MOLECULAR CARCINOGENESIS OF ENDOMETRIAL CANCER

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SUMMARY

In 1983, Bokhman proposed a dualistic model of endometrial tumorigenesis based on the clinical observations and clinicopathologic correlations. The majority of endometrial cancers (approximately 70–80%), designated as type I carcinomas, follow the estrogen-related pathway. Histologically, most of the type I tumors seem to arise in the background of hyperplastic endometrium, show an endometrioid differentiation, and are of low grade. Clinically, they are overall characterized by a favorable behavior. Another 10–20% of endometrial cancers, designated as type II carcinomas, follow the estrogen-unrelated pathway and arise in the background of atrophic endometrium. Type II tumors usually occur at an older age, approximately 5–10 years later than type I tumors. They are typically high-grade carcinomas of nonendometrioid differentiation, most frequently serous, less frequently clear cell. Type II carcinomas behave as an aggressive clinical course and poor prognosis. This dualistic model was subsequently supported by the molecular studies, approximately a decade later. At present, endometrioid and serous carcinoma, which represent the major phenotypes of types I and II endometrial carcinomas, respectively, are characterized by distinctive types of genetic instability and molecular alterations. In endometrioid (type I) carcinoma, four major genetic changes are responsible for the tumorigenesis, i.e. silencing of PTEN tumor suppressor gene, presence of microsatellite instability due to alterations of the mismatch repair genes, mutation of K-ras protooncogene, and alteration of β-catenin gene. On the other hand, p53 mutation and overexpression of Her2/neu oncogene are two major genetic alterations in serous and clear cell (type II) carcinomas. However, like in any model, there is evidence for exceptions. Many endometrial carcinomas are in the gray zone with overlapping clinical, morphologic, immunohistochemical, and molecular features of types I and II endometrial cancers. Finally, a small group of endometrial carcinoma is noted to be hereditary. It is known as the most common extracolonic malignancy in hereditary nonpolyposis colorectal cancer (Lynch syndrome), an autosomal dominantly inherited disorder of cancer susceptibility. Inactivation of the mismatch repair genes MSH2 and MSH6 seems to play a central role in the tumorigenesis. [*Taiwanese J Obstet Gynecol* 2007;46(1):26–32]

Key Words: carcinogenesis, endometrial carcinoma, genetic alteration

Introduction

Endometrial cancer is among the three most common cancers in females in many industrialized countries. Known risk factors for this disease include obesity, hypertension, diabetes mellitus, late menopause, and exogenous estrogen use. Most of endometrial cancers are sporadic, but it has been estimated that 5% of patients with endometrial cancers diagnosed at age younger than 55 years have a family history of this cancer, i.e. hereditary origin [1].

Currently, two different pathways are distinguished for tumorigenesis of sporadic endometrial carcinoma. This dualistic model of endometrial tumorigenesis is based on a hypothesis by Bokhman in 1983 [2], according solely to clinical observations and clinicopathologic correlations. The majority of sporadic endometrial carcinomas (at least approximately 70–80%), designated as

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type I carcinomas, follow the estrogen-related pathway. They seem to arise in the background of unopposed estrogenic stimulation [3], since they are associated with endometrial hyperplasia, express estrogen (ER) and progesterone receptors (PR) [4]. Histologically, most of the type I tumors show endometrioid differentiation and are of low grade. The rare mucinous adenocarcinomas are also considered type I carcinomas, since they usually express ER and/or PR and are of low histopathologic grade. Clinically, type I carcinomas are overall characterized by a favorable behavior.

About 10–20% of sporadic endometrial carcinomas, designated as type II carcinomas, follow the estrogen-unrelated pathway and arise in the background of atrophic endometrium [5]. ER and PR expression in these tumors is usually negative or weakly positive. Type II tumors usually occur at an older age, approximately 5–10 years later than type I tumors. They are typically high-grade carcinomas of nonendometrioid differentiation, most frequently serous, less frequently clear cell. Both serous and clear cell carcinomas are frequently associated with endometrial intraepithelial carcinoma (EIC), which is considered the putative precursor for these tumors [6,7]. Type II carcinomas are characterized by an aggressive clinical course and poor prognosis. The clinical and pathologic features of these two types of endometrial cancer are summarized in Table 1.

The dualistic model was subsequently broadened by the inclusion of molecular aspects, approximately a decade later. At present, endometrioid and serous carcinoma, which represent the major phenotypes of types I and II endometrial carcinomas, respectively, are characterized by distinctive types of genetic instability and molecular alterations. However, like in any model, there is evidence for exceptions. For instance, a subset of low-grade endometrioid carcinoma with ER and PR expression, clearly type I carcinoma, occurs unrelated to estrogen in the background of atrophic endometrium. On the other hand, it has been shown that an occasional papillary serous carcinoma may develop from a preexisting endometrioid carcinoma as a result of tumor progression. These tumors may share the pathologic and molecular features of types I and II endometrial cancers. Therefore, in daily practice many endometrial carcinomas are in the gray zone with overlapping clinical, morphologic, immunohistochemical, and molecular features.

Molecular Genetic Alterations in Endometrioid (Type I) Carcinoma

Endometrioid carcinoma is characterized by a variety of genetic alterations, in particular, those affecting proteins bound to the cell membrane and responsible for cell adhesion and signaling transduction. Currently, the most frequently altered gene in endometrioid carcinoma is PTEN, which is located on chromosome 10 and codes for a protein with tyrosine kinase function [8]. The PTEN protein has both lipid and protein phosphatase activity. The lipid phosphatase activity may cause arrest of cell-cycle progression at G1/S, mediated at least partially through the upregulation of the cyclin-dependent kinase inhibitor p27. In addition, agonist-induced apoptosis is mediated by PTEN through the upregulation of proapoptotic machinery, involving caspases and BID, and the downregulation of antiapoptotic proteins, such as Bcl2. The protein phosphatase activity of PTEN is involved in the inhibition of focal adhesion formations, cell spreading, and migration, as well as the inhibition of growth factor-stimulated MAPK signaling. Therefore, the combination of the losses of PTEN lipid and protein phosphatase activity may result in aberrant cell growth and an escape from apoptosis, as well as abnormal cell spreading and migration [9]. Up to 83% of endometrioid carcinomas and 55% of precancerous lesions reveal altered PTEN, characterized by loss of expression [10]. Therefore, loss of PTEN function is an early event in endometrial tumorigenesis that may occur in response to known endocrine risk factors and offers an informative immunohistochemical biomarker for premalignant disease. The underlying genetic alteration in cases with lost PTEN expression and function is mostly

Table 1. Two types of clinicopathologic features of endometrial carcinoma

	Type 1	Type 2
Incidence	80%	≤ 20%
Age	Pre-/perimenopausal	> 60 yr
Histology	Endometrioid	Serous, clear
Cell differentiation	Low grade	High grade
Precursor lesion	Hyperplastic EM	Atrophic EM
Estrogen stimulation	Related	Unrelated
Clinical behavior	Indolent	Aggressive

mutation and, less frequently, loss of heterozygosity (LOH) without mutation [10]. However, promoter methylation was found in about 20% of tumors with altered PTEN, most of which were high-stage diseases [11]. Inactivation of PTEN caused by mutation is associated with early stage and favorable survival [12]. The 5-year survival rate is about 80% in those with mutations compared with 50% in those lacking mutations [12].

Microsatellite instability (MI) is another important genetic alteration in endometrioid carcinoma and its variants [13,14], occurring in about 20–45% of tumors [15]. It is characterized by minor genetic alterations, in particular, frame-shift mutations in repetitive DNA sequences of the genome. Inactivation of the mismatch repair gene MLH1 by methylation of the promoter seems to be the most frequent cause of MI in sporadic endometrioid carcinomas [16,17], followed by loss of expression of another two mismatch repair genes MSH2 and MSH6 [18,19]. The mechanism for inactivation of MSH2 is still not clear, since promoter methylation and mutations are rare [16,20]. MSH6 inactivation seems to be almost always caused by mutation [21]. MI is associated with PTEN mutation, absence of p53 overexpression, and a favorable outcome. The 5-year survival rate of those with MI is 77% compared with 48% of negative MI cases [22].

K-ras protooncogene encodes for a small inner plasma cellular membrane GTPase, functioning as a molecular switch during cell signaling, and it is largely related to tumor growth and differentiation. Constitutively activating mutations of the K-ras protooncogene are present in about 10–30% of endometrioid carcinomas [23]. They are predominantly found in exon 1 (codons 12 and 13) and rarely in exon 2 (codon 61) [24]. The presence of K-ras mutations in 16% of the cases of endometrial hyperplasia indicates that K-ras mutations may represent an early event within a subset of endometrial carcinoma [25]. K-ras mutations have been found more frequently in MI tumors, suggesting that both events may occur simultaneously before clonal expansion [26]. In contrast, K-ras and PTEN mutations do not seem to concur within the same tumor [27].

β-catenin mutation is present in about 20% of endometrioid carcinomas [28]. β-catenin gene is crucial in cell–cell adhesion through a complex with E-cadherin. In addition, it is an important member for the signal transduction pathway (Wnt), which is required for adult tissue maintenance, and perturbations in Wnt signaling promote both human degenerative disease and cancer [29]. The function of β-catenin in endometrioid tumorigenesis is still unknown; no correlation to MI, K-ras, or PTEN mutations have been found, suggesting that the Wnt pathway may play an independent role in endometrial cancer [30].

E-cadherin is a transmembrane protein with five extracellular domains and an intracellular domain that connects to the actin cytoskeleton through a complex with the cytoplasmic catenin. Decreased E-cadherin expression is associated with a loss of cell–cell cohesive forces and has been shown to precede tumor cell motility—a characteristic of tumor cell lines with high metastatic potential [31,32]. Decreased expression of E-cadherin is found in about 5–40% of endometrioid carcinoma. E-cadherin negative tumors are more likely to be poorly differentiated or nonendometrioid, and are associated with poorer outcome [33–35].

p16 is a tumor suppressor gene located on chromosome 9p21. It encodes for a cell cycle regulatory protein and inactivation of the p16 gene can lead to uncontrolled cell growth. In a large population-based study, loss of p16 expression was found in less than 10% of endometrioid carcinoma [36]. The underlying mechanism of altered p16 expression is not clear, since neither methylation nor deletion or mutation is frequently found [37–40]. Loss of p16 expression is correlated with K-ras and p53 mutations and is associated with high stage, high grading, nonendometrioid tumors, and poor survival [40].

p53 mutations were found in a subset of approximately 10–20% of endometrioid carcinomas, which were mostly grade 3 [41]. Grade 1 carcinomas and atypical hyperplasia seem to lack mutant p53. p53 mutations are almost always associated with aneuploidy and do not seem to concur with PTEN mutations in the same tumor [42].

Her2/neu oncogene codes for a transmembrane receptor tyrosine kinase involved in cell signaling. Overexpression of Her2/neu seems to play a role in 10–30% of grades 2 and 3 endometrioid adenocarcinomas [43,44]. Therefore, mutations in p53 and the amplification and overexpression of Her2/neu characterize late events during progression and the dedifferentiation of endometrioid carcinoma [41]. Both alterations are associated with high grade, advanced disease, and poor prognosis. Alternatively, these later molecular alterations might also be early events in *de novo*, occurring in poorly differentiated endometrioid carcinomas and those serous carcinomas developing from endometrioid carcinomas, based on findings from mixed endometrioid and serous carcinomas [45], where MI is a rare event, as are PTEN and K-ras mutations [46].

KAI1 is a metastasis suppressor gene located on human chromosome 11p11.2. It is a member of the structurally distinct family of cell surface glycoprotein, transmembrane 4 protein superfamily. KAI1 was initially

isolated as a gene that suppressed metastasis of prostate cancer [47]. In our study, downregulation but no mutation of KAI1 was found during the progression of endometrial cancer, in which most of the studied cases were endometrioid carcinoma [48]. KAI1 was well expressed in endometrial hyperplasia but was progressively lost from early stage (27.8%) to metastatic tumors (71.4%). In addition, patients with KAI1-negative tumors had a lower survival rate than those with KAI1-positive or decreased tumors.

Smad4 is a member of the Smad proteins, which are needed for mediating signals of TGF-β from the cell surface to the nucleus. Smad4 is also a tumor suppressor gene for several cancers. Using immunohistochemical study we noted that Smad4 protein expression was decreased progressively with tumor grade [49]. Decreased Smad4 mRNA was also observed in the endometrioid carcinomas with myometrial infiltration [50].

Molecular Genetic Alterations in Serous and Clear Cell (Type II) Carcinoma

The most striking genetic alteration, present in about 90% of serous carcinoma, is p53 mutation [51]. It is still unresolved as to which carcinogenic influence causes these frequent p53 mutations. In contrast to endometrioid carcinoma, MI is extremely rare among serous carcinoma, as is K-ras and PTEN mutation [41,52,53]. Thus far, MI has only been detected in mixed endometrioid and serous carcinoma, but not in pure serous carcinomas [54]. Other genetic alterations that seem to occur more frequently in serous than in endometrioid carcinoma are inactivation of p16 and overexpression of Her2/neu as previous description. p16 inactivation was found in about 45% of serous carcinomas, including some clear cell carcinomas. Her2/neu overexpression and gene amplification were found in about 45% and 70% of serous carcinomas, respectively [55,56]. Furthermore, negative and reduced E-cadherin expression occurred in 62% and 87%, respectively, of serous and clear cell carcinomas [33,57]. However, alteration and overexpression of β-catenin are rare in serous carcinoma [30,58]. Clear cell carcinoma has rarely been studied alone because of the uncommon occurrence. Based on immunohistochemical results and mutational analysis, there was evidence that p53 alterations play a minor role compared with serous carcinoma [7,59]. Since p53 mutation was also infrequently observed in ovarian clear cell carcinoma comparing to the other epithelial subtypes [60], it is possible that the pathogenesis of clear cell carcinoma in the female genital tract arises from a unique pathway [61]. As in serous carcinoma, MI and PTEN inactivation are rarely found in clear cell carcinoma. K-ras mutation is also absent in this tumor.

Comparison of the major genetic alterations between types I and II endometrial carcinomas as analyzed on endometrioid and serous carcinomas, respectively, is seen in Table 2.

Progression Model for Endometrioid (Type I) Carcinoma

Most of the genetic alterations found in endometrioid carcinoma seem to occur very early in endometrioid tumorigenesis, although it is not clear which are associated with the earliest changes of malignant transformation and progression to neoplasia. In atypical hyperplasia, alterations of PTEN, β-catenin, K-ras, and MI are present, of which PTEN inactivation occurs in about 50% of the cases [10]. Methylation of MLH1 promoter was found in adjacent non-neoplastic endometrium of MI + endometrioid carcinoma [62]. In contrast, p53 mutations, amplification, and overexpression of Her2/neu and p16 inactivation are considered late events during progression and dedifferentiation

Table 2. Comparison of major genetic alterations between type I and type II endometrial carcinomas as analyzed on endometrioid and serous carcinomas

Genetic alteration	Type I carcinomas (%)	Type II carcinomas (%)
PTEN inactivation	50–80	10
Microsatellite instability	20–45	0–5
K-ras mutations	10–30	0–5
β-catenin mutations	20	0–5
p53 mutations	10–20	90
Her2/neu overexpression	10–30	45–80
p16 inactivation	10	40
E-cadherin alteration	10–20	80–90

of endometrioid carcinoma, since they are predominantly found in grade 3 tumors, rarely in grade 1 tumors and are absent in atypical endometrial hyperplasia [43]. On the other hand, it is hypothesized that p53 mutations and Her2/neu amplification might also be early events in *de novo* occurring poorly differentiated endometrioid carcinomas, detouring atypical hyperplasia and low-grade carcinoma on an alternative pathway.

Progression Model for Serous (Type II) Carcinoma

Mutations of p53 were found in about 80% of endometrial EIC, the putative precursor of serous carcinoma, but in contrast to most serous carcinoma, there is no LOH at the locus of p53. Thus, it was hypothesized that p53 mutation of one allele occurs early during the development of serous carcinoma's precursor, whereas loss of the normal second allele accompanies progression into serous carcinoma [51]. Another hypothesis is that serous carcinoma may develop from endometrioid carcinoma through p53 mutation based on findings in mixed endometrioid and serous carcinomas [45]. The alterations of E-cadherin, p16, and Her2/neu seem to occur during the progression from EIC to serous carcinoma. It is not clear whether other genetic alterations that are present in serous carcinoma occur early during tumorigenesis, since no analyses on EIC exist.

Molecular Genetic Alterations in Hereditary Endometrial Carcinoma

Endometrial carcinoma is the most common extracolonic malignancy in hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome), an autosomal dominantly inherited disorder of cancer susceptibility [63]. It was reported that the cumulative incidence of endometrial cancer in HNPCC was 20% by age 70, compared to 3% in the general population, and the highest risk years was between age 40 and 60 [64]. Therefore, endometrial cancer in HNPCC develops at a significant earlier age than in the general population. In addition, more than half of the cases had a second primary tumor and most of these cancers were colorectal cancers [65]. To date, the only known cause of HNPCC is an inherited mutation in one of the following mismatch repair genes: MLH1, MSH2, MSH6, PMS1, and PMS2 [66,67]. In endometrial carcinomas, however, inactivation of the MSH2/MSH6 complex seems to play a central role in tumorigenesis [68]. The endometrial carcinomas arising in HNPCC are related to type I tumors, since they occur at young age and are histologically of mucinous or endometrioid type [69], but their pathway is driven by germline mutations and is, thus, distinctive. In MSH2 mutaion carriers, a high MI status was already present in endometrial hyperplasia without atypia [70]. It is thus considered an early event during tumor development.

In addition to endometrial cancer arising from HNPCC, occasional families show clustering of endometrial cancer alone, without colon or other cancers. This group of endometrial cancer was termed as familial site-specific endometrial cancer [71]. One recent study investigated 23 such families and found that only two families (8.7%) had germline mutation in MSH6 and MSH2, respectively [72]. This finding suggests another as yet unknown etiology in most of the families with site-specific endometrial cancer.

Conclusion

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. Recently, using cDNA microarray technology, the differences in gene expression patterns between histologic types of endometrial cancer were identified. [73]. This comprehensive analysis of endometrial cancer may help us to understand differences in the biology and clinical outcome of the different histologic types. Further stratification of endometrial cancer subtypes according to their genetic alterations may improve prognostic impact and provide us with new targets for treatment.

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