MESOTHELIN AS A NEW DIAGNOSTIC MARKER FOR OVARIAN CANCER

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RUNNING TITLE New marker for ovarian cancer
KEYWORDS ovarian cancer, mesothelin, Ca-125
WORD COUNT 1442
CONFLICT OF INTERESTS no conflicts of interest

ABSTRACT

Ovarian cancer (OC) is the most aggressive of all gynecological cancers. The disease is most frequently diagnosed at a very advanced stage, because the tumor is asymptomatic for a long time. Even then, the signs are not specific. Researchers are still looking for markers which detect OC at the early stage. Mesothelin is expected to become such marker in the future. This protein exhibits high specificity to ovarian cancer and according to clinical trials could be detected in urine, serum and ascites. Nevertheless, its accurate function in the body remains unknown. It is presumed that mesothelin is involved in the pathogenesis of ascites and tumor cell migration. Evaluation of this new molecule in women may be a chance to increase overall survival and decrease mortality rate among ovarian cancer patients.
BACKGROUND

Ovarian cancer (OC) has still the highest mortality rate among gynecological tumours. It is observed most frequently in the postmenopausal period. First symptoms are usually present when the disease is quite advanced, in III and IV FIGO stage (International Federation of Gynecology and Obstetrics). Epithelial ovarian cancer (EOC) is the most common type of ovarian cancers which are further grouped into histological types as follows: high-grade serous, endometrioid, clear-cell, mucinous, and low-grade serous [1]. On the basis of grade, genotype and molecular phenotype OC are classified into two main groups: type I- low-grade carcinomas and type II- high-grade carcinomas. Type I is characterized by slow growth and chemotherapy resistance while the type II is a group with aggressive growth and drug sensitivity.

Etiology

Ovarian cancer cells stem from surface epithelial cells of ovary or ovary cyst cells [2]. The etiology of this cancer is in about 90-95% unknown and these cases are called sporadic ovarian cancer [3]. In 5 to 10% the causes are known and there are 3 genetic syndromes in which ovarian cancer occurs familiar: HBOC (Hereditary Breast Ovarian Cancer), HOCC (Hereditary Ovarian Cancer) and Lynch Syndrome - HNPCC (Hereditary Nonpolyposis Colorectal Cancer). HBOC is the most common and it is caused by BRCA-1 gene mutation. HOCC is related to both BRCA-1 and BRCA-2 mutations. HNPCC is very rare and is correlated with many other cancers, primarily colon cancer but also bladder, intestinal or stomach cancer [4]. According to clinical trials, BRCA-1 and 2 carriers have a better prognosis than noncarriers [5]. Although the pathogenesis of OC is not clear, certain factors are implicated in the etiology of this disease, such as early age at menarche and late age at menopause, infertility, PCOS (Polycystic Ovary Syndrome), endometriosis, benign gynecological tumours, gynecological surgery, radiotherapy, obesity, stimulation of ovulation, another cancer in the past, cigarette smoking, and the others [1].

Atypical Symptoms

The symptoms of OC can be difficult to recognize, particularly in the early stages. The most characteristic sign of advanced OC is ascites, and it is usually the first symptom observed by the patient herself [6]. The other symptoms are less specific, for example pain, decreasing body weight, permanent fatigue, intestinal disorders like constipation and depend on tumour location, size and histological type. Lack of characteristic symptoms, difficulties in early diagnosis, insufficient accurate tumor markers and heterogeneity of ovarian tumor biology, contribute to the poor prognosis in these patients. Therefore, the identification of new biological factors, predictive of individual disease course, and prognosis would be extremely useful. The detection of biomarkers that are released into the circulation can aid the diagnosis and/or monitor the therapeutic responses of ovarian cancer patients.

Markers of ovarian cancer

Nowadays we still have no useful markers which can detect OC at the early stage. Although, the glycoprotein carcinoantigen 125 (Ca-125) is a “gold standard” biomarker for OC screening it is not very specific. Thus, new serum biomarkers need to be sought to replace or complement CA-125 for greater detection of ovarian cancers. Only two markers - HE4 (Human Epididymis Protein 4) and mesothelin exhibit high specificity to ovarian cancer. HE4 and mesothelin are the most specific markers of OC, but still little is known about early stage detection methods. Recent studies concerned other markers associated with advanced FIGO stage-KLK6 (kalikrein 6) and OPN (osteopontine). Reserchers tried to obtain a complex test including KLK6, OPN, SMRP (soluble mesothelin-related peptide), HE4 and Ca-125, but the complexes of these molecules and IgM antibodies had low sensitivity and specificity [7]. Scientists aim for creating a simple test which would become useful for screening in ovarian cancer.

Some remarks about mesothelin

Mesothelin is a 40-kDa glycoprotein expressed physiologically on the surface of the mesothelial cells of the pleura, the peritoneum, the pericardium and on the surface of epithelial ovarian cells, and also can be overexpressed in: lung cancer, ovarian cancer, pleural mesothelioma or pancreatic cancer [8]. It is encoded by the MSLN gene. Moreover, this protein has very high specificity for ovarian cancer, especially the serous type. Mesothelin is commonly detected in plasma, tissues and peritoneal fluid of OC patients. As a low mass protein mesothelin can be detected in urine, as it is removed by the kidneys. Badgwell et al. [9] show that mesothelin detection in urine is even better than plasma detection. The accurate biological function of mesothelin is unknown but one of the probable roles of this protein is contribution to cell adhesion. There is also a hypothesis that mesothelin is a receptor for Ca-125 antigen (MUC-16), and that they bind to each other with a high specificity [10]. This probable role of mesothelin could lead to metastases, for example peritoneal metastases in ovarian cancer. The recently recently discovered molecule MORAb-009, anti-MSLN monoclonal antibody, probably would be able to prevent metastases inhibiting mesothelin and Ca-125 interaction [11]. Rump et al. [12] confirmed Ca-125/mesothelin connection has a role in cancer cells adhesion. In turn Gubbels et al. [13] show that mesothelin binds ovarian cancer cells OVCAR3, which have Ca-125 expression. Also studies about pancreatic ductal carcinoma demonstrate that co-expression of MUC16 and mesothelin may lead to tumour development [14]. Recent reports also indicate that mesothelin may play an important role in chemoresistance [15]. This evidence demonstrates that mesothelin and Ca-125 have a great role in pathogenesis of cancer.

Clinical aspect

Mesothelin concentration can be also related to overall survival and disease-free survival [16]. Interesting, results by Cheng show that chemoresistance depends on the stage of cancer, age, ascites volume. What is more, such features like tumour grading, histological type and pre-operative MUC16 serum concentration were quite similar. This study also reveals that patients with endometrioid, serous or mixed types and more advanced
stage, have significantly higher MUC16 concentrations than patients with mucinous or clear-cell types and early stage. According to this study, concentration of mesothelin is also correlated with grading and staging of OC, the higher histological grade and stage, and the higher level of MSLN. Mesothelin level was also significantly higher in chemoresistance patients [16]. Lowe et al. examined a group of healthy postmenopausal women and discovered the factors which have an influence on mesothelin, Ca125 and HE4 levels in this group. Among all factors, age was the most significant, but another agents like BMI, past application of talcum to the genital area and smoking are also related to the expression of these markers [17]. Moreover high mesothelin serum concentration correlates with poor overall survival in patients with advanced stage of cancer and going through optimal debulking surgery [18]. Interestingly, scientists revealed mesothelin in urine in about 42% and in serum in 12% patients with early stage of cancer. This finding indicates that mesothelin could become a screening marker for OC [18]. Mesothelin has also a correlation with ERK (extracellular-signal regulated kinase), which is a mediator of cell proliferation. MSLN activates the ERK signal pathway what in turn facilitates cancer cell migration. It can cause more aggressive cancer invasion [19]. Another molecule, MMP7 (matrix metalloproteinase 7) has also an influence on OC spread in conjunction with MSLN. Mesothelin triggers the expression of MMP7 through the activation of ERK pathway. Due to this dependence, cancer progression could be significantly accelerated [11]. It is probable that inhibition of this pathway could terminate the development of some cancers. Other studies show that MORAb-009, the monoclonal antibody, could stave off the emergence of metastases via blocking the MSLN/MUC16 interaction [11].

CONCLUSIONS

Evaluation of promising tumor markers opens new horizons in ovarian cancer detection and therapy. The accurate detection method based on molecular profiles for ovarian cancer has been poorly established due to the fact that disease exhibits a wide range of biological, clinical and genetic variations during the course of tumor progression. It is possible that two most specific molecules for epithelial ovarian cancer- mesothelin and HE4 could become routinely applied for screening purposes.

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ABBREVIATIONS

BMI – Body Mass Index
BRCA1/BRCA2 – human breast and ovarian cancer genes
Ca125 – carcinoma antigen 125
EOC – epithelial ovarian cancer
ERK – extracellular-signal regulated kinase
FIGO – International Federation of Gynecology and Obstetrics
HBOC – Hereditary Breast Ovarian Cancer

HE4 – Human Epididymis 4
HOC – Hereditary Ovarian Cancer
HNPPCC – Hereditary Nonpolyposis Colorectal Cancer
KLK6 – kalikrein 6
MMP7 – matrix metalloproteinase 7
MSLN – mesothelin
MUC16 – Ca125, the name of the gene encodes Ca125
OC – ovarian cancer
OPN – osteopontine
OVCAR3 – ovarian cancer cell 3
PCOS – Polycystic Ovary Syndrome
SMRP – soluble mesothelin-related protein

REFERENCES


