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Application of Molecular Diagnosis in Ovarian Cancer Diagnosis

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Abstract

Among all diseases of malignant tumors in female genitalia, the ovarian cancer is the disease with highest death rate. However, the early clinical symptoms of this disease are latent, which results in the lack of effective early diagnosis method. Therefore, many patients with this disease have been in the later period clinically at the time of definite diagnosis. According to the statistics, the survival rate of patients with ovarian cancer in the later period within 5 years is only 30%, while the survival rate of patients with ovarian cancer in the early period within 5 years can be 70% -90%. Therefore, the early diagnosis plays an important role in improving the prognosis of ovarian cancer. In recent years, with its high specificity and high sensitivity, the molecular diagnosis technology is widely used to monitor the content of tumor markers in ovarian cancer tissue and also used in screening the high risk group to improve the prognosis of patients with ovarian cancer. The adoption of several methods in the molecular diagnosis technology usually used to monitor tumor markers in ovarian cancer diagnosis is discussed about in this paper.

Keywords

Ovarian cancer; Molecular diagnosis; Proteomics; Antibody Microarray

1. Introduction

Among all female reproductive system malignant tumors, the ovarian cancer has the highest death rate, and it is also one of the most common causes of death among women with cancer. The early diagnosis is very important to the prognosis of ovarian cancer. The common ovarian cancer diagnosis methods at present include conventional gynecological examination, tumor marker detection, medical image examination, cytological and histological detection, etc. However, in conventional gynecological examination, only the physician with very rich clinical experience can guarantee to discover the palpable abnormity in pelvic cavity. The medical image diagnosis includes ultrasonic testing, CT, MRI, etc., as well as the ultrasonic testing method through vagina developed in recent years, all of which can only show whether there is any abnormity in the shape of ovary from its appearance, but other methods are still needed for further confirmation. In addition, the cytological detection and tissue immunological detection usually involve puncture sampling. It may cause certain trauma, so it is usually used as an approach to further definite diagnosis and seldom used in conventional screening [1]. In recent years, the molecular diagnosis technology has been widely used in the clinical diagnosis, disease monitoring and curative effect observation of ovarian cancer. The molecular diagnosis refers to detecting the structure of genetic material and change in expression level in the body of patient by the molecular biological method through levels of DNA, RNA and protein to monitor disease changes. The detection of tumor markers is the main method used in molecular diagnosis for screening cancer.

The tumor markers commonly used for screening ovarian cancer include human epididymis protein 4 (HE4), CA72-4, soluble mesothelin related proteins (SMRP), osteopontin (OPN), human kallikrein (Hk), etc.[1] It is reported that, the methods used to detect the protein with abnormal expression in ovarian cancer tissue usually include the two kinds as below, antibody microarray technology and SELDI-TOF-MS technology.

2. Application of antibody microarray technology in ovarian cancer diagnosis

The antibody microarray is also called as immunochip, which can simultaneously detect and make a comparison of all different pathogenic factors and different protein expression levels in biological samples. In addition, it can also be used to research phosphorylation level change or even protein interaction and so on. However, the antibody microarray is mostly used in the research field of quantitative determination of protein. The antibody microarray not only retain the speediness, sensitivity and specificity of antigen-antibody response, meanwhile, the rapid, sensitive and specific monitoring method promoted by the chip technology can be also used in many samples [2].

In ovarian cancer tissue, the abnormal protein portion is attached to the surface of cytomembrane, and will be released to the extracellular fluid partly. The abnormal protein can be detected in ovary tumor tissue, ascites, cell line and blood. Zhang H et al. [3] detected 82 cases of patients with benign lesion in ovary, 51 cases of patients with ovarian cancer and the serum of 100 healthy people by use of the test method with protein microarray, and the result showed that, the positive rate in patients with ovarian cancer is 86. 2%, higher than that in the other two groups remarkably. Michael [4] et al. used the antibody microarray including 5,005 kinds of antibodies to detect the serum of patients with ovarian cancer in all stages, and found by comparison with that in the control group with health people that, the

liveness of four kinds of antigen, SSRP1, LaminA /C, ZNF265, RALBP1 in the serum of patients strengthened remarkably [5, 6].

The antibody microarray technology remarkably improves the specificity and sensitivity in ovarian cancer detection. However, during the process of application, it still lacks enough diagnosis sensibility for the detection of a single tumor marker, so its clinical application value is limited to some degree. Nevertheless, compared with the conventional immunoassay methods in tumor marker, it is still more practical in the detection of tumor series of markers.

3. The application of SELDI-TOF-MS in ovarian cancer diagnosis

Born in 2000, the SELDI-TOF-MS technology offers a powerful tool to the research on tumor proteomics. SELDI-TOF-MS consists of three parts, protein microarray, flight time mass spectrum system and analysis software. The core of this technology lies in its unique protein microarray. It includes two kinds of chips in biological surface and chemical surface, so it can catch the protein of more kinds. The best advantage of this technology is to analyze the raw materials of biological samples directly without any elaborate separation or sample treatment. And the mass spectrum can directly show the information such as various molecular weights and richness degrees of protein in the sample [5].

At present, it is found that, most biological markers obtained by SELDI protein fingerprint technology are the protein fragments with low molecular mass generated in specific tumor microenvironment. It is indicated by detecting various tumors that, their sensibility and specificity are superior to conventional tumor markers. The sensibility of some tumors has been reached to 100％, and the specificity has also been over 95％, so they have important clinical application value in early diagnosis and early warning of tumors. As reported by Petricoin and so on, the peptides with low molecular mass of ovarian cancer with specificity were found by SELDI-TOF-MS technology, with 100％ of sensitivity, 95％ of specificity and 94％ of positive predictive value, and they were important to ovarian cancer diagnosis. Also as indicated in recent research, the SELDI-TOF-MS technology has high sensibility and specificity in ovarian cancer detection [5, 6, 7].

SELDI-TOF-MS technology is still in the early development stage at present. Its own limitations include the bad stability and repeatability of operating platform and other problems, so it shall be still further solved to comprehensively increase the application value of this technology in the field of ovarian cancer diagnosis. However, it is worth mentioning that, SELDI-TOF-MS offers a new technology platform and wider research thought to the aspects such as the early diagnosis and curative effect monitoring or adjuvant therapy of ovarian cancer. It has huge potentials and a very good application prospect in ovarian cancer and other tumor research fields [7].

4. Other molecular diagnosis methods commonly used to monitor the ovarian cancer

In addition to the above-mentioned two methods to monitor the tumor markers in ovarian cancer tissue, other common methods also include luminescence immunoassay, immunosensor and other measuring methods. Compared with the above methods, the sensitivity of these methods in monitoring is poor obviously. In addition, miRNA can be taken as a new type of biological marker in peripheral blood of ovarian cancer, and the detection of it will help to screening the patients with ovarian cancer without

obvious clinical symptoms in the early stage. However, the technology for screening the ovarian cancer by monitoring miRNA is just in the beginning, the relationship between miRNA and the generation, development and prognosis of ovarian cancer and its function in ovarian cancer diagnosis and treatment still need further exploration and research [8,9].

5. Conclusion

The future research on ovarian cancer diagnosis shall still place emphasis on looking for the tumor markers with high specificity and high sensitivity[10]. And the reasonable selection of multi- tumor marker combined detection method can not only remedy the disadvantage in single tumor marker detection, but also improve the accuracy and sensibility in tumor diagnosis effectively, and can thus carry out screening in high risk group and better improve the prognosis of patients with ovarian cancer. With the rapid development of molecular biology technology, molecular diagnosis technology will pave a wider way for ovarian cancer diagnosis. And validation studies will be necessary prior to bypassing the use with tumor mass biopsies, the use of exosomal microRNA profiling could extend this approach to screening of asymptomatic individuals, as well as for monitoring disease recurrence.

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