Review

Endometrial Carcinogenesis

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ABSTRACT Endometrial cancer is among the three most common cancers in females in many industrialized countries. Currently, two different pathways are distinguished for tumorigenesis of sporadic endometrial carcinoma. Type I, those with endometrioid histology, are associated with unopposed estrogen exposure and are often preceded by premalignant disease. In contrast, type II endometrial cancers have nonendometrioid histology (usually papillary serous or clear cell) with an aggressive clinical course. Hormonal risk factors have not been identified, and there is no readily observed premalignant phase. The morphologic and clinical differences are paralleled by genetic distinctions, in that type I and II cancers carry mutations of independent sets of genes. The morphologic differences in these cancers are mirrored in their molecular genetic profile with type I showing defects in DNA-mismatch repair and mutations in PTEN, K-ras, and beta-catenin, and type II showing aneuploidy and p53 mutations.

KEY WORDS *endometrial carcinoma, carcinogenesis, estrogens*

Introduction

Endometrial adenocarcinoma may be classified in dichotomic genotypic types, defined by the polarized frequency of the inactivity of the specific genes. The genetic model of the endometrial carcinogenesis is based on the dual evolution of the endometroid (type 1) and non-endometroid (type 2) subtypes (14).

Most of the endometrial carcinomas included under type I- endometroid, have as fundamental mechanism of the carcinogenesis, estrogen-dependency. Histologically, they present endometroid differentiation, hormonal receptors for estrogen and progesterone, law aggression and a better prognosis.

Genesis follows a nonhormonal mechanism for approximately 20% of the endometrial carcinomas, appearing from the atrophic endometrium of the women who are usually at menopause. The behavior of these carcinomas included under type II is more aggressive through the lack of hormonal receptors and of the compliance to the treatment. They present a non endometrial differentiation, a serous one most of the times.The dualistic model has been later expended by including the aspects of molecular biology.

The classical way of the endometrial carcinogenesis (type I)

The genesis of the endometrial carcinomas follows a multistadial classical mutational model which has its correspondence in the histopathological changes.

Endometrial carcinoma appears and develops in tight connection to the plasmatic and tissular levels of the sex steroids and their receptors, knowing its relation with the atypical endometrial hyperplasia associated to one prolonged estrogen stimulus of endogen or exogen origin, nonbalanced by the progesteron (3).

The hormonal levels reflect the multiple interrelational processes including the exposure, the catabolism and the excretion which also reflect the functional activity of the metabolic specific enzymes into the uterus , liver and other organs (1, 12). This process has a tridimensional aspect through the fact that the estrogenic imbalance may be systemic or local, having the endometrium as a common point.

The biological basis of this role of the estrogens and that of other steroid hormones is represented by the differentiated control of the genetic expression and by the stimulation of the uterine epithelial cells through various mechanisms of the critical genes for the cycle of the cell (2, 19).

The estrogen on one hand, may be tied to the estrogenic nuclear receptors, initiating thus the genetic expression; on the other hand, its bound with the plasmatic receptors, stimulating cellular proliferation (20).

Induced- estrogen carcinogenesis implies the induction of cathepsin-D estrogen-mediated and of the perioxidase, cellular reparatory proliferation, aneuploidia, proto-oncogenes and the expression of the suppressor genes such as the amplification of c-myc (6, 7, 11, 9, 10). The prolonged hyper

expression of the genes of the primary estrogenic answer such as c-fos and c-myc is suspected for generating the inducted genomic instability of estrogen (9), which is a mechanism of activating these genes into transforming oncogenes. It is supposed that tumors grow starting from a distinct layer of growing cells which overexpress c-fos, c-myc and c-jun and other genes of the primary estrogenic answer (6, 7).

Carcinogenesis implies genetic levels which compromise the integrity of the genetic material such as: smooth changes of the sequences of basis through substitution, omission or insertions, alterations in the number of chromosomes such as losing or obtaining whole chromosomes, chromosomal translocations or genetic amplifications.

Some data from the literature underline the fact that the role of the estrogen in tumorigenesis do not limit just to the stimulation of the proliferation but also by damaging and modifying the DNA (21). Experimental data suggest the fact that p450, CYP 1B1 (both belongs to the cytochrome P450 superfamily) enzyme which is largely distributed in many human organs may transform the estrogens into 4-hydroxy catecoli which may damage the DNA. In conclusion, the high levels of intratissular estrogen may, theoretically, promote carcinogenesis through two mechanisms: by damaging the DNA and by stimulating proliferation (13).

Histopathological examination suggest the fact that grade III endometrial adenocarcinomas develop from the grade I carcinomas under the influence of clonal evolution and differentiation. This process of tumoral progression may be associated with the loss of hormonal receptors and mutation p53.

Identifying the microsatellite instability in the atypic glandular hyperplasia associated to the endometroid carcinomas but not in the atypic glandular hyperplasia without carcinoma association, suggests that errors of the genetic repairing of mechanisms may take place in the transition from one lesion to another (12, 22).

The factors related to the acquisition by the endometrial hyperplasia of the atypia are not completely studied, but some data suggest that atypic glandular hyperplasia has common characteristics with the carcinoma, characteristics which are not seen in the glandular hyperplasia without atypia. Atypic glandular hyperplasia is represented under the form of a clone lesion associated with microsatellitic instability in *ras* and PTEN (phosphatase and tensin homolog) (16). Additionally, cells of the disputed histogenesis, known as "foam cells", are frequently found in the carcinoma and its benign predecessors and they may be involved in tumorigenesis through the production of inflammatory mediators which stimulate the production of aromathasis and proliferation.

Molecular Carcinogenesis

Endometroid carcinoma is characterized by a variety of genetic alterations, especially of those which codify the proteins responsible for intercellular adhesion and signalization.

The most important alterated gene involved in carcinogenesis is the PTEN gene. It is situated on chromosome 10 and it codes a protein with tyrosine-kinasic function. This type of mutation represents the most frequent molecular event described so far in the uterine carcinomas, the loss of PTEN expression appearing in approximately 2/3. PTEN mutations have been associated with favorable histopathological features for the endometrial carcinoma: low level, the lack of miometrial invasion, the predominance of the endometroid type. One of the earliest changes which can be demonstrated in the endometrial carcinogenesis is represented by the presence of the PTEN-negative glandular structures at the part of the endometrium exposed to estrogens. This fact may orient the progression of neoplasia and prognosis.

Microsatellite instability is another aspect involved in carcinogenesis which is due to the inactivation of the MLH1 and MSH2 (DNA mismatch repair proteins) reparatory cells. Due to the fact that microsatellite instability is rarely met in the case of endometrial hyperplasia which did not progress towards the endometrial carcinoma, we may consider that it represents a late case in the transition from the hyperplasia to carcinoma. These considerations may be used in differentiating hyperplasia with complex atypia from the early endometrial carcinoma.

β – catenine is crucial for the intercellular adhesion through the complex it fulfills with E-cadherine.

E cadherine has an essential role in the intercellular adhesion as well as for establishing the cellular polarity, glandular differentiation and layering. It concentrates the plasminogen and the receptor of the factor of epidermal growing towards the cellular surfaces.

The low expression of the E-cadherine is associated with the loss of the forces of intercellular adhesion, thus representing a first phase of the cellular motility, a characteristic specific to the cellular lines containing a potential.

Negative E –cadherine tumors have a high aggression, early metastasis and low ling rate (4).

Gene p53 acts at cellular level as well as at the level of the whole organism. As far as the normal endometrial cells are concerned, gene p53 acts under „stress" conditions which endangers the integrity of the cellular genetic material. Delaying the cells towards the "S" phase, gene p53 facilitates the repair of the lesions of the DNA and , if these lesions remain unrepaired, they direct the cell towards apoptosis. At the level of the normal endometrial cells, p53 does not participate in the growing and cellular development processes, but it fulfills the important function of inhibition of the tumoral growing. The allelic losses of the p53 are, in general, late events, produced after the pressure produced by the conditions of cellular stress selected cells carrying mutations. Even the simple reduction to half of the quantity of normal p53 may be enough so as to abolish the biological effects.

The loss of the intrinsic function of inhibition of the tumoral growth, will allow these cells unlimited proliferation. These effects of the inactivation of gene p53 will accelerate the development of the tumor which shall acquire metastasis potential.

Alternative way (type II)

The histological support of an alternative way of endometrial carcinogenesis unrelated to the hormonal disturbances derives from the clinic-pathological studies of the serous carcinoma. Serous carcinoma and the one from clear cells normally develops at elder women with an atrophic endometrium (5). The risk factors for the serous carcinoma have not been identified , but the record suggests that the high levels of estrogens does not represent a risk factor for the development of serous tumors. The age is seen as the only risk factor, while the serous carcinomas are usually diagnosed in women elder than 60 years old and very rarely in younger women (17).

The examination of factors which seem to be associated with p53 mutations may be one experimental solution for discovering the genesis of this tumor. The detection of mutations of p53 gene in most of the serous carcinomas and in their predecessors, EIC suggests the fact that the mutations of p53 gene represent the molecular signature and possibly define this entity with morphology (18, 13).

The distinct particularity which differentiates the serous carcinoma from the endometroid carcinoma is represented by the fact that inside the serous carcinoma, a well- differentiated architecture defined as a conglomeration of glands and papilles is usually accompanied by a high level of the nuclear atypia, while inside the endometrial carcinoma, the architectural degree and the nuclear one are almost all the time concordant. Due to the fact that all the serous carcinomas are through definition highly differentiated, their grading represents a surplus and, as compared to the endometrial carcinomas, the depth of the myometrial invasion does not reflect objectively the stage of the tumor. Tumors with mixed differentiation, where 25% of the neoplasma belong to the serous carcinoma, usually behave as aggressive as a pure serous carcinoma; consecutively, these tumors will be considered as serous carcinomas from clinical considerations.

Molecular changes in serous carcinomas and with clear cells (type II)

The most striking genetic alteration, present in about 90% of serous carcinoma, is p53 mutation. Microsatellite instability is extremely rare as well as PTEN and K-ras (Kirsten rat sarcoma viral oncogene homolog) mutations, aspects which are specific to the endometroid carcinomas. Moreover, the reduced expression of the E-cadherine appears in over 60% of the serous carcinomas. Alterations of β- catenine expression are rarely seen in this type of cancer. The carcinoma with clear cells has rarely been studied all by itself due to its low incidence. P53 mutation is inconstantly noticed in carcinomas with clear ovarian cells comparatively to other histological variants. It may be considered that the pathogenesis of carcinomas with clear cells of the genital tract has an own mechanism of making its appearance (4, 8).

Another genetic alteration found in the nonendometroid carcinogenesis is the inactivation of p 16 gene and the superexpression HER2/neu (Human Epidermal growth factor Receptor 2). The suppressor tumoral gene p16 is localized on chromosome 9p21 and encodes a regulatory protein of the cellular cycle. HER2/neu is an oncogenes which encodes a tirozin-kinazic transmembranary receptor implicated in the cellular signalization (15).

Conclusions

For the most part, the dichotomous classification of endometrial cancers holds up to genetic analysis and the histologic subtypes are underscored by systematic changes in a limited set of genes.With the aid of molecular studies,

knowledge of the pathogenesis of endometrial cancer has extensively broadened over the last decade. Nevertheless, an enormous amount of work remains to be done to clearly understand the biologic processes behind the development of this disease.

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