VIA MEDICA

REVIEW PAPER / GYNECOLOGY

Ginekologia Polska
2017, vol. 88, no. 6, 331–336

ISSN 0017–0011

DOI: 10.5603/GP.a2017.0062

Biological markers with potential clinical value in endometrial cancer — review of the literature

Nadia Taoussi, Ali Alghamdi, Konrad Futyma, Tomasz Rechberger

2nd Department of Gynecology, Medical University of Lublin, Poland

ABSTRACT

Endometrial carcinoma (EC) is the most common malignancy of the female genital tract encountered in western countries, making it the fourth most common cancer in women. The incidence of uterine cancer is on the rise throughout the developed world where diagnosis is increasingly observed among younger patients. With regard to this, attention has been focused on conducting more studies to achieve a better understanding of the molecular genetics related to endometrial carcinogenesis. Over the years, EC has been classified into two broad histopathological subtypes based on the mechanism of development, and we can therefore observe specific biomarkers related to the respective subtype. Based on this idea, more research has been carried out in the last decade, using biotechnological methods, with the aim to identify new potential tumor markers. By translating these findings into clinical use one may facilitate accurate diagnosis and prognostic prediction, and contribute to individualized treatment. Without a doubt, there is a demanding need to identify biomarkers that can be adopted in clinical practice in order to reduce the time needed to obtain diagnosis. Such markers may be of great value in improving patient outcome. However, a number of problems remain to be solved before this becomes a reality. This paper briefly reviews the current status of rising biomarkers in EC.

Key words: endometrial cancer, array-based technology, proteomics, gene expression, prognostic markers, screening method

Ginekologia Polska 2017; 88, 6: 331–336

INTRODUCTION

Endometrial cancer (EC) is the most frequent type of gynaecological malignancy in developed countries [1]. The diagnosis is commonly observed among postmenopausal women that seek medical attention following initial presentation of atypical vaginal bleeding prior, during or after menopause. Despite being one of the most common gynaecological malignancies, routine screening is not recommended as majority present with an early stage disease (stage I or II) resulting in favourable prognosis and excellent survival rate (5-year overall survival 75–90%) [2]. However, women encountering more advanced or recurrent disease will have an extremely poor clinical outcome. Thus, renewed research focus on better understanding the molecular changes associated with EC, which is mainly promoted by the dramatic increase in incidence observed in the recent years [3]. In contrast to cervical cancer, there is still insufficient evidence to recommend any cost-effective screening method in women with average to high risk and without symptom presentation [1]. However, papanicolaou (Pap) smear, tranvaginal ultrasound, and endometrial sampling are techniques under investigation for their ability to reveal EC at an early stage [4]. For the same purpose, different molecular techniques have been applied in the search for markers that can be associated with EC stag, prognosis, and therapeutic response. Therefore, the aim of this paper is to briefly outline a panel of promising biomarkers that can be adopted as serum screening in cancer detection and prediction of outcome.

BIOMARKERS RELATED TO HISTOPATHOLOGICAL SUBTYPES OF EC

Based on the mechanism of development, we distinguish between two broad clinicopathological variants. Type I (endometrioid) cancers comprise the large majority (70–80%) and is know to be estrogen-responsive. This subtype is as-

Corresponding author:
Nadia Taoussi
2nd Department of Gynecology, Medical University of Lublin
Jaczewskiego St. 8, 20–954 Lublin, Poland
e-mail: nad.taou@gmail.com

sociated with unopposed estrogen stimulation and is more frequently observed among perimenopausal middle-aged women [2]. By contrast, type II (non-endometrioid cancer) follows the estrogen-unrelated pathway, which seems to arise from a background of atrophic endometrium. Type II tumors are commonly diagnosed in older postmenopausal women, and are generally less differentiated accounting for a poor prognostic outcome [2, 3]. A wide variety of proposed biomarkers have been examined for EC of the respective subtype. Defects in DNA mismatch repair genes, microsatellite instability, and mutations in the PTEN and K-ras and/or B-catenin genes are mutated in high rates for type I, whereas alteration in the p53 suppressor gene with mutation of Her-2/neu are commonly observed in type II [2, 3]. Based on the significantly different gene expression profile, one can suspect that the two types may have distinct underlying etiologies, which in turn is responsible for the pathogenesis and progression [3]. For that reason, these biomarkers are currently used as diagnostic clues representing the most common basis for prognostic estimation of this gynaecological malignancy [2].

ESTABLISHED MOLECULAR PROFILING TECHNIQUES

Array-based technology

This is a well-established method for the investigation of gene expression in organs or tissues undergoing pathological changes [5]. Several studies have used array analysis to investigate genomic features of EC, resulting in detection of a large range of molecular alterations. To illustrate, Xue-Lian and colleagues performed oligonucleotide microarray to examine the global expression pattern of tumor-associated endothelial cells from EC [6]. The study was able to identify a consistent overexpression of certain marker genes in addition to loss of several tumor suppressor activities associated with EC.

Meanwhile, in a different article, cDNA microarray was applied in the investigation of expression profiles for genes encoding extracellular matrix (ECM) proteins by comparing level of markers in early and advanced stage of EC [7]. Initially, the authors presented an overexpression of six different ECM components shown to play an important role in the carcinogenesis of EC; aggrecan, collagen type VIII chain α1, collagen type XI chain α2, vitronectin, nidogen, and tenascin R. Gene microarray have attracted wide attention because of its ability to investigated hundreds to thousands of genes in parallel providing unique information about the expression of different genes related to EC [8]. Thus, becoming an important analytical tool in cancer research and clinical diagnostics.

Next-generation sequencing (NGS)

In a paper published by Creighton et al. a panel of novel miRNAs were discovered in the female reproductive organs using next-generation sequencing (NGS) technique (Tab. 1). Similarly, by performing whole-exome sequencing, Liang and colleges were able to identified 12 potential cancer genes. However, AT-rich interactive domain 1A (ARID1A) was the gene attracting most attention because of its suggested role in suppressing cell proliferation of ovarian and endometrial cancer cell lines [9]. The recent introduction of sequencing technology have aided in the discovery of new RNA molecules while providing more detailed understanding

Table 1. Novel miRNAs in the female reproductive organs

miRNA	Expression level	Potential clinical role	References
miR-200 family	Up-regulated	Mostly pronounced in early phase EEC	20, 21, 22
miR-205 and miR-210	Up-regulated	Potential biomarkers for early diagnosis and prognosis of EC	22
miR-185, miR-106a, miR-181a, miR-210, miR-423, miR-103, miR-107, miR-let 7c	Up-regulated	Transition from normal endometrium through atypical hyperplasia to cancer. No association between the expression level and cancer stage/grade	23
miR-77 family	Up-regulated	Clinically advanced tumors	22
hsa-miR-196a-5p, hsa-miR-328-3p, hsa-miR-337-3p, and hsa- miR- 181c-3p	Deregulated	Potential diagnostic markers of EC	18
miR-let 7i, miR-221, miR-193, miR-152, miR-30c	Decreased expression	Transition from normal endometrium through atypical hyperplasia to cancer. No association between the expression level and cancer stage/grade	23
miR-92a, miR-96, miR-200a, miR-203, miR-429, miR-449a	Dysregulation	FIGO staging	21
miR-200b*, miR-429, miR-9, miR-92, miR-449a	Dysregulation	Histological grading	21
miR-96, miR-183, miR-449a	Dysregulation	Cancer relapse	21
miR-203, miR-429	Dysregulation	Lymph node metastasis	21

of biological pathways related to endometrial tumorigenesis [10]. Compared with traditional microarrays, which can only detect a limited number of miRNA, NGS enables in-depth characterization of the global range of miRNAs [10, 11]. Also, it is suggested that genomic analysis of cells collected during Pap smears holds promise for early detection of EC [4, 10]. Thus, genome-wide studies using NGS can provide insight into the genomic alteration in association to EC.

Proteomics

Microarray and NGS studies have both provided unique information related to gene expression profile in EC, however, information at a protein level is crucial in order to include post-translational events [7]. In several papers, proteomics has been used to assess the clinical utility of biomarkers to evaluate their diagnostic and prognostic sensitivity and specificity by comparing protein profiles between pathological and normal tissue. It is belived that proteins are directly linked to the phenotype and the malignant nature of cancer, which explain the increased interest for studying global protein expression [11]. A study performed by Li et al. exemplifies the value of proteomics where three potential EC-associated proteins were identified; Cyclophilin A (CypA), epidermal fatty acid-binding protein (E-FABP), and caclyphosine (CAPS) [11]. Additionally, increase in both E-FABP and CAPS in relation to EC were also reported in a different paper [12]. Implementing this method, both papers conclude that the overexpression of E-FABP and CAPS is correlated to histodifferentiation but not to clinical staging [11, 12].

As identified by plasma membrane proteomics technique, an overexpression of bone marrow stromal antigen 2 (BST2) was demonstrated in EC at both mRNA and protein level. Based on this finding, it was proposed that BST2 might have a suppressor effect on tumor growth by either blocking the function of target signalling molecules or receptors, or by stimulating apoptosis. For that reason, it is suggested that BST2 might have a potential value as a molecular therapeutic target [13]. Lastly, Maxwell et al. performed global differential proteomic to identify the level of proteins associated with in stage I EC [14]. Interestingly, an overexpression of specific ribosomal proteins (RS3, RS9, RS14, RS18, RLA1, RLA2, RL8, RL11, RL22, RL18, RL24, RL10A, RL27A), which has not been previously described in acquaintance to EC, was established in this report. More importantly, a deregulation was found to include the following set of proteins; (1) multiple members of peroxiredoxin family (PRDX1, PRDX3, PRDX4, PRDX5, PRDX6), (2) prohibitin 2 (PHB2), and (3) members of the annexin family (ANXA1, ANXA2). As demonstrated by the abovementioned findings, we can emphasise that proteomic is an innovative approach for the identification of proteins and biomarkers that can be clinically adopted for diagnosis of EC [14].

BIOMARKERS WITH DIAGNOSTIC, PROGNOSTIC AND THERAPEUTIC VALUE IN EC

Astrocyte elevated gene-1 (AEG-1/MTDH/LYRIC)

While some papers are primarily focusing on further investigation of the already known set of genetic alterations, others are aiming to detect newer cancer genes (Tab. 2). The comprehensive list of novel biomarkers related to EC includes the recent discovery of Astrocyte elevated gene-1. AEG-1 is located at chromosome 8q22 [15] and is also known as metadherin (MTDH) and lysine-rich CEACAM1 coisolated (LYRIC) [17]. Since its discovery in 2002, as HIV- and TNF--α-inducible gene in primary human fetal astrocytes [15], several authors have described its tumor-promoting activity which is related to the activation of diverse signal transduction pathways (PI3K/ AKT, NF-κB, MEK/ERK, WNT/β-catenin) involved in cancer progression, in addition to its role in pathogenesis, metastasis, invasion, angiogenesis and overall patient survival [16]. It should be noticed that AEG-1 is an important oncogene were its expression status is firmly established in a subsequent array of cancers.

More importantly, AEG-1 has been described to play a central role in carcinogenesis and progression of endometrial cancer in a study conducted by Song et al. [17]. The expression rate of AEG-1 was investigated in 35 normal endometrial tissue, 40 atypical hyperplasia, and 174 EC tissue (161 cases being endometrioid carcinoma) showing a gradual elevation with the transition from normal to cancerous tissue. Thus, AEG-1 was found to be significantly correlated with clinicopathological parameters including FIGO stage ($p < 0.001$), depth of myometrial invasion ($p = 0.015$), lymph node metastasis ($p = 0.005$), lymph vascular space invasion ($p < 0.001$), recurrence ($p < 0.001$), and Ki-67 expression ($p = 0.032$). Several authors have implied that an up-regulation of AEG-1 enhances characteristics of malignant aggressiveness making it an independent prognostic factor for unfavourable clinical outcome. This suggests that AEG-1 is valuable as a prognostic biomarker of disease progression and survival in patients with EC [16–18].

MicroRNAs

Since the discovery of microRNA (miRNA), several authors have been intensively studying their role as diagnostic and prognostic markers, and predictors of drug response. MiRNA have aroused wide attention because of their suggested role as important regulators of gene expression in a broad spectrum of diseases, including solid and hematologic malignancies [18]. This is a family of small (21–22 nucleotides) non-protein-coding RNAs responsible for messenger-RNA (mRNA) stability and expression of proteins at a post-transcriptional level [18, 19]. For that reason, miRNAs has become well-established group of markers for the development and progression in a wide range of malignancies. In general,

Table 2. The most significant molecular markers in EC detection

Biomarkers	Normal endometrium	Atypical hyperplasia	EC	Association with prognosis?	References
Extracellular matrix (ECM) proteins (aggrecan, collagen type VIII chain α1, collagen type XI chain α2, vitronectin, nidogen, tensacin R)	No expression	No expression	High expression in stage III	Yes	7
Epidermal fatty acid-binding protein (E-FABP)	Weakly positive (79.5 %)	Weakly to strongly positive (100%)	Significantly stronger (100%)	No	11
Caclyphosine (CAPS)	Weakly positive (76.9 %)	Weakly to moderately positive (91.3%)	Significantly stronger (100%)	Yes (correlated with poor survival)	11
Bone marrow stromal antigen 2 (BST2)	No detectable expression		Significantly overexpressed (up to 10-fold)	No	13
Astrocyte elevated gene-1 (AGE-1)	Weak or no expression	Gradually elevated	High expression	Yes	17
Cyclophilin A (CypA)	Weak or no expression		Up-regulated 27.23-fold	Yes, but further studies need to be conducted	12
Human epididymis protein 4 (HE4)	Weak or no expression	Gradually elevated	Strongly expressed	Yes	29
Matriptase (MT-SP1)			Strongly expressed	Yes	32

miRNAs may either act as oncogenes or tumor suppressors presenting increased or decreased expression in tumor cells [19]. This alteration in miRNA expression may be involved in the initiation, cancer progression, and metastatic process in different cancer types. In the course of EC, a study done by Tsukamoto et al. suggest that miRNAs are predominantly involved in cell proliferation, differentiation, apoptosis, and carcinogenesis of endometrium [19]. Because 118 differently expressed miRNAs associated to EC have been reported so far, clinically important miRNAs that contribute in the cancer progression has to be identified [20].

During the past decade, several miRNAs including hsa-miR-503, hsa-miR-205, and hsa-miR-200b were shown to be dysregulated in endometrioid endometrial carcinomas (EEC) [19, 20]. Moreover, a comparison of EC tissue to normal tissue control detected an up-regulation of miR-200 family, which contains five miRNAs localized in two genomic clusters, chromosome 1 and 12 [20]. Corresponding with these findings Torres et al. reported a significant up-regulation of all miR-200 family members, mostly pronounced in the early phase of EEC [21]. Additionally, an over expression was found to encounter miR-205 and miR-210, suggesting them to be selected as biomarkers for the early diagnosis and prognosis of EC [22]. Xiong and colleges studied miRNAs in relation to early stage (stage I) EEC, and identified a deregulation of hsa-miR-196a-5p, hsa-miR-328-3p, hsa-miR-337-3p, and hsa-miR-181c-3p indicating their clinical value as potential diagnostic markers [18]. By comparing gene expression patterns in normal endometrium, atypical hyperplasia and EC tissue, Boren et al. described a total of 13 miRNAs that demonstrated a significance difference in level of expression [23]. In the transition from normal endometrium through atypical hyperplasia to cancer, five miRNAs (miR-let 7i, miR-221, miR-193, miR-152, miR-30c) exhibited a decrease in expression, leaving the remaining eight miRNAs (miR-185, miR-106a, miR-181a, miR-210, miR-423, miR-103, miR-107, miR-let 7c) with a relative increase in expression. Initially, there were no association between the miRNA expression and cancer stage or grade [23]. In another study aiming to investigate the clinical and pathological characteristics, a set of miRNAs was found to be dysregulated in regards to FIGO staging (miR-92a, miR-96, miR-200a, miR-203, miR-429, miR-449a), histological grade (miR-200b*, miR-429, miR-9, miR-92, miR-449a) occurrence of relapse (miR-96, miR-183, miR-449a), and lymph node metastasis (miR-203, miR-429) [21]. Additionally, an overexpression of miR-77 family was contributed to clinically more advanced tumors. The set of miRNAs presented in this paragraph were all identified by means of microarray technology and/or next-generation sequencing (NGS) with further conformation using qRT-PCR. To investigate miRNA profiles, both plasma and tissue were collected form patients with EEC revealing their potential as future noninvasive biomarkers for early detection, diagnosis and prognosis of EC [18, 21]. Finally, it is suggested that miRNA can aid as potential therapeutic target by either blocking or mimicking the miRNA activity, however, further research need to be carried out [22, 23].

Cyclophilin A (CYPA)

CypA is among the proteins that have been repeatedly reported to be involved in pathogenesis of several diseases including cancer, cardiovascular disease, and viral infections. This is a cytosolic binding protein that belongs to the immunophilin family, which are found in all prokaryotes and eukaryotes and is belived to have an important role in regulating protein folding process, T-cell activation, differentiation, cell migration, proliferation, and Bcl-2 expression in various cells [24]. Research confirm its involvement in several types of cancer, were an up-regulation is belived to be correlated with poor outcome of the patients [25]. To date, only one proteomic study on CypA has been reported which presented an overexpression of CypA in EC based on individual-matched cancer specimen and normal endometrial tissue. Among 99 proteins identified, CypA was found to be one of the most significantly overexpressed protein in all EC tissues examined. Perhaps the clinically proved up-regulation of CypA in EC may be applied as an independent predictor of survival. Its potential value as a biomarker for prognosis and clinical treatment is supported by a selection of criteria, which include involvement and overexpression in EC, significant difference between EC specimen and control tissue, and its identification by mass spectrometry [26]. However, the precise role of CypA in targeted treatment of endometrial cancer remains to be established.

Complementary to this, other studies have also aimed to investigate CypA as a potential marker in different cancer types. The results of those studies were similar and the CypA overexpression was shown to be significantly more likely to present with poor differentiation and decreased survival.

Human epididymis protein 4 (HE4)

In gynaecological malignancies, HE4 have merged as a promising biomarker and was first described by Kirchhoff et al. by means of cDNA screening. This protein is also known as Whey acidic protein (WFCD2) localized on human chromosome 20q12-13.1 and is identified as one of four cDNAs highly expressed in the epididymis, trachea, lung, prostate, endometrium and breast [27]. In 2001, the United States Food and Drug Agency (FDA) approved this protein for monitoring of recurrence and progression in epithelial ovarian cancer. Because EC possesses many similarities to ovarian cancer it was desirable to investigate HE4 and its relations to EC. Brennan et al. performed a large population-based cohort study to evaluate if serum HE4 can offer preliminary pre-operative risk stratification for EC. Specifically because of the high expression level of HE4 in EC tissue, and the increased serum level in this group of patients [28, 29]. The result strongly implied that serum HE4 was an independent poor prognostic marker, and it was suggested to use HE4 serum assay as a cost-effective approach to avoid unnecessary lymphadenectomy in patients with low risk EC. In a different paper the expression of HE4 in EC and its relations to clinicopathological parameters and prognosis of EC was studied. The goal was to detect the expression rate of HE4, by means of immunohistochemical using streptavidin-peroxidase, in EC, endometrial atypical hyperplasia, and normal endometrial tissue samples, respectively [27, 29]. The results implied that the intensity of HE4 expression increased with degree of malignancy. Thus, the level of HE4 in EC was significantly higher than that of hyperplasia and normal endometrium. Furthermore, the investigation showed no relations of HE4 to the pathological subtype but rather a strong relation to other factors like cancer stage, metastasis, myometrial invasion depth, recurrence, degree of differentiation and the overall survival rate. However, in another paper there was a lack of evidence to estimate the clinical value and to support the application of HE4 in EC [30]. In conclusion, further researches have to be carried out in order to evaluate the clinical specificity and sensitivity of HE4 and its benefits as a serum marker for EC.

Matriptase (MT-SP1)

The type II transmembrane serine protease (TTSP) family has recently gained increased interest because of their link and potential to enhance the aggressive nature of cancer cells [31]. The matriptase, a subfamily of TTSP, which is normally expressed by cells of epithelial origin, is suggested to be involved in the degradation of the extracellular matrix (ECM), including interstitial basement membrane (BM) in certain tumor entities. Therefore, high levels of matriptase will in many cases be correlated with poor clinical outcome [31, 32]. Matriptase, originally isolated from breast cancer cells, is thought to have a pleotropic function where its carcinogenetic properties are to facilitate cellular invasion and activation of oncogenic pathways [32]. Protease is functionally involved in tumor growth and spread in a variety of benign and malignant tumors where its overexpression is confirmed in a large number of studies.

Nakamura et al. studied matriptase in association to human EC assessed by immunohistochemistry for evaluation of epithelial cells [33]. The expression level was compared in normal endometrium, endometrial hyperplasia and in EC tissue respectively. The immunostaining patterns of matriptase were then classified into strong, moderate, and weak cell staining. EC showed the strongest expression in comparison to normal and endometrial hyperplasia. It was concluded that matriptase elevation was associated with clinicopathological parameters such as advanced stage, high grade, myometrial invasion depth, cervical involvement, lymph node metastasis, lymph vascular space involvement and peritoneal cytology. Strong matriptase expression is therefore linked to an overall lower survival rate [30–33].

Furthermore, matriptase is showed to be effective in prevention of tumor growth and metastasis formation, which makes it both a potential new target for anti-cancer therapy as well as a novel prognostic diagnostic marker in several cancer types including EC [32].

CONCLUSIONS

The increase in incidence of EC raises the need for discovery of more convenient methods that may contribute to early detection and better prognostic assessment. A panel of new genes and proteins have therefore been intensively studied during the past decade. Some of which are aforementioned in this paper have aroused considerable attention making them promising in future clinical application. However, each biomarker provides only limited information and the search for biomarkers with higher sensitivity and specificity is required for screening, diagnosis, prognosis, and individualized therapy.

Financial disclosure

Authors have nothing to disclose.

REFERENCES

1. American Cancer Society (ACS). Endometrial (Uterine) cancer. Retrieved from. http://www.cancer.org/acs/groups/cid/documents/webcontent/003097-pdf.pdf (2.10.2016).
2. Talhouk A, McAlpine JN. New classification of endometrial cancers: the development and potential applications of genomic-based classification in research and clinical care. Gynecol Oncol Res Pract. 2016; 3: 14, doi: 10.1186/s40661-016-0035-4, indexed in Pubmed: 27999680.
3. Banno K, Kisu I, Yanokura M, et al. Biomarkers in endometrial cancer: Possible clinical applications (Review). Oncol Lett. 2012; 3(6): 1175–1180, doi: 10.3892/ol.2012.654, indexed in Pubmed: 22783413.
4. Smith RA, Cokkinides V, Brawley OW. Cancer screening in the United States, 2009: a review of current American Cancer Society guidelines and issues in cancer screening. CA Cancer J Clin. 2009; 59(1): 27–41, doi: 10.3322/caac.20008, indexed in Pubmed: 19147867.
5. Li L, Tang H, Wu Z, et al. Data mining techniques for cancer detection using serum proteomic profiling. Artif Intell Med. 2004; 32(2): 71–83, doi: 10.1016/j.artmed.2004.03.006, indexed in Pubmed: 15364092.
6. Du XL, Jiang T, Zhao WB, et al. Gene alterations in tumor-associated endothelial cells from endometrial cancer. Int J Mol Med. 2008; 22(5): 619–632, indexed in Pubmed: 18949382.
7. Futyma K, Miotła P, Różyńska K, et al. Expression of genes encoding extracellular matrix proteins: a macroarray study. Oncol Rep. 2014; 32(6): 2349–2353, doi: 10.3892/or.2014.3493, indexed in Pubmed: 25231141.
8. Guo C, Song WQ, Sun P, et al. LncRNA-GAS5 induces PTEN expression through inhibiting miR-103 in endometrial cancer cells. J Biomed Sci. 2015; 22: 100, doi: 10.1186/s12929-015-0213-4, indexed in Pubmed: 26511107.
9. Liang H, Cheung LWT, Li J, et al. Whole-exome sequencing combined with functional genomics reveals novel candidate driver cancer genes in endometrial cancer. Genome Res. 2012; 22(11): 2120–2129, doi: 10.1101/gr.137596.112, indexed in Pubmed: 23028188.
10. Le Gallo M, Bell DW. The emerging genomic landscape of endometrial cancer. Clin Chem. 2014; 60(1): 98–110, doi: 10.1373/clinchem.2013.205740, indexed in Pubmed: 24170611.
11. Li Z, Huang C, Bai S, et al. Prognostic evaluation of epidermal fatty acid-binding protein and calcyphosine, two proteins implicated in endometrial cancer using a proteomic approach. Int J Cancer. 2008; 123(10): 2377–2383, doi: 10.1002/ijc.23808, indexed in Pubmed: 18729184.
12. Li Z, Min W, Huang C, et al. Proteomics-based approach identified differentially expressed proteins with potential roles in endometrial carcinoma. Int J Gynecol Cancer. 2010; 20(1): 9–15, doi: 10.1111/IGC.0b013e3181a9026d, indexed in Pubmed: 20057284.
13. Yokoyama T, Enomoto T, Serada S, et al. Plasma membrane proteomics identifies bone marrow stromal antigen 2 as a potential therapeutic target in endometrial cancer. Int J Cancer. 2013; 132(2): 472–484, doi: 10.1002/ijc.27679, indexed in Pubmed: 22729361.
14. Maxwell GL, Hood BL, Day R, et al. Proteomic analysis of stage I endometrial cancer tissue: identification of proteins associated with oxidative processes and inflammation. Gynecol Oncol. 2011; 121(3): 586–594, doi: 10.1016/j.ygyno.2011.02.031, indexed in Pubmed: 21458040.
15. Emdad L, Das S, Dasgupta S, et al. AEG-1/MTDH/LYRIC. Advances in Cancer Research. 2013: 75–111, doi: 10.1016/b978-0-12-401676-7.00003-6.
16. Lee SG, Kang DC, DeSalle R, et al. AEG-1/MTDH/LYRIC, the beginning: initial cloning, structure, expression profile, and regulation of expression. Adv Cancer Res. 2013; 120: 1–38, doi: 10.1016/B978-0-12-401676-7.00001-2, indexed in Pubmed: 23889986.
17. Song H, Li C, Lu R, et al. Expression of Astrocyte Elevated Gene-1. International Journal of Gynecological Cancer. 2010; 20(7): 1188–1196, doi: 10.1111/igc.0b013e3181ef8e21.
18. Gilabert-Estelles J, Braza-Boils A, Ramon LA, et al. Role of microRNAs in gynecological pathology. Curr Med Chem. 2012; 19(15): 2406–2413, indexed in Pubmed: 22455593.
19. Tsukamoto O, Miura K, Mishima H, et al. Identification of endometrioid endometrial carcinoma-associated microRNAs in tissue and plasma. Gynecol Oncol. 2014; 132(3): 715–721, doi: 10.1016/j.ygyno.2014.01.029, indexed in Pubmed: 24491411.
20. Xiong H, Li Q, Chen R, et al. A Multi-Step miRNA-mRNA Regulatory Network Construction Approach Identifies Gene Signatures Associated with Endometrioid Endometrial Carcinoma. Genes (Basel). 2016; 7(6), doi: 10.3390/genes7060026, indexed in Pubmed: 27271671.
21. Torres A, Torres K, Pesci A, et al. Diagnostic and prognostic significance of miRNA signatures in tissues and plasma of endometrioid endometrial carcinoma patients. Int J Cancer. 2013; 132(7): 1633–1645, doi: 10.1002/ijc.27840, indexed in Pubmed: 22987275.
22. Gilabert-Estelles J, Braza-Boils A, Ramon LA, et al. Role of microRNAs in gynecological pathology. Curr Med Chem. 2012; 19(15): 2406–2413, indexed in Pubmed: 22455593.
23. Boren T, Xiong Y, Hakam A, et al. MicroRNAs and their target messenger RNAs associated with endometrial carcinogenesis. Gynecol Oncol. 2008; 110(2): 206–215, doi: 10.1016/j.ygyno.2008.03.023, indexed in Pubmed: 18499237.
24. Nigro P, Pompilio G, Capogrossi MC. Cyclophilin A: a key player for human disease. Cell Death Dis. 2013; 4: e888, doi: 10.1038/cddis.2013.410, indexed in Pubmed: 24176846.
25. Obchoei S, Wongkhan S, Wongkham C, et al. Cyclophilin A: potential functions and therapeutic target for human cancer. Med Sci Monit. 2009; 15(11): RA221–RA232, indexed in Pubmed: 19865066.
26. Li Z, Zhao X, Bai S, et al. Proteomics identification of cyclophilin a as a potential prognostic factor and therapeutic target in endometrial carcinoma. Mol Cell Proteomics. 2008; 7(10): 1810–1823, doi: 10.1074/mcp.M700544-MCP200, indexed in Pubmed: 18421009.
27. Li X, Gao Y, Tan M, et al. Expression of HE4 in Endometrial Cancer and Its Clinical Significance. BioMed Research International. 2015; 2015: 1–8, doi: 10.1155/2015/437468.
28. Li J, Dowdy S, Tipton T, et al. HE4 as a biomarker for ovarian and endometrial cancer management. Expert Rev Mol Diagn. 2009; 9(6): 555–566, doi: 10.1586/erm.09.39, indexed in Pubmed: 19732003.
29. Brennan DJ, Hackethal A, Metcalf AM, et al. ANECS Group. Serum HE4 as a prognostic marker in endometrial cancer--a population based study. Gynecol Oncol. 2014; 132(1): 159–165, doi: 10.1016/j.ygyno.2013.10.036, indexed in Pubmed: 24211402.
30. Bie Y, Zhang Z. Diagnostic value of serum HE4 in endometrial cancer: a meta-analysis. World J Surg Oncol. 2014; 12: 169, doi: 10.1186/1477-7819-12-169, indexed in Pubmed: 24885319.
31. Uhland K. Matriptase and its putative role in cancer. Cell Mol Life Sci. 2006; 63(24): 2968–2978, doi: 10.1007/s00018-006-6298-x, indexed in Pubmed: 17131055.
32. Nakamura K, Hongo A, Kodama J, et al. The role of hepatocyte growth factor activator inhibitor (HAI)-1 and HAI-2 in endometrial cancer. Int J Cancer. 2011; 128(11): 2613–2624, doi: 10.1002/ijc.25606, indexed in Pubmed: 20715109.
33. Nakamura K, Hongo A, Kodama J, et al. Expression of matriptase and clinical outcome of human endometrial cancer. Anticancer Research. 2009; 29(5): 1685–1690.