

Molecular Biomarkers: New Approaches in Ovarian Cancer Diagnosis

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Formation of tumors is associated with accumulation of different genetic and epigenetic changes. The current review summarizes the recent data on molecular markers of human ovarian cancer, as well as provides analysis of the contribution of epigenetic markers for early cancer diagnostics. Specificities of functioning of signaling pathways are considered in the context of searching for possible oncomarkers. The importance of complex evaluation of molecular changes for correct diagnostics and prognosis of ovarian cancer is demonstrated.

Keywords: ovarian tumor, early diagnostics of cancer, epigenetic markers, tumor suppressor, microarrays.

The review summarizes the data on potential molecular markers of ovarian tumors and makes effort to assess the possibilities of their application in medicine.

Tumor markers in clinics Tumor markers are both genes and their products, related to malignant tumors formation [1]. Cancer antigens (high-molecular weight glycoprotein CA125, detected using monoclonal antibodies, and CA72-4) are basic clinical markers in cases of ovarian cancer of different malignancy degrees [2, 3]. It is noteworthy that the increase in CA125 concentration can be connected not only with

malignization development, but also with formation of various benign tumors, chronic inflammatory processes, as well as normal physiological cycle of women, which influence the reliability of diagnostics [4].

Initial stages of ovarian tumor formation take place almost asymptotically. In 70% of ovarian cancer patients, the tumors are diagnosed at metastasized condition [5]. Determining the set of molecular markers for ovarian tumors would allow conducting effective screening and therapy at early stages of cancer diagnostics, detecting micrometastases in the course of treatment, and performing monitoring during the stage of remission.

Epigenetic markers in ovarian cancer diagnostics

All cell processes are controlled by means of methylation [6]. As a rule, methylation of DNA is performed by CpG-sites in non-coding sequences. Changes in methylation status were defined for variety of genes - ovarian cancer markers, and the progressing increase in hypomethylation due to increase of malignancy degree was demonstrated [7].

14-3-3y factor, participating in DNA reparation, shows methylation of all 17 CpG-islands in cases of ovarian carcinomas [8]. Increase in MBD2 expression (methyl-CpG binding domain protein) is correlated with its hypomethylation and progression in ovarian cancer [7, 9]. However, the inverse relation could be observed in tumorigenesis, for instance, it has been found in case of colorectal cancer [10].

Changes in methylation in the course of tumor formation may be predicted long before, sometimes a year before malignization detection by other methods. The use of NotI-microarrays enables performing simultaneous detection of deletions, amplifications, and also epigenetic methylation of genes [11], which would allow the definition of markers at early stages of tumor development.

Markers of early ovarian cancer diagnostics The following potential markers of benign and borderline ovarian tumors are to be indicated: G-CSF cytokine (granulocyte colony stimulating factor) [12]; OGP (oviduct glycoprotein), significant for gameto- and embryogenesis [13]; GLUT-4 (glucose transporter 4), regulator of glucose level [14], P-LAP (placental leucine aminopeptidase), responsible for amino acids exchange [14], Ki-67 antigen, which participates in rearrangements of chromatin during cell cycle interphase [15, 16]; IGF 1 growth factor (insulin-like growth factor) [17]. Increase in expression of these genes results in changes in cell homeostasis and stimulation of growth. Decrease in expression level from benign to malignant tumors was shown for transcription factor BRCA1 (breast cancer 1, product of tumor suppressor gene) [18].

Borderline tumors are of special interest. Molecular markers for borderline tumors are adequate to those of early malignancy stages. Panel of antigens has been suggested as molecular oncomarkers for early ovarian cancer diagnostics [19]. According to Lu et al. [20],

complex evaluation of markers (CLDN3 (claudin 3), MUC1 (mucin 1), VEGF (vascular endothelial growth factor), CA125) allowed diagnosing ovarian cancers with the probability higher than 99%.

The increase in level of TADG-15 (tumor associated differentially expressed gene 15 protein) expression at the first stage of ovarian cancer, as well as its decrease during tumor progression, is typical of tumors [21]. Increase in telomerase activity, in particular, in serous carcinomas of ovaries, and the relation between hTERT (human telomerase reverse transcriptase) activation and high microsatellite instability were shown [22, 23]. The difference in expression of ribosomal genes for borderline and malignant tumors [24], and hypermethylation of GC-rich clusters of ribosomal genes were detected [25]. High level of somatic mitochondrial mutations, e.g. for DNA region encoding 12S and 16S RNA, has been observed in cases of ovarian cancer [26]. Differences in Ras mutations in borderline and malignant tumors were shown. Many genes, considered to be potential markers of ovarian cancer, are expressed under the control of cytokines. At the same time, cytokines can be used for assessment of malignization in different combinations, including those together with CA125 [12, 27].

Change of methylation status was shown for BRCA1 in case of ovarian cancer: methylation frequency was shown to be higher in serous carcinomas than in mucinosal and endometrioid ones. Loss of heterozygosity (LOH) for BRCA1 was not detected in benign tumors, weakly demonstrated in borderline tumors, and turned out to be specific for the majority of malignant ovarian tumors [18]. Increase in satellite DNA quantity in two chromosomal areas was demonstrated at early malignization stages [28, 29].

Cell signaling pathways at ovarian cancer Many potential ovarian tumor markers are known to be important members of cell signaling pathways. The key role in malignization is performed by PIK3K (phosphatidylinositol 3-kinase)/Akt-pathway [30]. Insulin and VEGF activate Akt-kinase; tumor suppressor PTEN (phosphatase and tensin homolog), either mutated or with decreased expression, causes the same effect. In current pathology activation of PI3K/Akt involves c-Src, cytoplasmic tyrosine kinase and Ras. Akt activation is often connected with high

level of Akt expression or changes in PI3K, and rarely it is connected with the absence of functional PTEN. Other signaling pathways, depending on NF κ B (nuclear factor κ B), MAPK (mitogen-activated protein kinase), PKC (protein kinase C), cross-talk with PI3K/Akt-cascade at ovarian cancer.

Increased level of telomerase expression, the activity of which is correlated with clinical stage of the disease, is observed in more than 90% of malignant ovary tumors [31]. JNK-(c-jun-terminal kinase) signaling pathway is involved in regulation of telomerase activity at ovarian cancer. Oestrogen (ER) – in endometrial and endometrioid cells may be activated by MEKK1, apparently, via p38/JNK signaling pathways [32]. ER may also be activated via K-Ras-dependent cascade by the way of ER Erk phosphorylation. Activation of K-Ras is often detected in ovarian carcinomas [33]. ER interacts with ovarian oncogene AIB1 (amplified in breast cancer 1), which results in acetylation of core histones and activation of expression of gene, involved in regulation of anti-apoptosis, immortalization, angiogenesis, and invasion. In case of BRCA1 binding with ER, deacetylation of histones blocks expression of the genes listed above.

The abovementioned increase in expression level of AIB1, Src, and Ras oncogenes, as well as IGF-1R (insulin-like growth factor 1 receptor) and EGFR (endothelial growth factor receptor), and inactivation of such tumor suppressor genes as BRCA1, PTEN, p53 in case of ovarian cancer results in activation of several signaling pathways, including PI3K/Akt/PTEN, MAPK/ER6, JNK/p38/hTERT, Wnt/ β – catenin/Tcf [34], Jak/STAT3 [35], IGF-1/IGF-1R [30]. There are also other products of proto-oncogenes, participating in signaling pathways, listed as follows: JAK2 (janus kinase 2) [35], β -catenin [34], FGF20 (fibroblast growth factor) [36], as well as tumor suppressors (bikunin [37], BEXL1 (brain expressed X-linked-like 1) [38], ezrin [39], OPCML (opioid-binding protein/cell adhesion molecule-like gene) [40] with changed expression. There are also signaling molecules (hormones, transcription activators, mitogenic growth factors), which participate in activation of cascades and play an important role in ovarian cancer development.

Proteomic microarrays allow determining post-translational modifications, which are impossible to assess using genomic microarrays. The method of revealing the changes in the degree of phosphorylation of signaling proteins, derived from primary and disseminated tumors, was suggested in order to determine phenotypic variations with subsequent selection of specific kinase inhibitors as therapeutic means. It was revealed that in the majority of cases such difference is determined by expression of phosphorylated form of trans-membrane receptor tyrosine kinase c-kit, which is correlated with the last stages and resistance to chemotherapy in cases of serous ovarian carcinomas [41].

The correlation between histological tumors and changes at molecular level is of special interest. Individual signaling pathways components, specific changes for which were discovered in definite types/stages of ovarian cancer, were previously suggested to be used as markers. For cases of clear cell ovarian cancer, NHF-1 β was used as marker [42]. In serous and endometrial carcinomas, mutations (dysfunctions) of BRCA1 and BRCA2, as well as higher level of B7-H4 expression compared to the mucinous ones, were indicated. At early stages of serous carcinomas, RAS-RAF (MAPK)-signaling pathway is activated to a greater extent due to mutations in KRAS and BRAF. In mucinous carcinomas, mutation of KRAS [44] and increased expression of GAL4 (galectin 4) compared to benign and borderline tumors [45] have been revealed.

Conclusions The use of different methods often leads to principally dissimilar selections of genes, whose expression level changes in current pathology. Control for oncomarkers specificity presumes comparison of corresponding samples to the norm and benign tumors samples, as well as to those for diseases not connected with malignization. The presupposed marker cannot always be revealed in physiological fluids of the patient. Unfortunately, insufficient specificity of single markers, applied in medicine, allows diagnosing only some tumors.

Ovarian cancer integrates the group of neoplasms, which are characterized by high aggressiveness, which makes it more difficult to treat, and such treatment requires complex approach [46]. In oncotherapy the

emphasis from point targets is shifted to non-toxic agents of wide spectrum, i.e. tyrosine kinase inhibitors, angiogenesis inhibitors, cytokine balance regulators [47]. A number of genes-markers of ovarian malignant tumors are the objects for therapy elaboration, e.g. HNF1 β (hepatocyte nuclear factor beta), and HER2 [48, 49].

In future the use of single clinical factors as markers will be replaced by systematic approaches, including multiple factors, e.g. molecular and genetic markers. Improved and standardized microarray technology (NotI-microarrays are the most perspective at the moment) will allow defining various combinations of prognostic factors, and may be used in diagnostics by screening and comparison of genetic and epigenetic changes and expression on the level of genes and proteins.

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Молекулярные биомаркеры: новые подходы в диагностике опухолей яичников

Резюме

Процесс возникновения опухолей связан с накоплением различных генетических и эпигенетических изменений. В обзоре суммированы данные по молекулярным маркерам опухолей яичников, полученные благодаря развитию современных технологий, и проанализирована роль эпигенетических маркеров в ранней диагностике рака. Особенности функционирования сигнальных путей рассматриваются в контексте поиска вероятных онкомаркеров. Отмечено значение комплексной оценки молекулярных изменений для корректного диагноза и прогнозирования развития рака яичников.

Ключевые слова: опухоли яичников, ранняя диагностика рака, эпигенетические маркеры, супрессоры опухолей, NotI-микрочипы.

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