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Original Articles

Molecular factors in endometrial cancer

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Summary

Endometrial cancers (EC) can be assigned to two groups that differ in epidemiology, clinical course, and prognosis. Type I EC is diagnosed in 80% of all patients with EC, the majority of whom suffer from metabolic syndrome. Type I EC manifests a slow course with a favorable prognosis and demonstrates hormonal receptors for estrogens and progesterone, mutations in the suppressor *PTEN* gene and the PI3K/Akt signaling pathway, K-ras, β-catenin, *MMR,* and in *ARID1A*. The more aggressive, though less common Type II EC, is associated with several histological types: serous, light cell, and low differentiated carcinomas. Mutations occur in p53, HER2/neu, E-cadherin, and in ERα, which has a poor prognosis. In 2013, four groups of EC were distinguished on the basis of molecular alterations. Studies continue on associating histopathological and molecular alterations in various types of cancer to distinguish the group with the poorest outcome in order to precisely determine prognosis in EC.

Key words: Endometrial carcinomas type I and II; Gene mutations; Genome atlas.

Introduction

Incidence of endometrial cancer (EC) accounts for 6.2% of all incidences of malignant tumours in women worldwide, but epidemiological data of the last decade show an upward trend. Though the cancer tends to be diagnosed in older women, it is increasingly encountered in women under the age of 45 [1, 2].

In 1983, Bokhman was the first to distinguish two types of EC, differing in etiology, clinical course, and prognosis [3]. EC is currently thought as an even more heterogenous disease involving numerous variables, including life style. Molecular factors and related genetic disturbances further support this dichotomic division [4-6].

Endometrial cancer Type I

Type I endometrial cancer, diagnosed in 80% women with EC, is associated with unbalanced estrogen stimulation, it manifests a slow course, favorable prognosis, and has the following typical molecular traits:

1) Estrogen receptor (ER) and progesterone (P) receptor-positive, the expression of which decreases with FIGO advancement stage and histological maturity grading (G). In type II, EC receptors for estrogens are detected in a lower proportion of cases. The profile of ER and P isoform expression may serve as an additional parameter in histological evaluation of EC [7, 8].

2) Mutation in *PTEN* is present in 30-83% cases of EC. *PTEN* is a suppressor gene participating in cell cycle control and apoptosis through its interaction on the PI3K/AKT signaling pathway. Mutation in the gene takes place at the early stage of carcinogenesis and it is linked to the absence of inhibition of the PI3K/AKT signaling pathway, resulting in an excessive cellular proliferation and disturbances in apoptosis [7, 9, 10].

3) Phosphatidylinositol kinase 3 (PIK3CA) is a lipid kinase. It contains two subunits: controlling and catalytical. Through phosphorylation and activation of apoptosis-inhibiting *Akt* protein, it promotes protein synthesis and cellular proliferation, promoting progression of the cancer. Mutation in PIK3CA has been detected in 68% cases of type I EC [10, 11].

4) K-ras is a proto-oncogene involved in cell cycle control. Its mutation represents an early event in the development of type I EC and it is detected in 15% endometrial hyperplasias with atypia and in 30% cases of EC. K-ras mutation is also linked to cancer progression [7, 9].

5) β-catenin represents the protein coded by *CTNNB1* gene and plays a key role in the *Wnt* signaling pathway. Activation of this pathway takes place through several mechanisms; the WNT/β-catenin complex controls, i.e., c-myc oncogene and cyclin D_1, which results in the intensification of cell proliferation, inhibition of apoptosis, enhanced cell motility, and cancer invasiveness [9, 10].

6) Mutations in mismatch repair (*MMR),* as seen in Lynch Syndrome, are detected in 3-5% cases of EC. The lifetime risk of developing type I EC amounts to 40-60%. The most pronounced risk is linked to mutation in *MSH2*

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(40%), followed by mutations in *MLH1* (27%) and MSH6 (26%) [12, 13]. In women with Lynch syndrome identified by genetic screening, precancerous condition and cancer can be detected earlier, which is linked to a better prognosis [7, 14].

7) *ARID1A* – mutation in the suppressor gene affects the expression of several genes (MLH, PIK3/Akt, CDKN1A). It is detected in endometriosis and endometrioid ovarian cancer. In type I EC it is linked to the early development of cancer, and to precancerous hyperplasia of EC. A link between *ARID1A* mutation and satellite instability detected in *MLH1* gene silencing in endometrial cancer has been demonstrated.

Endometrial cancer Type II

Type II (non-endometrioid) cancer manifests high biological aggressiveness and poorer clinical course [11, 15]. The group includes serous, light cell, and low differentiated cancers. Uterine serous carcinoma (USC) in particular should be treated as a separate morbid unit. USC, similarly to ovarian cancer, is potentially linked to *BRCA1* mutation. Genotyping of *BRCA1* mutations revealed over 25% of women carried *BRCA1* mutations. If this were so in at least a proportion of USC cases, it would influence prophylactic (adnexectomy) treatment and therapeutic application (use of PARP inhibitors) [16-20]

EC type II contains the following molecular alterations:

1) Mutation in the p53 suppressor gene occurs in 80-93% of cancers (and also in around 30% of type I ECs). This gene controls cell cycle, is responsible for the DNA synthesis and repair, and directs the injured cells towards apoptosis.The presence of mutated p53 is linked to low histological maturity of EC, higher clinical advancement, presence of metastases, and a less favorable prognosis [16, 17].

2) HER2/neu, the product of *c-erbB2* gene, belongs to the family of epidermal growth factor receptor (EGFR), kinases responsible for the control of cellular pathways involved in cell proliferation, their differentiation, and apoptosis. It is evaluated that such disturbance of amplification type is present in 18-67% of type II ECs. Overexpression of HER correlates with lower total survival and higher cancer aggressiveness, simultaneous overexpression of hormonal receptors (ER and P) in serous cancer is linked to better prognosis [9, 21].

3) E-cadherin is an adhesion protein responsible for cell adherence. Through catenins, and also adhesion proteins, it is linked to cytoskeleton elements of neighboring cells, forming integral complexes. In 57-73% of type II EC, it undergoes mutation, which weakens cell adherence, promoting cell movement, and development of metastases. It is associated with poorer prognosis [9, 22].

4) Although the expression of ER was described in type I EC, its presence has also been demonstrated in USC. Overexpression of ERα occurred in advanced stages of the cancer together with the p53 mutation, and is linked to poorer prognosis and indicates the dissemination of lesions outside of the uterus [23].

In 2013, classification of EC was published based on genomic analysis. The distinction of four subtypes of endometrial cancer was based on a study involving 307 cases of type I EC and 66 cases of type II EC [24]. The four types are as follows: 1) super-metastatic group with high frequency of mutations and a unique spectrum of nucleotides (POLE group – replication and repair of DNA),2) a pronouncedly mutated group with microsatellite instability, mainly with methylation of MLH1 promoter, 3) a group of low frequency mutations that also includes cancer with microsatellite instability. This group involves likewise cancers with p53 mutation, and 4) a group of serous-resembling cancers with low frequencies of mutations and numerous alterations in gene copy numbers.

Discussions continue related to clinical aspects, and to pathological and specific molecular alterations, aiming to identify the group of EC cancers with the worst prognosis during their course.

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