Neuroendocrinology Letters Volume 36 No. 7 2015
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

REVIEW ARTICLE

New molecular aspects of endometrial carcinoma

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Submitted: 2015-08-26 Accepted: 2015-09-23 Published online: 2015-12-28

Key words: **endometrial carcinoma; DNA methylation; mismatch repair system; epigenetic changes; biomarkers**

Neuroendocrinol Lett 2015; **36**(7):638–643 **PMID:** 26859584 NEL360715R03

Abstract

Endometrial cancer is the most commonly diagnosed gynecological cancer and its incidence is increasing worldwide. The number of patients with this disease is likely to continue to grow, including younger patients. It is a complex disease driven by abnormal genetic and epigenetic alterations, as well as environmental factors. Many endometrial cancers show estrogen-dependent proliferation. The carcinogenic mechanisms are unknown or not completely explained beyond mutations of single oncogenes and tumor suppressor genes. Possible carcinogenic mechanisms include imbalance between endometrial proliferation by unopposed estrogen and the mismatch repair (MMR) system; rmethylation changes and mutation of genes. Epigenetic changes resulting in aberrant gene expression are dynamic and modifiable features of many cancer types. A significant epigenetic change is aberrant DNA methylation. In this review, we review evidence on the role of different changes in relation to endometrial carcinogenesis. Carcinogenic mechanisms of endometrial cancer involve both genetic and epigenetic changes. Determination of the detailed carcinogenic mechanisms will be useful for prevention and diagnosis of endometrial cancer, risk assessment, and development of new treatment strategies targeting genes.

INTRODUCTION

Endometrial carcinoma is the most common gynecologic malignancy, especially in high-income countries. It is the 4th most common cancer for women, with 42,160 new cases and 7,780 deaths occurring in the United States in 2009. More than 4000 women died from endometrial cancer in the USA in 2011 (Siegel *et al.* 2011). In Japan, the annual morbidity increased from 48 in the 20–30 years in 1975 to 478 in 2005 (Matsuda *et al.* 2012). The annual mortality per 100 000 population in Japan increased from 0.4 in 1975 to 3.2 in 2012 and the total morbidity increased from 229 to 2092 (Center for Cancer Control and Information Services 2013). The incidence of endometrial cancer is likely to continue to increase based on these recent trends. Discovering the causes of the increase and establishment of prophylactic measures and new therapeutic strategies requires an improved understanding of the carcinogenic mechanisms of endometrial cancer (Banno *et al.* 2014).

According to the estimation from National Cancer Institute, there will be around 52,630 new cases and 8,590 deaths from endometrial cancer in USA in 2014 (American Cancer Society 2014) , therefore the exploration of the mechanisms for carcinogenesis and development for cost-effective treatment approaches are important and urgent.

Based on differences in clinicopathological characteristics, there are two subtypes of endometrial carcinoma. Type I , endometrioid endometrial carcinoma, accounts for approximately 80% of cases. Commonly develops in premenopausal or perimenopausal women and occurs in an estrogendependent manner via atypical endometrial hyperplasia. This type is significantly related to a history of unopposed estrogen exposure or other hyperestrogenic risk factors. The tumor is positive for the estrogen and progesterone receptor, shows well-differentiated endometrioid adenocarcinoma, has a lower frequency of lymph node metastasis, shows little muscular invasion. This type often has a relatively favorable prognosis and most patients present with early-stage of the disease. In contrast, type II, non-endometrioid endometrial carcinoma, tends to develop in postmenopausal women in an estrogen-independent manner, and is thought to be due to de novo carcinogenesis that develops directly from the normal endometrium, rather than via endometrial hyperplasia or undiagnosed precancerous lesions. The tissue type is specific, including extremely poorly differentiated endometrioid adenocarcinoma and serous adenocarcinoma, and the prognosis is often poor. Patients with type II tumors are more likely to have metastasis and are at high risk of relapse (Banno *et al.* 2014; Metzger *et al.* 1995).

There have been identified multiple risk factors, such as age, obesity and postmenopausal hormone therapy, but the understanding of the etiologics of the two subtypes of endometrial cancer continues to evolve. Environmental factors, including estrogen, an abnormal mismatch repair (MMR) system, genetic abnormalities, and aberrant methylation of DNA are currently proposed as major mechanisms of carcinogenesis in endometrial cancer. This review focuses on the mechanisms of carcinogenesis in endometrial cancer that have recently emerged.

MOLECULAR BIOLOGY OF ENDOMETRIAL CANCER

Role of estrogen in carcinogenesis of endometrial cancer

Estrogen is a steroid hormone that promotes the development of female genitalia, including the endometrium, vagina, vulva and mammary gland. Estrogen passes through the cell membrane and binds to estrogen receptor in the cytoplasm. Estrogen receptor forms dimers and regulates gene expression via estrogen response elements in promoter regions of target genes.

Role of mismatch repair system

The mismatch repair (MMR) system is responsible for repairing base mismatches that arise during DNA replication. Typical MMR proteins include hMLH1, hMSH2, hPMS2, hMSH3 and hMSH6. Genes encoding these proteins are called MMR genes and aberrations in these genes prevent correct repair of mismatched bases, resulting in DNA strands with different lengths. This phenomenon occurs in microsatellite regions of the human genome and is referred to as microsatellite instability (MSI) (Hecht *et al.* 2006). Aberrations in MMR genes are involved in carcinogenesisof type I endometrial cancer. These aberrations are caused by epigenetic changes independent of the DNA sequence, that is, gene inactivation by aberrant hypermethylation of promoter regions. Such inactivation of MMR genes permits accumulation of gene mutations and leads to carcinogenesis. In endometrial cancer, carcinogenesis most frequently involves aberrant methylation of *hMLH1* and mutation of *hMLH1* is detected in 30% of cases. Mutations of *hMLH1* are also found in atypical endometrial hyperplasia, which suggests that *hMLH1* is implicated in the early stage of carcinogenesis (Muraki *et al.* 2009). MMR genes are also causative genes in Lynch syndrome (hereditary nonpolyposis colorectal cancer). Lynch syndrome is a typical familial tumor with autosomal dominant inheritance.

Miyamoto *et al.* suggested that mismatch repair (MMR) deficiency was the most important abnormality in early-stage endometrial cancer, and examined the correlation between MMR and estrogen. Expression of hMLH1 and hMSH2, which are important MMR proteins, was examined by immuno staining and showed a strong positive correlation with blood estrogen. MMR activity in endometrial epithelial cells *in vitro* also showed a dose-dependent increase with higher estrogen levels. This suggests that cancer is unlikely to occur in a high estrogen environment because increased cell

growth is paralleled by increased MMR activity. In contrast, hMLH1 and hMSH2 were absent or had extremely low expression at estrogen levels ranging from 20 to 60 pg/mL, but some cell growth still occurred. Therefore, cells dividing in a low-estrogenenvironment are more likely to accumulate genetic errors due to low repair activity and may be at high risk of carcinogenesis. Based on these results, Miyamoto*et al*. suggested that the incidence of growth-induced genetic errors should be low in young women with high estrogen levels and sufficient repair activity of MMR proteins, making carcinogenesis unlikely. In older women with lower estrogen but an atrophic endometrium, carcinogenesis would also be unlikely because of the absence of cell growth. However, under perimenopausal conditions, the carcinogenic risk would be increased because sufficient estrogen is present to promote cell division, but MMR activity is low. This intermediate status was defined as the cancer window.

Mutation of genes in carcinogenesis of endometrial carcinoma

It becomes clear that the initiation, progression and metastasis of endometrial cancer is similar to other gynecologic malignities like cervical cancer (Visnovsky *et al.* 2014; Kudela *et al.* 2014) and is controlled both by genetic and epigenetic events. Genetic alterations associated with endometrial cancer carcinogenesis involve several critical genetic events such as high frequent mutations of PTEN, K-RAS, P53 etc., these genetic changes result in interfering corresponding signaling pathways (for examples: PI3K/AKT/mTOR; WNT/β-catenin, MAPK/ERK). Thereafter the cells obtain the transforming capabilities to form the endometrial cancer phenotype (Ma *et al.* 2014).

Several gene mutations have emerged as candidates for roles in carcinogenesis of type I and II endometrial cancer , based on observation of the mutation in endometrial hyperplasia and at least a similar incidence of mutation in endometrial cancer. Different genes are involved in carcinogenesis of the two types of endometrial cancer. Gene mutations found in type I endometrial cancer include those in *PTEN*, *β-catenin* and *K-ras*. *PTEN* is a tumor suppressor gene on chromosome 10. PTEN protein induces apoptosis and carcinogenesis occurs in cells with *PTEN* mutation due to avoidance of apoptosis. *PTEN* mutations have been detected in 20–33% of cases of atypical endometrial hyperplasia and 33–50% of cases of endometrial cancer. *PTEN* appears to be involved in the early stage of carcinogenesis (Kanaya *et al.* 2005).

β-catenin (*CTNNB1*) mutations are found in 20–40% of cases of type I endometrial cancer (Schlosshauer *et al.* 2000). β-catenin is acomponent of E-cadherin, which has an important role in cell adhesion and is involved in the Wnt signaling pathway that regulates cell proliferation and differentiation. *β-catenin* mutations are also detected in atypical endometrial hyperplasia and are implicated in the early stage of carcinogenesis. The *K-ras* oncogene encodes a protein of 21 kDa that has a signaling function from activated membrane receptors in the MAPK pathway. If mutations occur, K-ras continuously functions as activated Ras and excessive signaling causes cell proliferation and induces carcinogenesis (Matias-Guiu *et al.* 2001). *K-ras* mutations have been detected in 6–16% of cases of endometrial hyperplasia and 10–31% cases of endometrial cancer (Tsuda *et al.* 1995). *K-ras* is involved in two stages of carcinogenesis- a shift from endometrial hyperplasia to endometrial cancer and invasive proliferation of well-differentiated tumor cells.

Mutations in type II endometrial cancer are linked to the oncogene *HER-2/neu* and tumor suppressor gene *p53*. *HER-2/neu* is a tyrosine kinase membrane receptor in the epidermal growth factor (EGF) receptor family. Mutations of this gene are also found in breast and ovarian cancers. *HER-2/neu* expression in endometrial cancer has a strong inverse correlation with differentiation. However, the incidence of gene amplification differs from 14% to 63% in all cancers and over expression of the protein ranges from 9% to 74% (Cianciulli at al. 2003). A *p53* gene mutation is the most frequent mutation in human cancer. Normal *p53* regulates cell proliferation, apoptosis induction and DNA repair. Point mutations in *p53* are found in 90% of cases of type II endometrial cancer, but in only 10–20% of cases of Grade 3 type I endometrial cancer. The incidence is low in endometrial hyperplasia and type I endometrial cancer of other grades (Sherman *et al.* 1995).

Epigenetic modifications

Epigenetics is widely studied in wide variety of gynecological malignities (Zubor *et al.* 2005, Visnovsky *et al.* 2013; Galo *et al.* 2005; Culbova *et al.* 2011). The genetic alterations (changes DNA sequences) have been extensively explored also in carcinogenesis of human endometrial cancer (Yeramian *et al.* 2013; Llobet *et al.* 2009), but these studies do not provide a reasonable explanation of why the gene sequences are not changed in many endometrial cancer cases. Increasing evidence from recent research shows that the epigenetic regulation for gene expression is critical for endometrial carcinogenesis (Sakuragi *et al.* 2009). The epigenetic modifications do not change DNA sequences, but alter the side chain groups of DNA base or histone proteins, and then regulate gene expression to affect the biological function of cells (Ma *et al.* 2014).

The epigenetic modifications can be structurally classified as DNA methylations/demethylations, histone methylations/demethylations, histone acetylations/deacetylations, histone phosphorelations/dephosphorelations and other modifications. In addition, the concept of epigenetic regulation has been extended to microRNAs (miRNA) and LncRNA regulations, since these RNA molecules regulate the gene expression by partially match to target (complementary

RNA strand) mRNA and then lead to inhibition and/or mRNA degradation. We review the impact of epigenetic modifications and related biological implications in carcinogenesis of human endometrial cancer.

DNA methylation/demethylation is one of the most popular epigenetic modifications and play fundamental role in regulation of gene expression. The methylation status of promoter region determines if gene activation or inactivation, also control gene expression level. Abnormal DNA methylation patters (higher or lower than normal methylation level) have been associated with human tumors, as well as other neoplastic diseases (Tao *et al.* 2010).

The DNA methylation is catalyzed by DNA methyltransferases, which consist of three members – DNMT1, DNMT3A and DNMT3B. DNMT1 is the most abundant DNA methyltransferase among these enzymes. DNMT1 catalyzes the methylation of the 5'-cytosine in the CpG dinucleotide sequence, and plays an important role in maintaining the DNA methylation patterns during cell division. The DNMT3A/3B catalyzes de novo methylation of DNA (Okano *et al.* 1999). These three enzymes cooperatively catalyze the methylation reactions of CpG islands, which are often located in promoter regions of target genes (Jones *et al.* 2012).

Hypermethylation means the methylation exceeds physiological level of target DNAs, the hypermethylation of promoters leads to inactivate the expression of tumor suppressor genes and loss of corresponding proteins to repress carcinogenesis, thereby promoting carcinogenesis and enhancing the metastases of cancer cells. A number of tumor suppressor genes have been determined with frequent hypermethylation on promoter regions during endometrial carcinogenesis.

Other tumor suppressor genes frequently detected with promoter hypermethylation in EC by similar procedures include RASSF1A (Ras associated domain gene family) (33–85%) (Fiolka *et al.* 2013); APC (Adenomatous polyposis coli) up to 46.6%) (Moreno-Bueno *et al.* 2002); RUNX3 (86%) (Yoshizaki *et al.* 2008), CDH13 (cadherin 13) (90%) (Seeber *et al.* 2010), E-cadherin (79.8%) (Leal Rojas *et al.* 2009). In addition to these tumor suppressor genes, some potential tumor suppressor genes were also frequently detected: for example: 14-3-3σ gene was hypermethylated in 40–60% endometrial cancer and ovary cancer (Mhawech *et al.* 2005).

Similar with hypermethylation, the promoter hypomethylation (demethylation) is also a dynamic process presented in mammalian cells. In fact, during carcinogenesis, the DNA methylation pattern has paradoxical alteration: global DNA hypomethylation (demethylation) and local hypermethylation of certain genes. With almost all of the attention on the epigenetic modifications of DNA is focused on the promoter hypermethylations of tumor suppressor genes, very few publications have described the demethylation or hypomethylation in carcinogenesis for all cancers. Nonetheless, hypomethylation of oncogenes also play an important role in carcinogenesis as hypermethylation of tumor suppressor genes do (Ma *et al.* 2014).

In endometrial cancer, the hypomethylation of oncogenes is associated with early stage of carcinogenesis of endometrium through enhancing the ability of cell proliferation. Recently Erling *et al.* reported CTCFL/BORIS gene (paralogue of CTCF-like factor, brother of the regulator of imprinted site) was hypomethylated on the promoter region and overexpression of this gene was significantly associated with endometrial tumorigenesis and poor survival of patients.

Histones are proteins that the DNA wraps itself to form chromatin. Tails of histone proteins are extensively modified post translationally in normal eukaryotic cells to maintain the functional structure of chromatin. Cancer cells frequently harbor aberrations in histones. Locus-specific alterations in histone modifications may have direct effects on expression of nearby genes. Moreover cancer cells also exhibit alterations in global level modifications, among these epigenetic modifications in histones, the acetylations/deacetylations and methylations/demethylations are the major histone modifications that have been reported to play a crucial role in carcinogenesis of EC.

Methylations are one of the most frequent epigenetic modifications on core histones; the histone methylation is mediated by histone methyltransferase (HMT), which contain SET domain to catalyze the reaction of transferring methyl group from donor such as S-adenosyl methionine onto lysine or arginine residues of the H3 and H4 histones. The HMTs can be classified into two groups, group 1 (such as EZH2, Enhancer of Zeste Homolog 2) HMTs transfer methyl group to lysine residues of histone, group2 (such as PRMT, Protein Arginine Methyltransferase) HMTs transfer methyl group to arginine residues of H3 and H4 histones (Hoivik *et al.* 2014). After the determination of biochemical function of chromatin repress complex (PRC2), whose core components include EZH2, EED and SUZ12. More and more researchers are focused on the study of EZH2 and PRC2, which transfers methyl group to lysine 27 and 9 residues of H3.

Generally, the EZH2 acts as an oncoprotein during carcinogenesis, Yang *et al.* found the EZH2 was upregulated in endometrial cancer resulting in hypermethylation of histone 3 lysine 27 of APC promoter, subsequently inactivated the expression of APC tumor suppressor. Zhou *et al.* also reported that EZH2 was overexpressed in high-grade endometrial tumors.

CONCLUSION

In this review, we summarized new findings on the carcinogenic mechanisms of endometrial cancer. Carcinogenesis cannot be completely explained by endometrial proliferation due to estrogen and a single gene mutation. However, the core carcinogenic mechanisms of type I endometrial cancer are DNA methylation (an

epigenetic change) and subsequent breakdown of the MMR system. These actions cause oncogene mutation, inactivation of tumor suppressor genes, and oncogene activation, and contribute to chaotic cell proliferation, that is, carcinogenesis.

Recent developments in the field of epigenetics, especially studies of DNA methylation, have provided valuable insights for understanding the role of epigenetic alterations in normal cellular processes and abnormal changes leading to endometrial carcinogenesis. These new insights hold tremendous potential in the diagnosis, treatment and prevention of endometrial cancer. There is accumulating evidence that DNA methylation changes may contribute to carcinogenesis in the endometrium, although evidence regarding these changes induced by dietary/ lifestyle and environmental factors in endometrial cancer is quite limited.

Candidate biomarker studies have consistently identified a number of specific molecular alterations in endometrial carcinoma, including mutations, DNA methylation, microsatellite instability, copy number alterations and gene expression patterns. Among the many characteristic molecular alterations that could provide early detection markers in endometrial carcinoma. DNA methylation is notable because of its early occurrence in carcinogenesis, stability and detectability using highly sensitive and specific assays.

ACKNOWLEDGEMENTS

I would like to thank you to every member of our Department of Obstetrics and Gynaecology who has contributed to this article .Special thanks goes to financial support grants: Center of Excellence for Perinatology research (05/2009-04/2011), (01/2010-06/2012).

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