REVIEW

HIGHLIGHTS

This review describes recently used molecular biomarkers for the detection of endometrial carcinoma. Gene expression of these markers depends not only on carcinoma progression but also on individual specifications of each patient. The data of this review can be transferred into clinical use for detection or monitoring of endometrial cancer progression and improve the care of patients.

ABSTRACT

Most of endemically occurring tumors in an advanced state remains even after the combined treatment methods incurable diseases or difficult therapeutic diseases, respectively. Basic research in molecular biology and genetics has moved at a high level, many cancers produce a new tumor entities and circulating molecules with different characteristics offering a new target structures for targeting in personalized medicine. At the forefront of advance in personalized medicine of cancer, has recently been a gene expression profiling. The value of gene expression signatures was demonstrated for the prediction of tumor behavior in several types of cancer, distinguishing groups of patients with specific tumor grades and/or prognosis. Endometrial cancer is the most common malignancy of the gynecologic tract. It is the sixth most common cancer in women worldwide. Prognostic factors of endometrial cancer into the group of uterine and the extraterine factors. Uterine factors include the histologic type, grade of differentiation, depth of invasion of the myometrium, vascular invasion and others meanwhile extraterine factors include positive peritoneal cytology, spreading to the pelvic and para-aortic lymph nodes. This review article is summarizing the present knowledge regarding recently used biomarkers for personalized detection of endometrial carcinoma, considering how such markers could be used for clinical challenges in the handling of this disease. The ability to target surgical and systemic therapies to well selected patient populations, will increase the likelihood of benefits and diminish side effects related to treatment.

KEY WORDS

Endometrial carcinoma, molecular markers, gene expression, personalized medicine

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INTRODUCTION

During recent years the current oncology has noticed a large progress in the study of diagnostic, prognostic and predictive biomarkers. Therapeutic molecules for targeted therapies of cancer indications and a number of results of intensive research in this field are currently being implemented in the diagnostic and therapeutic practice. At the forefront of scientific interests is getting particularly anti-tumor therapy, specific to the particular type of cancer, and biomarkers that reasonably define a group of patients who will benefit not only due to improvements in diagnosis but also prognosis.

Most of endemically occurring tumors in an advanced state remains even after the combined treatment methods incurable diseases or difficult therapeutic diseases, respectively. Basic research in molecular biology and genetics has moved at a high level, many cancers produce a new tumor entities and circulating molecules with different characteristics offering a new target structures for targeting in personalized medicine.

Medicine is becoming an interactive science of combining information from many disciplines together (e.g. the molecular, biochemical, biological, bioanalytical, biostatic). Despite the efforts of development and registration of new therapeutic compositions of the personalized medicine, most of which increases the time of disease progression, without significant effect on the length of survival. The basic principle for improvement of the efficiency of cancer therapy seems to be the identification of biomarkers as prognostic factors that propose the next therapeutic, pharmacokinetic interventions for selected tumor types, not only in terms of diagnostics and anti-tumor response but also in terms of the toxicity of the treatment. Characterization of cancer biomarkers is very difficult, because it is a heterogeneous group of measurable characters that can be reliably distinguish and characterize tumor cell from a non-tumor cells. Due to the extensiveness of the mentioned area is the following text dealing with basic characteristic and summarization of predictive biomarkers usage in clinical practice in the diagnosis of endometrial carcinoma.

**Characterization of endometrial carcinoma**

Endometrial cancer is the most common malignancy of the gynecologic tract. It is the sixth most common cancer in women worldwide. In United States was new case incidence around 60 050 women and reported 10 470 dead cases during 2016 [1]. Approximately 75% of women with endometrial cancer are postmenopausal, with postmenopausal bleeding what is common symptom. Remaining 25% of endometrial cancers are perimenopausal or premenopausal patients. Endometrial cancers are classified into 2 histologic types. Type I consists of endometrioid carcinoma (EMC) and its histologic subvariants, encompasses about 85% of cases. Type II includes serous carcinoma (ESC), clear cell carcinoma, and carcinosarcoma, and accounts for approximately 10% of cases. Both types have biologically distinct disease entities, characterized by their divergent histologies, molecular genetics, tumorigenesis, and clinical behavior [2, 3]. ESC has a higher propensity for lymphovascular invasion and intraperitoneal as well as extra-abdominal spread than EMC that is the reason of more aggressive treatment which often consists of a combination of surgery, chemotherapy, and radiation therapy [4]. In general, most cases of ESC and EMC are readily differentiated from one another based on their distinct histologic features, growth patterns, and clinical presentation [5].

At the forefront of advance in personalized medicine of cancer, has recently been a gene expression profiling. The value of gene expression signatures was demonstrated for the prediction of tumor behavior in several types of cancer, distinguishing groups of patients with specific tumor grades and/or prognosis [6, 7]. Gene expression profiling is the analysis of the activity (the expression) of thousands of genes, in isolation or all at once, to create a global picture of biological functions. This technique allows the measure of the entire genome activity simultaneously in a particular cell or tissue or even organ. Several studies have aimed to detect and develop more applicable and improved markers for risk stratification for tailored treatment strategies. Several markers that could classify patients with endometrial cancer into low-risk, intermediate-risk, and high-risk groups have been suggested [8].

The molecular basis for endometrial carcinoma is only partially understood. Several molecular alterations are related to the distinction of both types of endometrial carcinoma. Type I is characterized by its association with obesity and other hyperoestrogenic risk factors, it is usually hormone receptor positive, diploid, microsatellite unstable, and related to KRAS or PTEN mutations. By contrast, the type II cancers are more prevalent among older women, and often aneuploid and with alterations in CDKN2A, TP53, and ERBB2 [9].
Currently used and perspective markers

In the current diagnostic practice is the most commonly used Cancer Antigen 125. It is a mucin glycoprotein present in all humans and present in mesothelial cells of the pleura, pericardium, peritoneum and Mullerian epithelium derivatives such as tubal, endometrial, and endocervical cells. CA 125 is the most reliable serum marker for ovarian cancer. Elevation of serum CA 125 has been detected in a number of physiological and pathological conditions associated with endometrial proliferation, including menstrual cycle, pregnancy, endometriosis and endometrial carcinoma [10]. In detail, raised CA 125 levels (>35 U/ml, independent predictor for poor survival [11]) have been reported in 11% - 33.9% of patients with endometrial cancer [12]. Ginath et al. found that 21.4% of 28 patients with endometrioid endometrial carcinoma had elevated serum CA 125, whereas the percentage of patients with positive tissue immunostaining for the antigen was 89.3%, which appeared to suggest the presence of mechanisms preventing the access of CA 125 into the circulation [13].

<table>
<thead>
<tr>
<th>GENE</th>
<th>FUNCTION</th>
<th>ALTERATION</th>
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<tbody>
<tr>
<td>CDKN2A (cyclin-dependent kinase inhibitor 2A) [23]</td>
<td>tumor suppressor protein</td>
<td>Overexpression, mostly serous type aggressiveness</td>
</tr>
<tr>
<td>MIB-1 (Mindbomb E3 Ubiquitin Protein Ligase 1) [23]</td>
<td>positively regulates Notch signaling</td>
<td>Overexpression, mostly serous type aggressiveness</td>
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<tr>
<td>p53 (cellular tumor antigen p53) [23]</td>
<td>tumor suppressor protein</td>
<td>Increased mutations with poor prognosis</td>
</tr>
<tr>
<td>HER2 (Receptor tyrosine-protein kinase erbB-2) [24]</td>
<td>proto oncogene</td>
<td>Overexpression, type 2 cancers</td>
</tr>
<tr>
<td>EGFR (Epidermal growth factor receptor) [25]</td>
<td>growth factor receptor</td>
<td>Overexpression, type 1 cancers</td>
</tr>
<tr>
<td>VEGF-A/VEGFR-2/3 (Vascular endothelial growth factor/receptor) [26]</td>
<td>growth factor receptor</td>
<td>Overexpression, useful for staging of EC</td>
</tr>
<tr>
<td>PTEN (Phosphatase and tensin homolog) [27]</td>
<td>tumor suppressor</td>
<td>Mutations, loss of function</td>
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<tr>
<td>hMLH1 (MutL homolog 1) [28]</td>
<td>DNA repair</td>
<td>Inactivation by methylation</td>
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<tr>
<td>APC (Adenomatous polyposis coli) [29]</td>
<td>tumor suppressor</td>
<td>Methylitation</td>
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<tr>
<td>RASSF1A (Ras association domain-containing protein 1) [30]</td>
<td>tumor suppressor</td>
<td>Methylitation</td>
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<tr>
<td>E-cadherin (epithelial cadherin) [31]</td>
<td>cell adhesion protein</td>
<td>Methylitation</td>
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<tr>
<td>EPHA 2 (ephrin type-A receptor 2) [32]</td>
<td>tyrosine kinase receptor</td>
<td>Overexpression</td>
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<tr>
<td>Claudin ¾ [33]</td>
<td>component of the tight junctions</td>
<td>Overexpression, mostly serous type aggressiveness</td>
</tr>
<tr>
<td>K-Ras (V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog) [34]</td>
<td>proto oncogene</td>
<td>Overexpression</td>
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<tr>
<td>MSLN (Mesothelin) [35]</td>
<td>megakaryocyte potentiating factor</td>
<td>Overexpression</td>
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<tr>
<td>Trop-2 (Tumor-associated calcium signal transducer 2) [36]</td>
<td>oncogene</td>
<td>Overexpression</td>
</tr>
<tr>
<td>Beta-catenin [37]</td>
<td>Proto oncogene</td>
<td>Mutations, loss of function</td>
</tr>
<tr>
<td>miR-194 [38]</td>
<td>Regulatory miRNA</td>
<td>Low expression related to poor prognosis, mostly type 1 cancers</td>
</tr>
<tr>
<td>miR-125b [39]</td>
<td>Regulatory miRNA</td>
<td>Overexpression, mostly type 2 cancers</td>
</tr>
<tr>
<td>miR-34a [40]</td>
<td>Regulatory miRNA</td>
<td>Overexpression</td>
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<tr>
<td>miR-218 [41]</td>
<td>Regulatory miRNA</td>
<td>Overexpression</td>
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<tr>
<td>miR-888 [42]</td>
<td>Regulatory miRNA</td>
<td>Overexpression</td>
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<tr>
<td>miR-205 [22]</td>
<td>Regulatory miRNA</td>
<td>Overexpression</td>
</tr>
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Table 1. The list of perspective markers for detection and progression monitoring of endometrial carcinoma
HIF-2α - Hypoxia-Inducible Factor 1α, Ki-67, VEGF, EGFR, and HER2, EZH2, tumor markers such as SCC, TPA, TPS and CYFRA 21-1, and M-CSF. From the large miRNA family was as a primary diagnostic marker confirmed miR-205 [22]. The brief summary of perspective biomarkers is in Table 1.

CONCLUSION

Advances in understanding of neoplastic progression at a cellular and molecular level have augmented the interest for molecularly based individualized therapy for patients with endometrial cancer. In this mini review we summarized the present knowledge regarding recently used biomarkers for personalized detection of endometrial carcinoma, considering how such markers could be used for clinical challenges in the handling of this disease. The ability to target surgical and systemic therapies to well selected patient populations, will increase the likelihood of benefits and diminish side effects related to treatment.

CONFLICT OF INTEREST

The author declares no competing interests.

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Review


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