

Study on Osteopontin and Its Clinical Application to Ovarian Cancer

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Abstract. Osteopontin (OPN) is a kind of phosphorylated acidic glycoprotein, human beings' osteoclasts, macrophages, T cells, and vascular smooth muscle cells can secrete OPN, the gene is located on chromosome 4q13. OPN has a function of adhesion to protein, which can be combined with CD₄₄, integrin $\alpha_v\beta_3$ and $\alpha_v\beta_5$, OPN is also involved in bone remodeling, the formation of new blood vessel and the reflection of inflammation. OPN can play the synergistic function in tumor metastasis. In this paper, it takes the introduction of biological function of OPN. As for the aspect of early diagnosis of ovarian cancer and prognosis monitoring, it can be used as the supplement of CA₁₂₅ and markers of other cytokines.

Introduction

The mortality rate of ovarian cancer can rank the first place among gynecologic tumors, and the incidence rate has been rising in recent years, the overall five-year survival rate is about 30%. Different patients in different period can have great difference in prognosis. The cause of being dead for patients with ovarian cancer is not limited to the primary tumor itself, which is often caused by the reason of the distant metastasis and recurrence. About three fourths of patients had been in stage III-IV, which mainly dues to the lack of effective method for the detection of tumor metastasis. Therefore, through the effective diagnostic index to detect those patients at high risk of distant metastasis and recurrence, so as to have effective treatment on these patients, which can significantly improve the survival rate and survival time, improve the quality of life for patients with ovarian cancer and reduce the mortality, at the same time. In recent years, many studies have showed that expression of osteopontin and its ligands can be expressed in a variety of tumors, osteopontin (OPN) can transduct the pathway to promote cell survival through the activation of CD₄₄V₆ mediated signal, which also can improve the ability of chemotaxis, homing, adhesion, as well as the invasiveness ability of tumors.

The Biological Function of OPN

OPN is a kind of phosphorylated acidic glycoprotein, containing Arg-Gly-ASP (shorted for RGD structure) residues, its relative molecular mass is about 325000. human beings' osteoclasts, macrophages, T cells, and vascular smooth muscle cells can secrete OPN. While the gene of OPN is located on chromosome 4q13, which consists of seven exons and six introns. At the same time, its molecular structure is composed of signal peptide sequence, seven to ten consecutive sequences of ASP, RGD domains, $\alpha_9\beta_1/\alpha_4\beta_1$ domains and heparin combined domains. Molecular central region can be divided into two functional areas by a variety of thrombin protease, after the terminal of N through phosphorylation, it can be combined with the integrin receptor binding, especially having strong specificity to the energies of integrin $\alpha_v\beta_3$ and $\alpha_v\beta_5$; the terminal of C and adhesion molecule CD₄₄ can be combined with the splice variant V₆, the 170 and 300. The amino acid residues of the two heparin binding sites, namely, site 170 and site 300 can form a connecting bridge with the variant of CD₄₄v₃. In addition, in the RGD fragment and CD₄₄ binding site, there is a recognition site, containing integrin β_1 . During the period of appearing tumor, the functional area of N terminal can have relation with the spread of tumors. The functional area of C terminal can be related to the immune escape; RGD structure can play an important role for the adhesion function of OPN.

OPN and Diagnosis of Ovarian Cancer

From April 2013 to March 2014, taking the thirty two cases of gynaecology surgery resection epithelial ovarian cancer specimens as experimental group from a Medical University Department. At the same time, selecting twenty cases of benign epithelial ovarian tumors (median age 43.4 ± 0.81 years old) and eight cases of normal ovarian tissue (median age of 52.8 ± 0.3 years old) as the control group, all the patients did not accept any radiotherapy and chemical therapy. In the experimental group, the age of patients can be ranged from 18 to 76 years old, and median age was 53.7 ± 0.56 years old. After operation, the standards of the International Federation of gynecology and Obstetrics (FIGO 2000) can be used to classify staging, including four cases of stage I; twelve patients in stage II; ten cases of stage III; six cases in stage IV; histological grade can be as follows: thirteen cases are in G_1 grade; ten cases are in G_2 grade, nine cases are in grade G_3 ; as for the aspect of lymph node metastasis: eight cases are positive and twenty four cases are negative. After having operation on resection of the primary lesion, it should immediately cut fresh ovarian tumor tissue as specimen, after washing with physiological saline, it should be stored immediately in liquid nitrogen at -196°C .

This experiment adopts the reverse transcriptase polymerase chain reaction (RT-PCR) as the method, with the gel imaging analysis system, on gel doc 2000 analyzer, using BIOS consort 30 analysis software to compare the gene amplification bands with β -actin bands (the comparison ratio value is A), so as to compare the changes of A.

Statistical Method. The experimental data are measurement data, adopting t inspection and χ^2 inspection. Using the statistical software SPSS 12.0 to have data processing, there is significant difference when $P < 0.05$, instead, when $P > 0.05$, there is no significant difference between the two groups.

The Positive Expression Rate of OPN and CD44v6 in Different Ovarian Tissues

Among thirty two cases of ovarian cancer specimens, there are thirty two cases that can be amplified bands of OPN, while thirty one cases can be amplified bands of CD44v6. Among twenty cases of benign tumor specimens, there are nine cases can be amplified target gene; among eight cases of normal ovarian specimens, there are three cases can be amplified bands of OPN and two cases can be amplified bands of CD44v6. The expression rate of OPN and CD44v6 in ovarian epithelial cancer is 100% and 96.9% respectively, which is significantly higher than that in normal ovarian tissue (OPN is 37.5%, CD44v6 is 0%) as well as in benign epithelial ovarian tumor tissue (OPN is 55%, CD44v6 is 45%), therefore the difference has statistically significance ($P < 0.05$).

The Relationship between OPN and CD44v6 in Ovarian Cancer

By means of bivariate correlation analysis, it showed that ovarian cancer in the expression of OPN and expression of CD44v6 can be positively correlated ($r = 0.35$, $P < 0.01$), which can be shown in Table 1, indicating that the expression of OPN and expression of CD44v6 can be related in ovarian cancer, the co-expression of them can have more significant meaning for predicting metastasis of ovarian cancer.

Table 1 The Correlation between Expression of OPN and CD₄₄v₆ in Ovarian Cancer Tissues

The expression of CD ₄₄ v ₆	The expression of OPN		Total	Value of χ^2	P	r
	Negative	Positive				
Negative	2	2	4			
Positive	3	25	28	6.875	0.009	0.35
Total	5	27	32			

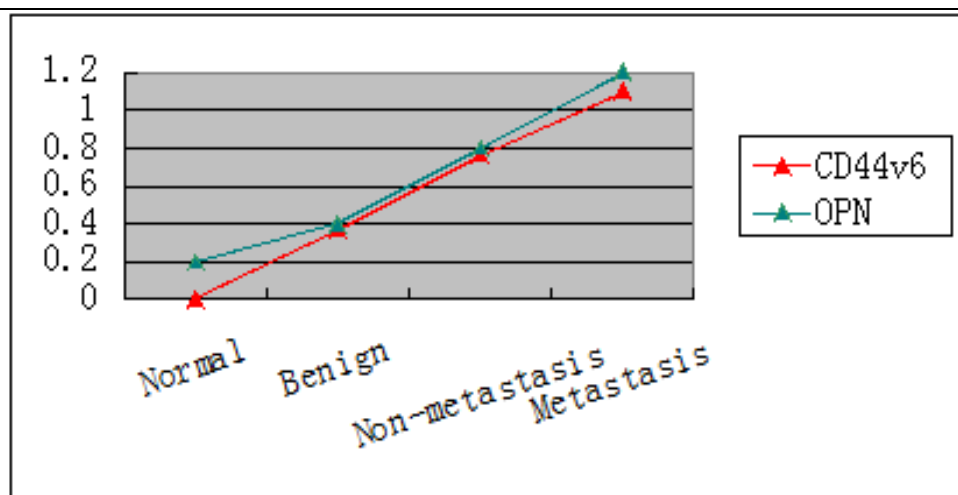
Note: $r=0.35$, positive correlation, $P<0.01$

The Relationship between Clinic opathological Features and Expression of OPN and CD44v6 of Ovarian Cancer

Among epithelial ovarian cancers, in different clinical stages between OPN and CD₄₄v₆, there is different content of mRNA, for example, cases in late stage (III-IV) are significantly higher than that of early cases (I and II), there is significant difference ($P < 0.05$), and the content of mRNA of OPN and CD₄₄v₆ is related to the differentiation degree of the organization. The relative content in low differentiation group is significantly higher than that in high differentiation group, there is significant difference ($P < 0.05$); the comparison between lymph node metastasis group and non-metastasis group, which also has significant difference ($P < 0.01$); but the content of OPN and CD₄₄v₆ has no significant difference with the patient's age, as well as the pathological type of tumors ($P > 0.05$).

Table 2 The Expression of OPN and CD₄₄v₆ in Different Ovarian Tissues

	Normal	Benign	Malignant	
			Non-metastasis	Metastasis
OPN	0.15±0.02	0.33±0.01	0.73±0.22	1.13±0.16
CD ₄₄ v ₆	0	0.30±0.04	0.69±0.13	1.07±0.06

Fig. 1 The Content of CD₄₄v₆, mRNA, OPN in Different Ovarian Tissues

Conclusion

At present, the clinical principle on the diagnosis and treatment of malignant tumor is: striking for early detection, as early as possible to have surgical resection, aided with radiotherapy chemotherapy and supportive treatment, so as to take the improvement of life quality of the patients as the primary purpose. OPN as an important participant in the the mechanism of tumor metastasis, its peripheral blood concentration and receptor can be regarded as the cancer screening indicator for the non-destructive injury. As for the aspect of treatment, it explored the mechanism between osteopontin and CD₄₄v₆, having intervention from gene starting to signal transduction pathway, which can effectively reduce the malignant degree of tumor, so as to prolong the survival time of patients and improve the quality of life.

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