The potential mechanism of chemosensitive difference between 2 types of ovarian cancer

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ABSTRACT

Objective: To study the potential molecular mechanism of chemosensitive difference between human malignant epithelial and germ cell tumor of the ovary by testing the expression of *p53* (mutation), Bcl-2, topoisomerase II alpha (Topo II alpha).

Methods: Immunohistochemical analysis was performed on paraffin embedded tumor tissue microarray from malignant epithelial (n=53) and germ cell tumor of the ovary (n=25) in the Department of Gynecology and Obstetrics, Second West China Hospital of Sichuan University, China from the year 2000 to 2004. The expression of *p53*, Bcl-2 and Topo II alpha in the 2 types of ovarian cancer was compared and data were analyzed by student t test, Wilcoxon rank sum test and Spearman rank correlation test.

Results: The expression of *p53* (mutation) in ovarian epithelial cancers (56.6%) was significantly higher than that in the malignant germ cell tumors of the ovary (28%), whereas the expression of Bcl-2 and Topo II alpha had no significant difference between the 2 groups. The expression of *p53*, Bcl-2 and Topo II alpha had no relationship with the Federation Internationale de Gynecologie Obstetrique (FIGO) stage. The age, FIGO stage and the chemotherapy response were significantly different between the 2 groups.

Conclusion: The expression of *p53* in ovarian cancer was related to chemosensitivity. Our results suggest that p53 may have a role on the difference of chemosensitivity between human malignant epithelial and germ cell tumor of the ovary.

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Ovarian cancer is one of the 3 major gynecological malignancies. Although improvement has been made in the chemotherapy to the epithelial ovarian cancer since the appearance of Taxol, the 5-year survival rate is still approximately 30-40% for advanced epithelial ovarian cancer.[1] However, the 5-year survival rate of malignant germ cell tumor of the ovary is approximately 95-100% with the use of bleomycin, etoposide and cisplatin (BEP) and bleomycin vincristine and DDP (BVP) regimens. Some advanced malignant germ cell tumor patient had a good prognosis after the chemotherapy even though the surgical treatment was a conservative one for maintaining their reproductive ability. Some clinical experiences and many chemotherapeutic researches showed that the chemosensitivity of the 2 types of ovarian cancer are different. Why there are so many chemosensitive differences between the 2 types of ovarian cancer that appeared from the same organ. Why is it that the potential mechanism behind this phenomenon is unknown? Many factors are associated with different chemosensitivity. According to tumor cell proliferation kinetics, the chemosensitivity of the tumor is related to the size of the tumor,[2] the growth fraction (GF),[3] the doubling time of tumor cell (Tc)[4] and the doubling time (DT).[5] As the progress of modern molecular biology, the chemosensitivity of the tumor is also related to the oncogene, anti-oncogene, apoptosis-related gene, drug resistance gene and so on. It is confirmed that *p53* has a role in the chemosensitivity of tumor; its mutation and deletion will lead to the decrease of the chemosensitivity.[6] Some researches also inferred that Bcl-2 and topoisomerase II alpha (Topo II alpha) are related to the chemosensitivity of tumor, the up regulation of Bcl-2 will lead to the decrease of chemosensitivity and the up regulation of Topo II alpha will lead to the increase of chemosensitivity of tumor.[7,8] The aim of the present study is to compare the different expression of *p53* (mutation), Bcl-2 and Topo II alpha between malignant epithelial and germ cell tumor of the ovary and to study the potential molecular mechanism of the difference of

chemosensitivity between the malignant epithelial and germ cell tumor of the ovary by tissue microarray and immunohistochemical staining.

Methods. Archival materials from 53 patients with ovarian epithelial cancer (OEC) and 25 patients with malignant germ cell tumor of the ovary (MGCTO) were studied and their characteristics were shown in **Table 1**. All patients received surgery prior to the chemotherapy. Formalin-fixed, paraffin-embedded tissue samples of primary OEC and MGCTO were collected from the Department of Pathology of the West China Second Hospital of Sichuan University in China from the year 2000 to 2004. An independent pathologist revised the histopathology, and the diagnosis was confirmed in all cases. Hematoxylin and eosin (H&E) stained standard slides from the formalin-fixed, paraffin-embedded tumor tissue blocks were reviewed by a pathologist. Representative tumor regions were marked in the tumor tissue blocks according to the review of the H&E stained slides. One to two cylindrical core tissue samples (diameter 1.5 mm, height 8 mm) of the OEC and 3 cylindrical core tissue samples of the MGCTO were taken from marked region of tumor tissue blocks (donor blocks) with a needle (inside diameter 1.5 mm). The tissue cores were precisely arrayed into holes of a new recipient paraffin block that was drilled into holes every 2 mm distance with the same needle before the recipient paraffin block was fixed completely. Two tissue microarray blocks containing representative tumor regions were constructed manually. After block construction was completed, 5 μm sections were prepared for the next H&E staining and immunohistochemistry.

Sections (5 μm) of tissue microarray blocks were deparaffinized in xylenes and rehydrated in serials dilutions of ethanol. Endogenous peroxidase activity was blocked by incubation in 3% H_2O_2 for 10 minutes at room temperature. Antigenic sites were revealed after the tissue microarray sections were heated in a microwave processor at 97^0C twice for 5 minutes in citrate buffer solution. The primary monoclonal mouse anti-human mutated p53 (diluted 1:50, Boster Biological Technology Ltd, Wuhan China), Bcl-2 (diluted 1:100, Zhongshan Golden Bridge Biotechnology Co, Ltd. Peking China) and Topo II alpha antibodies (diluted 1:100, Zhongshan Golden Bridge Biotechnology Co, Ltd. Peking, China) were applied for 2 hours at 37°C after the sections have been incubated with rabbit non-immune serum for 10 minutes at room temperature. The sections were then incubated with avidin-biotin peroxidase complex for 30 minutes at 37°C after been incubated with the secondary biotinylated rabbit anti-mouse antibody (diluted 1:200) for 40 minutes at 37°C. 3,3`-diaminobenzidine (DAB) was used as the chromogenic substrate then counterstained with hematoxylin. The sections were dehydrated with serials dilutions of ethanol and mounted under a covership. Ovarian cancer for p53 (mutation), tonsil for Bcl-2 and breast carcinoma for Topo II alpha were used as positive control. Negative controls were processed with phosphate buffered saline (PBS) instead of the primary antibody.

Two experienced gynecological tumor pathologists evaluated all slides for immunostaining without any knowledge of the clinicopathological data. Nuclear stained brown cells for p53 (mutation), Topo II alpha and membrane stained brown cells for Bcl-2 were evaluated immunoreactivity. When >10% tumor cells for p53 (mutation) and 5% tumor cells for Bcl-2 and any one tumor cell for Topo II alpha showed immunoreactivity, the result was interpreted as positive. The positive result was interpreted as 1 + (weak), 2 + (medium), 3 + (strong) when 10-25%, 25-75%, >75% of the tumor cells were positive for p53 (mutation); when 5-25%, 25-50%, >50% of the tumor cells were positive for Bcl-2 and when <25%, 25-50%, >50% of the tumor cells were positive for Topo II alpha. All cases were divided into OEC group and MGCTO group. The difference of age between the 2 groups was analyzed by student t test. Wilconxon rank sum test was used to analyze the difference of Federation Internationale de Gynecologie Obstetrique (FIGO) stage, chemotherapy response, p53, Bcl-2 and Topo II alpha expression between the 2 groups. Spearman rank correlation test was used to analyze the relationship between the p53, Bcl-2, Topo

Table1 - Patients' characteristics by group.

Characteristics	OEC	MGCTO	*P* value
Age (year)			0.000
Range	18 - 71	9 - 54	
Mean	50.04 ± 1.57	24.72 ± 2.39	
FIGO stage			0.000
I	9	18	
II	7	1	
III	36	6	
IV	1	0	
Chemothery response			0.013
Complete response	35	23	
Partial response	12	2	
Stable disease	4	0	
Progressive disease	2	0	

OEC - ovarian epithelial cancer, MGCTO - malignant germ cell tumor of the ovary, FIGO - Federation Internationale de Gynecologie Obstetrique

II alpha expression and the FIGO stage in the 2 groups. For all statistical tests, we used the Statistical Package for Social Sciences Version 11.5 software (SPSS Inc, Chicago, USA) and the difference was considered as significant at $p<0.05$.

Results. The histological type of the OEC included serous (n=40), mucinous (n=5), endometrioid (n=3) and others (n=5) while that of the MGCTO included immature teratoma (n=13), dysgerminoma (n=4), endodermal sinus tumor (n=6), and mixed malignant (n=2). The 53 OEC patients had 6-8 cycles of DDP-based chemotherapy after operation using PC (DDP and Cytoxan) or TP (DDP and Taxol) regimens. The 25 MGCTO patients had 6 cycles of chemotherapy using BEP (Bleomycin, Etoposide, DDP) or BVP (Bleomycin, Vincristine, DDP) regimens after operation. The age, FIGO stage and the chemotherapy response of the 2 groups were summarized in **Table 1**. The difference of age ($p=0.000$; $p<0.05$), FIGO stage ($p=0.000$; $p<0.05$) and chemotherapy response ($p=0.013$; $p<0.05$) between the 2 groups were statistically significant (**Table 1**). In the OEC and MGCTO groups, the FIGO stage had no statistically relationship with the expression of *p53*

Table 2 - The relationship between Federation Internationale de Gynecologie Obstetrique (FIGO) stage and the expression of p53, Bcl-2 and topoisomerase II alpha (Topo II alpha) in the 2 types of ovarian cancer.

Sub-heading	No. of OEC					No. of OMCTO					r_s	P value
	Negative	+	++	+++	Total	Negative	+	++	+++	Total		
P53												
I	6	1	2	0	**9**	13	4	1	0	18		
II	3	1	2	1	**7**	1	0	0	0	1		
III	14	9	3	10	**36**	5	1	0	0	6		
IV	0	1	0	0	**1**	0	0	0	0	0	0.193*, 0.141†	0.167*, 0.503†
Bcl-2												
I	8	0	1	0	**9**	13	3	2	0	18		
II	7	0	0	0	**7**	1	0	0	0	1		
III	24	12	0	0	**36**	3	2	1	0	6		
IV	1	0	0	0	**1**	0	0	0	0	0	0.217*, 0.156†	0.118*, 0.456†
Topo II alpha												
I	5	4	0	0	**9**	11	4	3	0	18		
II	3	4	0	0	**7**	0	1	0	0	1		
III	19	12	5	0	**36**	3	2	1	0	6		
IV	0	1	0	0	**1**	0	0	0	0	0	0.078*, 0.109†	0.579*, 0.603†

*Number of the ovarian epithelial cancer (OEC) group. In the OEC group, the FIGO stage had no significant relationship with the expression of *p53* ($p=0.167$), Bcl-2 ($p=0.118$), Topo II alpha ($p=0.579$). †Number of the malignant germ cell tumor of the ovary (OMCTO) group. In the OMCTO group, the FIGO stage had no significant relationship with the expression of *p53* ($p=0.503$), Bcl-2 ($p=0.456$), Topo II alpha ($p=0.603$).

Table 3 - The expression of *P53* (mutation), Bcl-2, topoisomerase II alpha (Topo II alpha) in the 2 types of ovarian cancer.

Sub-heading	Negative	+	++	+++	Total	Positive rate %	*P* value
P53							
Ovarian epithelial cancer	23	12	7	11	**53**	56.6	
Malignant germ cell tumor of the ovary	18	6	1	0	**25**	28	0.006
Bcl-2							
Ovarian epithelial cancer	40	9	4	0	**53**	24.5	
Malignant germ cell tumor of the ovary	17	5	3	0	**25**	32	0.267
Topo II alpha							
Ovarian epithelial cancer	27	21	5	0	**53**	49.1	
Malignant germ cell tumor of the ovary	14	7	4	0	**25**	44	1.000

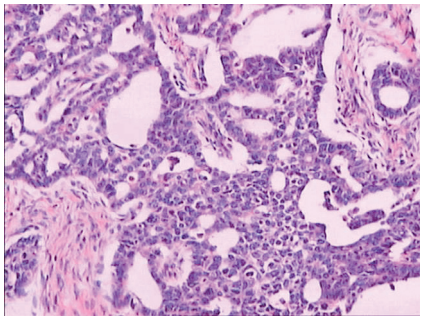

Figure 1 - The tissue microarray sample shows hematoxylin and eosin staining. The representative grade 2 papillary cystadenocarcinoma area (x200).

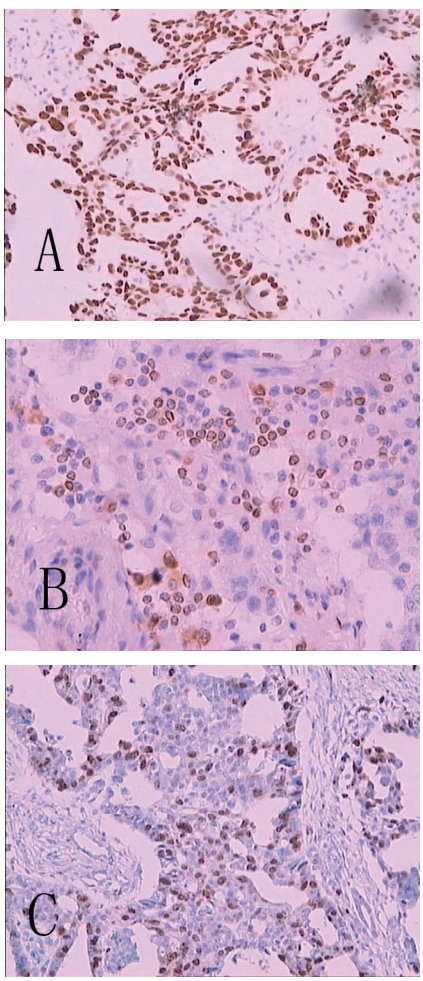

Figure 2 - Ovarain carcinoma showing immuno-histochemical staining of p53, Bcl-2 and topoisomerase II alpha (Topo II alpha). **a)** Serous papillary adenocarcinoma shows nuclear staining for p53 (x200). **b)** Immature terotoma shows membrane staining for Bcl-2(x200). **c)** Grade 2 serous papillary cystadeno carcinoma shows nuclear staining for Topo II alpha (x200).

(p=0.167, p=0.503), Bcl-2 (p=0.118, p=0.456), and Topo II alpha (p=0.579, p=0.603) when analyzed by Spearman rank correlation test (**Table 2**). The tissue microarray contained representative cancer area (**Figure 1**). The nuclear stained brown cells in the immunohistochemistry were *p53* positive cells and Topo II alpha positive cells. The membrane stained brown cells in the immunohistochemistry were Bcl-2 positive cells (**Figure 2**). The expression of *p53* is significantly higher in the OEC (positive rate 56.6%) than that in the OMCTO group (positive rate 28%, p=0.006; p<0.05), while the expression of Bcl-2 and Topo II alpha had no significant difference (p=0.267, p=1.000) between the 2 groups when analyzed by Wilconxon rank sum test. (**Table 3**).

Discussion. The chemosensitivity of malignant tumor is different between different histologic tumors and could be changed after chemotherapy.[9,10] Our result showed that the chemotherapy response of OEC was different to that of MGCTO. According to the classical tumor cell proliferation kinetics theory, many factors were related to the chemosensitivity of malignant tumor; DT was one of the most important factors because it was the colligation affects other factors.[11] It is very difficult to test the DT precisely, it could be estimated by 2 ways: one is by analysis of the distribution of the finding time of the tumor (majority is the diagnosis time), the other is by analysis of the distribution of the recurrent time of the tumor.[2] The earlier the tumor was found and the shorter the recurrent time was, the shorter the DT was. The shorter the DT was, the more sensitive the chemosensitivity of the tumor was. Our study found that the age of OEC group was older than that in the MGCTO group. Some researches showed that the recurrent time of OEC is longer than OGCC.[1,12] It could be deduced that the DT of the OEC is shorter than MGCTO. These maybe partly explain why the OEC is more sensitive to chemotherapy than MGCTO in the cell level. But, the molecular mechanism had not been clarified. If we could find the potential molecular mechanism, maybe it could lead us a way to improve the chemotherapy effect of OEC. The anti-tumor mechanism of chemotherapy drugs included the direct killing effect and the inducing apoptosis of tumor cells.[13] There are some associations between the tumor chemosensitivity and some genes proteins that are involved in the growth, apoptosis and drug resistance of tumor.[14-19] *P53* gene is one of the most extensively studied gene. *P53* gene is an anti-oncogene and *p53* protein is a regulatory protein to the cell cycle and could suppress the growth of cell. Wild *p53* could monitor the integrity of the cell genome, when the DNA was damaged, the activity of *p53* is enhanced and stop the

growth of cell in the G0/G1 phase and suppress the growth of cell to the S phase. The cell repairs the DNA in the period and once the repair is failed, *p53* will lead the cell to death through apoptosis.[20] Some experiments had found that *p53* gene of the chemosensitive tumor cell is usually not mutated or deleted and it is easy for the drugs to induce apoptosis, while the *p53* gene of the non-chemosensitive tumor cell is usually mutated or deleted and the effect of chemotherapy is poor.[21,22] The half-life of normal wild type phenotype *p53* protein is 6-20 minutes while that of mutant p53 was from 1.4-7 hours; thus, the testing of the wild-type *p53* might acquired false negative result because of the degradation of the wild-type *p53*. The testing of mutation *p53* could reduce the false negative results. Our study found that the expression of *p53* (mutation) in the OEC was significantly higher than that in the MGCTO groups. Our *p53* positive rate is similar with the previous studies.[23,24] If *p53* gene is mutated or deleted, *p53* protein could not suppress the growth of tumor cell and this would increase the tumor burden of chemotherapy; at the same time, tumor cell could not lead to apoptosis in response to DNA damage induced by chemotherapy drugs, then the tumor cells would continue to cleavage and proliferate and the chemosensitivity of the tumor would decrease. The different expression of *p53* has an important molecular mechanism of chemosensitive difference between the 2 types of ovarian cancer. Because the FIGO stage of the 2 groups was significantly different in our study, we should exclude the influence of the FIGO stage on the expression of *p53*, Bcl-2 and Topo II alpha in the 2 groups. Our finding suggest that the FIGO stage had no statistical relationship with the expression of *p53*, Bcl-2 and Topo II alpha in the OEC and MGCTO. This could indicate that the different expression of *p53* between the 2 groups was not caused by the different FIGO stage of the 2 groups. Bcl-2 gene was the chief gene family, which regulates the apoptosis of cell. Bcl-2 protein was against the inducing-apoptosis factors including the effect of chemotherapy drugs; radioactive ray; *p53* protein and so on.[20] Topoisomerase II alpha is a vital nuclear DNA-binding enzyme that controls and modifies the topologic states of DNA by combining nuclease, helicase and ligase activity,[9] and it is a specific target of several chemotherapeutic agents. Some researches showed that the up-regulation of Bcl-2 will lead to the decrease of chemosensitivity and the up-regulation of Topo II alpha will lead to the increase of chemosensitivity of tumor.[7,8,25,26] In the present study, we found that the expression of Bcl-2 and Topo II alpha had no significant differences between the OEC and MGCTO. Some researches suggest that there was some relationship between the chemosensitive difference and the Bcl-2 gene family except for Bcl-2 alone,[27] and some Topo II alpha-targeting drugs, for example Etoposide had been both effective to OEC and MGCTO, thus, more researches should be carried out to testify whether Bcl-2 and Topo II alpha had no relationship to the chemosensitive difference of the 2 types of ovarian cancer.

In conclusion, data indicated that the DT of the MGCTO group is shorter than that in the OEC group, which could partly explain the reason of the chemosensitive difference between the 2 types of ovarian cancer in the cell level. Our study found the different expression level of *p53* in the 2 types of cancer, which well explained the reason of chemosensitive difference in the molecular level. This result could help us to draw an individual chemotherapy plan to the OEC by *p53* testing or other chemosensitive indicators, and maybe the result could illuminate us to invent new chemotherapeutic agent, which could elevate the chemotherapy effect of OEC by other apoptosis-inducing pathway rather than p53.

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