promoters, such as HOX [12]. Bmi-1 expression is associated with the characteristics of both normal and tumor stem cells, maintaining the normal size of stem cell pool [13, 14]. Recently published data testify that an acute small interfering RNA-mediated knockdown of Bmi-1, which resulted in apoptosis in cancer cells but not in normal cells [15]. Cells with overexpressed Bmi-1 have been indicated as the "tumor stem cell" in carcinomas [16].

More and more studies have suggested that *Bmi-1* is a proto-oncogene involved in the genesis of multiple carcinomas, such as B cell lymphoma, carcinomas of nervous system, etc. It has been demonstrated that *Bmi-1* is a target gene for SALL4, and SALL4 is expressed constitutively in human leukemia cell lines and primary acute myeloid leukemia (AML) cells [17]. *Bmi-1* was first proposed as an oncogene in the passage of lymphoma cells in transgenic mice [18], where researchers found a synergistic effect between *Bmi-1* and *c-myc*, and Bmi-1 induced the cellular transformation and tumor formation. Recent data had shown that Bmi-1 was a c-Myc target and its' promoter region contained a functional E-box, by which *c-myc* and *Mel-18* regulate expression of Bmi-1 during cellular senescence in human cells [19]. Bmi-1 was reported to induce the immortalization of breast epithelial cells [20], and was found to be overexpressed in nasopharyngeal carcinoma [21]. Bmi-1 gene alone could successfully induce the immortalization of nasopharyngeal epithelial cells, and its expression correlated with the infiltration range, survival and prognosis of nasopharyngeal carcinoma [21]. This data provides powerful evidences that Bmi-1 is an oncoprotein.

In this study, Bmi-1 was found to be upregulated in serous and mucous ovarian cancers, and the expression rate had nothing to do with pathological types, but related to histological grades and clinical phases. Expression rate of Bmi-1 in poorly differentiated tissues was notably higher than well differentiated tissues, and the expression rate was higher when clinical phase became more advanced. These results suggested that Bmi-1 could play important role in ovarian cancer progression.

In recent years, numerous researches have studied the telomerase expression in ovarian cancers. Telomerase is a nuclear ribonuclear protein that elongates the end of telomere. Once activated, telomerase can overcome the shortening effect of telomere during cell cycling and immortalize cells, which is necessary for malignancy. Telomerase activation is crucial in the genesis and development of tumors [9], and it generally found in ovarian cancers as demonstrated by Datar *et al* [22] and Park *et al* [23].

Results presented in this study indicated close and positive correlation of Bmi-1 expression and telomerase activity. Overexpression of Bmi-1 was clearly seen in tissues with positive telomerase activity. These data were consistent with previous studies [10, 24]. Dimri *et al* [25] observed overexpression of Bmi-1 protein in immortalized breast epithelial cells and breast cancer cells,

where *Bmi-1* oncogene could increase the cell replication time and lead to cell immortalization. Takeda *et al* [24] found that Bmi-1 regulates the human telomerase reverse transcriptase (hTERT) promoter via the c-myc pathway. Peptide deletion analysis of Bmi-1 protein indicated that the ring finger and helix-turn-helix structures were necessary to induce telomerase activation and immortalization of epithelial cells. Overexpression of Bmi-1 in breast epithelial cells was suggested to activate the hTERT transcription and further induce telomerase activation [26]. In another study, overexpression of Bmi-1 was found to prolong multiplication period and block apoptosis of the cells through inhibition of $p16^{INK4a}$ expression [27]. Based upon literature data and our results, we can speculate that Bmi-1 overexpression in tissues with positive telomerase could correlate with the following events: after activation, the oncoprotein Bmi-1 participates in cellular multiplicative division and causes the downregulation of $p16^{INK4a}$, which prolonges the life period of ovarian epithelial cancer cells, promotes the proliferation and decreases apoptosis rate. Meanwhile, Bmi-1 could have activated hTERT transcription and induced telomerase activation, therefore immortalized the relevant cells.

Our results also suggested the positive correlation between the Bmi-1 expression level and the telomerase activity in ovarian epithelial cancer tissues. Bmi-1 is presumed to play important roles in ovarian epithelial cancer progression and regulate telomerase activation. It is likely that blocking of Bmi-1 expression could decrease the telomerase activity, hence providing a new study direction for genetic treatment against ovarian cancer. Therefore, further studies are needed to clarify the mechanisms of Bmi-1 regulation of telomerase activation.

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КОРРЕЛЯЦИЯ ЭКСПРЕССИИ БЕЛКА BMI-1 И АКТИВНОСТИ ТЕЛОМЕРАЗЫ В ТКАНЯХ РАКА ЯИЧНИКА

Цель: **изучить корреляцию между экспрессией протеина Bmi-1 и активностью теломеразы при раке яичника.** ***Методы*****: подобраны оптимальные условия для SP-иммуногистохимии для выявления экспрессии белка Bmi-1 при эпителиальном раке яичника (n = 47). Для определения активности теломеразы был использован усовершенствованый протокол амплификации теломерных повторов (TRAP, методика окрашивания серебром).** ***Результаты:*** **в 80,85% (38/47) случаев рака яичника была выявлена экспрессия белка Bmi-1, в 46,81% (22/47) случаев – на очень высоком уровне. Уровень экспрессии Bmi-1 зависел от степени дифференцировки опухоли (при G3 экспрессия Bmi-1 (93,10%) была выше, чем при G2 (61,11%)) и от стадии заболевания (уровень экпрессии ниже в стадиях II и III (66,67%), чем в стадии IV (92,31%)). В тканях эпителиального рака яичника в 87,23% (41/47) случаев выявлена положительная теломеразная активность, в отличие от нулевой активности в нормальных тканях. В большинстве исследованных случаев рака яичника (90,24%) при положительной активности теломеразы был отмечен высокий уровень экспрессии Bmi-1. Корреляционный анализ Спирмана показал, что экспрессия белка Bmi-1 положительно коррелирует с повышенной теломеразной активностью.** ***Выводы:*** **белок Bmi-1 экспрессирован на высоком уровне злокачественными клетками эпителиального рака яичника, и экспрессия этого белка коррелирует с гистологической градацией и клинической стадией рака. Увеличение экспрессии Bmi-1 коррелировало с повышенной теломеразной активностью.**

Ключевые слова: **экспрессия Bmi-1, теломеразная активность, рак яичника.**

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