Endometrial Carcinogenesis and Molecular Signaling Pathways

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Abstract

The Endometrial Cancer (EC) is the most common gynecologic malignancy that starts in the endometrium of women. Carcinogenesis of EC is associated with several critical regulatory molecules, which involve in different signaling pathways. A number of signaling pathways have been identified to be involved in the multiple-step development of EC, including PI3K/AKT/mTOR signaling pathway, WNT/β-catenin signal transduction cascades (including APC/β-catenin pathway), MAPK/ERK pathway, VEGF/VEGFR ligand receptor signaling pathway, ErbB signaling pathway, P53/P21 and P16INK4a/pRB signaling pathways. This review mainly focuses on the molecular signaling pathways relevant to human endometrial cancer and discusses those critical capabilities of transforming endometrial cells, including evading apoptosis; enhancing cell proliferation; blocking differentiation; and inducing angiogenesis.

Keywords

Signaling Pathway, Endometrial Cancer (EC), Carcinogenesis

1. Introduction

Abnormal endometrial proliferation associates with the most common gynecological diseases, including the endometrial cancer, endometriosis and adenomyosis. The Endometrial Cancer (EC) is a type of malignancy that starts in the endometrium. Carcinogenesis of endometrial tissue can originate from abnormal hormone estrogen level/bleeding, chemical insult, radiation and viral infection, as well as genetic predispositions. Tumors developed in the epithelial layer of endometrium are classified as endometrial carcinomas (98% of endometrial tumors), while tumors developed in the muscle layer or stromal tissue are called sarcomas (2%). Given the high prevalence of the endometrial carcinoma, this review mainly focuses on the molecular signaling pathways relevant to human endometrial cancer and discusses those critical capabilities of transforming endometrial cells, including evading apoptosis; enhancing cell proliferation; blocking differentiation; and inducing angiogenesis.

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vant to this type of cancer.

The human endometrium is a dynamically remodeling tissue undergoing around 300 cycles of regeneration, differentiation, and shedding during the reproductive life of women. These cycles are controlled by a number of signaling pathways including estrogen and progesterone hormone signals. Mutations and abnormal expression of the genes related to these signaling molecules have been linked with the multistep development of endometrial carcinogenesis, and the proteins encoded by these genes are the key mediators of several signaling pathways, such as PI3K/AKT/mTOR signaling pathway, WNT/β-catenin signal transduction cascades (including APC/β-catenin signaling), MAPK/ERK pathway, VEGF/VEGFR ligand receptor signaling pathway, ErbB signaling pathway and P53-P16INK4a signaling pathways. Based on the fundamental biological function of these signaling pathways and pathological features of EC, we propose that four capabilities of transforming endometrial cells are critical to the primary carcinogenesis and metastasis: 1) evading apoptosis, 2) enhancing cell proliferation, 3) blocking differentiation, 4) inducing angiogenesis; other functions such as cell cycle arrest, microsatellite instability (even other pathological functions) can be integrated into these capabilities. In this paper we will discuss on the pathological roles of these pathways during the endometrial carcinogenesis.

2. Signaling Pathways and Carcinogenesis of Endometrial Cancer

2.1. PI3K/AKT/mTOR and EC

This signaling pathway integrates both intracellular and extracellular signals and serves as a central regulator of basic biological processes of cells such as metabolism, growth, proliferation, survival and angiogenesis (see Figure 1). mTOR nucleates at least two distinct multi-protein complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) [1]. mTOR pathway was identified to be activated during tumor formation, and is deregulated in human diseases including cancer and type 2 diabetes [2]. High-frequency mutation of PTEN within this pathway was detected from type I endometrial cancer, and accompanied the PI3K/AKT/mTOR activation [3] [4]. Molecular alterations in AKT are rare, but both type I and type II endometrial cancers showed a

Figure 1. PI3K/AKT/mTOR signaling pathway in endometrial cancer. This illustration encompasses mediators involved in PI3K/AKT/mTOR pathway, alternated genes or proteins (PI3K, PTEN and AKT/PKB, labeled with red color) in EC carcinogenesis. The flow pattern of the wild type signaling pathway is labeled with black arrow or black line; and the flow pattern of the alternated type signaling pathway is labeled with red arrow or red line. Changes for this signaling pathway results in causing tumor angiogenesis, evading apoptosis and enhancing proliferation.
high rate of mutations in the PIK3CA gene, which encodes the PI3K catalytic subunit alpha [5]. PIK3CA mutations were detected in 20% - 30% of endometrial cancers [6]. Amplification of the PIK3CA gene, however, is much more common in type II endometrial cancer, with a prevalence of about 46% [7] [8]. PTEN antagonizes PI3K function and negatively regulates AKT activities, which encompass mainly cell survival and anti-apoptosis. Research also showed that PTEN gene mutations were associated with the histology, early stage, and favorable clinical behavior of endometrial cancers [9]. Loss of PTEN activity in endometrial cancers is associated with increased activity of the PI3K with resultant phosphorylation of its downstream substrate AKT [10]. In turn, AKT upregulates mTOR activity, and hyper activation of mTOR signaling enhances translation of mRNAs encoding growth factors, cell cycle regulators, survival proteins, and angiogenic factors, therefore, dysregulation of the PI3K/AKT/mTOR pathway as a result of genetic mutations and amplifications has been thought to be a conduit for carcinogenesis [11] [12]. Interestingly, in a study of metastatic endometrial cancers, frequent mutations of KRAS, FGFR2 and PIK3CA were identified [13] [14]. The cellular location of the AKT activity is important in the behavior of the cancer, the nuclear p-AKT level was significantly higher in grade 1 (well-differentiated, G1) than in grade 3 (poorly differentiated, G3) cancers and associated with estrogen receptor (ER-alpha) expression. Hence, the nuclear p-AKT level was significantly correlated with the prognosis for EC of G1, and possibly resulting in inhibition of apoptosis. Activation of AKT frequently occurs in endometrial cancer, but is independent of PTEN or PIK3CA activation status. Expression of p-AKT was basically detected in the cytoplasm but some samples had both cytoplasmic and nuclear staining [15], also activation of AKT pathway by mutated PIK3CA or PTEN is possibly associated with favorable prognosis of EC [16]. PTEN also plays a role in cellular signaling by inhibiting the MAPK kinase pathway. MAPK pathway is another major intracellular signaling cascade, which transmits signals through phosphorylation by tyrosine kinase-type receptors on cell membranes, and will be reviewed in the next section of this paper.

2.2. MARK/ERK Pathway and EC

The mitogen-activated protein kinase (MAPK) pathway is also known as RAS-RAF-MEK-ERK signaling pathway. It regulates cell proliferation and differentiation via RAF-MEK-ERK signaling cascade (see Figure 2). MAPK is activated by the upstream growth factors and their receptors. An autonomous and constitutive activation of MAPK signaling is often induced by the overexpression of growth factors and their receptors in cancer [17]. K-RAS gene encodes a protein that is a member of the small GTPase superfamily and is involved in signal transduction pathways between cell surface receptors and the nucleus, K-RAS mutations have been identified in the 10% - 30% of endometrioid endometrial carcinomas [18] [19]. While some investigators have reported an almost complete absence of K-RAS mutations in serous and clear cell carcinomas of endometrium, other researchers found a higher frequency of K-RAS mutations in Microsatellite Instability (MSI)-positive carcinomas than in MSI-negative tumors [20] [21]. Moreover, K-RAS mutations were detected in endometrial hyperplasias at a similar rate compared to that observed in endometrioid endometrial carcinomas, suggesting that K-RAS mutations could be early events during endometrial carcinogenesis [22]. No association has been identified between K-RAS mutations and tumor stage, histologic grade, depth of myometrial invasion, age, or clinical outcome in endometrioid endometrial carcinomas [23].

2.3. WNT Signaling Pathway and EC

The WNT signaling pathway is one of the most evolutionary-conserved signal transduction pathways. The WNT signaling pathways include β-catenin dependent WNT signaling pathway (i.e. canonical WNT/β-catenin) and β-catenin independent WNT signaling pathway (i.e. Non-canonical, such as WNT/JNK pathway, WNT/calcium pathway) (see Figure 3). Among these WNT signaling pathways, the β-catenin dependent pathway has been associated with human endometrial cancer [24]. Four different intracellular (one canonical while 3 others non-canonical) signaling pathways of WNT are mediated by different downstream mediators and cause different biological activities as illustrated in Figure 3. For canonical WNT signaling pathways, the major effector is the transcription factor β-catenin.

2.3.1. WNT/β-Catenin Signaling Pathway

In the presence of WNT ligand, WNT binds to frizzled family proteins and several co-repressors such as lipoprotein receptor-related proteins (LRP-5/6, RYK or ROR2) [25], as a result, the APC/AXIN/CK1/GSK3β de-
Figure 2. MAPK/ERK signaling pathway in endometrial cancer. This illustration encompasses mediators involved in MARK/ERK pathway, the alternated genes or proteins (RAS, labeled with red color) in EC carcinogenesis. The flow pattern of the wild type signaling pathway is labeled with black arrow or black line; and the flow pattern of the alternated type signaling pathway is labeled with red arrow or red line. Changes for this signaling pathway results in evading apoptosis and enhancing proliferation.

Figure 2. MAPK/ERK signaling pathway in endometrial cancer. This illustration encompasses mediators involved in MARK/ERK pathway, the alternated genes or proteins (RAS, labeled with red color) in EC carcinogenesis. The flow pattern of the wild type signaling pathway is labeled with black arrow or black line; and the flow pattern of the alternated type signaling pathway is labeled with red arrow or red line. Changes for this signaling pathway results in evading apoptosis and enhancing proliferation.

struction complex is inhibited, leading to the stabilization of β-catenin and thus translocation to the nucleus where it interacts with TCF/LEF family transcription factors and then ensues the gene transcription activation. In the absence of WNT ligand, phosphorylated β-catenin is prone to be ubiquitinated and destroyed by the proteasome, thus the expression for TCF/LEF family transcription factors is not activated. The non-canonical WNT signaling pathways are less understood, and they work in a β-catenin independent manner, such as WNT/Ca2+ pathway, in which the WNT binds to Frizzled receptors, resulting in the release of calcium and activation of calmodulin and other calcium-related enzymes [26]. Moreover, the WNT/JNK/JUN pathway utilizes frizzled receptors, JNK and Rho family GTPases in the absence of β-catenin [27]. Progesterone inhibits WNT signaling by induction of DKK1 and FOXO1 expression, the inhibition of WNT signaling by progesterone was partly circumvented in WNT activated Ishikawa cells [28] and immunohistochemical (IHC) analysis of the WNT target gene CD44 showed that progesterone acted as an inhibitor of WNT signaling in hyperplasia and in well-differentiated endometrial cancer. IHC and loss of heterozygosity (LOH) analysis of tissue-specific inducible mouse model indicated the loss of the APC function in the endometrium leads to cytoplasmic and nuclear β-catenin abnormal accumulation and association with uterine hyperplasia and squamous cell metaplasia [29]. During the menstrual cycle, estradiol can enhance WNT/β-catenin signaling, and constitutive activation of WNT/β-catenin signaling will cause endometrial hyperplasia, which may develop further into endometrial cancer [30].

2.3.2. APC/β-Catenin Signaling Pathway
The APC/β-catenin signaling pathway plays important roles in normal and tumor cells [31]. In normal cells, in the absence of an extracellular WNT signal, the free (cytoplasmic) β-catenin level is low, since this protein is
Figure 3. WNT/β-catenin signaling pathway in endometrial cancer. This illustration encompasses β-catenin dependent WNT signaling pathway (i.e. canonical WNT/β-catenin) and β-catenin independent WNT signaling pathway (i.e. Non-canonical, such as WNT/JNK, WNT/calcium and WNT/TAK1 pathways) and even mediators involved in these pathways, the alternated genes or proteins (APC and β-catenin, labeled with red color) in EC carcinogenesis. The flow pattern of the wild type signaling pathway is labeled with black arrow or black line; and the flow pattern of the alternated type signaling pathway is labeled with red arrow or red line. Changes for these signaling pathways result in enhancing proliferation during EC carcinogenesis.

<table>
<thead>
<tr>
<th>Degradation complex</th>
<th>PLCγ</th>
<th>IP3</th>
<th>RhoA</th>
<th>CaCN</th>
<th>C-JUN</th>
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<tr>
<td>β-Catenin</td>
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<td>APC</td>
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<td>Axin</td>
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<td>NLK</td>
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<td>NFAT</td>
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<td>Target gene</td>
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<td>TCF-LEF</td>
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VEGFs (Vascular Endothelial Growth Factor) are secreted by tumor cells that stimulate a speed and reversible increase in permeability of microvascular without mast cell degranulation or endothelia cell damage [36], VEGFs ligands play angiogenic role by binding to specific VEGF receptors, resulted in dimerization of receptor VEGFR and activation of VEGF/VEGFR signaling pathway (Figure 4) [37] [38]. The VEGF receptors are presence on the membrane of endothelial cells, expression of VEGF receptors (VEGFR-1, VEGFR-2 and VEGFR-3) in endothelial cells varies among these 3 receptors, VEGFR-2 is expressed in most of endothelial cells, but VEGFR-1 and VEGFR-3 are expressed only in distinct vascular cells. The function of corepressors...
neuropilin-1 (NP-1) and neuropilin-2 (NP-2) are associated with increased binding affinity of VEGF ligands to these primary receptors, up-regulation of VEGFR in tumor cells suggests the critical role in tumorigenesis of endothelial cells [39]-[41]. VEGFR-3 promotes lymphangiogenesis in lymphatic endothelial cells in adults but not by adult vascular endothelium, and this receptor plays a key role in maintaining vascular integrity by modulating VEGFR-3 activity [42]. Related research work showed VEGFR-3 is activated in some solid tumors such as melanoma, in these solid tumors the increased VEGF-C and VEGF-D (VEGFR ligands) are linked to lymph node metastases [43], and there is also a strong association between lymphovascular density and VEGF-C expression in human malignant mesothelioma [44]. Since angiogenesis is a critical event in the growth and spread of tumors during carcinogenesis [45], and VEGFs and the angiopoietins are key factors in angiogenesis [46] [47]. The VEGF-C and VEGF-D have both been correlated with poor prognosis in endometrial cancer and atypical complex hyperplasia (ACH), in low grade endometrial tumors, expression of VEGF-B is increased, and experiment showed VEGF-A and VEGF-B, are differentially expressed in benign postmenopausal endometrium and endometrioid endometrial cancer [48]. High expression of VEGF-D in carcinoma cells and stroma cells, are closely related with high level of VEGFR-3 in carcinoma cells and endothelial cells, suggested that VEGF/VEGFR signaling pathway mediated by VEGF-D/VEGFR-3 plays a significant role to myometrial invasion and lymph node metastasis [49].

2.5. ErbB Signaling Pathway and EC

The ErbB (Erythroblastoma Virus B) receptor tyrosine kinase family consists of four related receptors: ErbB-1/EGFR/HER1, ErbB-2/HER2, ErbB-3/HER3 and ErbB-4/HER4. ErbB receptors are biochemically typi-
cal cell membrane receptor with tyrosine kinase activity that is activated following ligand binding and receptor dimerization. The ErbB receptors are mediators of cell proliferation, migration, differentiation, apoptosis, and cell motility by signaling transduction. Dimerization of ErbB receptors leads to autophosphorylation [50] [51], thus the phosphorylated tyrosine residues function as docking sites for binding of cytoplasmic proteins containing SRC homology 2 (SH2) and phosphotyrosine binding (PTB) domains [52] [53], following these modifications, recruitment of proteins then initiates intracellular signaling via following several pathways (Figure 5).

2.5.1. ERB/MARK/ERK Signaling Pathway
The MARK/ERK pathway regulates cell proliferation and survival as described above, for ERB mediating MARK/ERK signaling pathway, the RAS mutation was identified to be involved in early events of endometrial carcinogenesis [18] [19], and [22].

2.5.2. ERB/PI3K/AKT/mTOR Signaling Pathway
In this signaling pathway, PI3K is a heterodimer enzyme that contains regulatory subunit P85 and catalytic subunit p110, P85 offers an anchorage site for ErbB (Her) binding, then P110 generates phosphatidylinositol 3, 4, 5-triphosphate as the substrate of protein kinase AKT, which is a critical mediator of PI3K/AKT/mTOR [54], the AKT causes several down stream transcriptional factors activation including NF-KB, BAD, P27 and GSK3.

![Figure 5. ErbB signaling pathway in endometrial cancer. This illustration encompasses mediators involved in ErbB signaling pathway, the alternated genes or proteins (HER2, HER3, RAS, STAT3 and AKT labeled with red color) in EC carcinogenesis. The flow pattern of the wild type signaling pathway is labeled with black arrow or black line; and the flow pattern of the alternated type signaling pathway is labeled with red arrow or red line. Changes for these signaling pathways result in enhancing proliferation, evading apoptosis, blocking differentiation and causing tumor angiogenesis during EC carcinogenesis.](image-url)
as mentioned in this paper, activation of AKT is closely associated with endometrial carcinogenesis and prognosis by controlling specific gene expression, thereafter occurs new hallmarks for cell transformation such as angiogenesis, evading apoptosis, enhancing proliferation and blocking differentiation.

2.5.3. ERB/STAT Signaling Pathway
Signal transducers and activators of transcription (STAT) pathway are well known to regulate carcinogenesis and tumor progression the dimerized STAT proteins interact with phosphotyrosine residues via their SRC domain (SH2), then translocate into nucleus and active the expression of target gene promoters, increased activity of EGFR and ErbB-2 promote persistent STAT activation and subsequently induce carcinogenesis and tumor progression. Constitutive activation of STAT proteins (especially STAT-3 and STAT-5) is present in many primary cancers including endometrial cancers [56]-[58]. In EC, STAT3 activates the key oncogene gene such as survivin [57], Cycline D1 [58] expression to promote EC carcinogenesis.

2.5.4. ERB/SRC Kinase Signaling Pathway
The SRC kinase pathway is critical to regulate cell proliferation, migration, adhesion, angiogenesis, and immune function. SRC is a member of a 10 genes family (SRC, FYN, YES, BLK, FRK, FGR, HCK, LCK, LYN, SRMS). This pathway synergically interacts with other signaling pathways, such as PI3K and STAT pathways to regulate the cell function and possible carcinogenesis [59] [60]. It has been determined that SRC protein (for example, SRC-3) overexpressed in various cancers including EC [61] [62], and the SRC-3 expression is correlated with the clinical stage, depth of myometrial invasion and differentiation of EC.

2.5.5. ERB/\gamma PKC Signaling Pathway
Phospholipase C\gamma interacts with activated EGFR and ErbB-2 and hydrolyses phosphatidylinositol 4, 5 phosphate to inositol 1, 3, 5 triphosphate (IP3) and 1, 2 diacylglycerol (DAG), DAG is a cofactor of protein kinase C (PKC) activation, PKC activates MAPK and c-Jun NH2-terminal kinase (JNK) thus regulates the MARK/ERK signaling pathway during EC carcinogenesis [63] [64]. As critical molecule in ErbB signaling pathway, the ErbB-2 protein is localized baso-laterally in the glands and surface epithelial cells [65] [66], in unslected patients with EC, ErbB-2 amplification/overexpression represents a rare event, in patients with type I EC, it has been reported ErbB-2 receptor overexpression in 8% of cases and ErbB-2 gene amplification in 1.4% - 3% of cases [67] [68]. ErbB-2 amplification/overexpression is more common in patients with type II EC, for example, Konecny [68] reported that HER2 (ErbB-2) gene amplification with 17% frequency (18/105) in evaluable uterine serous papillary EC specimens. Interestingly, the frequency and regulation patterns of HER2 gene changes depend on the special populations for same type of tumor, Santin [69] reported that ErbB-2 was overexpression with 70% frequency for black patients, but 24% for white patients. ErbB-2 overexpression is an indicator for type II EC and its treatment prognosis. For ErbB-3, ErbB-4, in endometrium, these two proteins are localized to surface of epithelial cells [70]-[74], and overexpression of these two genes were detected in endometrial adenocarcinoma (vs. normal controls) [72], the clinical and pathological implication for ErbB-3 is associated with better survival of cancer cells under treatment conditions [75] [76]. ErbB4 protein was upregulated in type I endometrial carcinoma indicates an oncogenic function in endometrial carcinogenesis [77].

2.6. P53/P21 and P16INK4/pRB Signaling Pathways and EC
2.6.1. P53/P21 Signaling Pathway
As a multiple function protein, P53 plays a crucial role on cell cycle, and acts as a typical tumor suppressor to prevent carcinogenesis (Figure 6). A numbers of clinic researches have show P53 mutations are closely associated with the endometrial carcinogenesis, Janiec-Jankowska [78] reported in 81 endometrial cases, there were 40 cases (49.4%) had P53 mutations. Tashiro et al. reported in uterine serous carcinoma (USC) cases, there were 90% (19/21) cases contain the P53 mutations, and in endometrial intraepithelial carcinoma (EIC), there were 78% (7/9) cases contain P53 mutations [79], mutated P53 as a nonfunctional protein accumulates in the cells (especially in nucleus) acts as a dominate negative inhibitor of wild-type P53, leading to the function loss of G1 arrest, resulting in evading apoptosis of cancer cells. Overexpression of P53 was also frequently detected from clinical samples of EC, especially in early stage of endometrial cancer [80]. P53 has been suggested to be an indicator for identifying cases of aggressive carcinoma (especially in the early stage), also as a prognostic indicator for low-stage endometrial cancer [81].
2.6.2. P16INK4a/pRB Signaling Pathway

P16INK4a (known as P16) is a newly identified tumor suppressor, wild-type P16 acts as a inhibitor of CDK4/6, therefore pRB activation is inhibited, resulted in deactivation of E2F response promoters, thus the specific target genes will not be expressed (Figure 6), the downregulations of P16 was frequently detected in EC, for examples: Nakashima et al detected reduced expression of P16 in 5 of 19 (26%) cervical tumor and 4 of 25 (16%) endometrial tumors [82]. The alterations and abnormal epigenetic modifications for P16INK4a are also play an important role during EC carcinogenesis, Semczuk et al showed 50% P16INK4a gene alterations in sporadic endometrial cancer [83], high methylation of P16INK4a promoter was observed up to 75% of sporadic endometrial cancer [84]. Cross talk between P16INK4a/pRB pathway with P53 pathway is linked through the inhibition of wild-type CDK4/6 by P21.

Besides the above genes that we summarized in the different signaling pathways, some other important biomarker for human EC were also identified, such as tumor suppressor gene BCL2, E-cadherin, Baf250, oncogene FGFR2 [85]. The microsatellite instability (MI) was associated with endometrial cancer, five marker of NR-27, NR-21, NR-24, BAT-25 and BAT-26 showed instability in 16, 21, 11, 15 and 17 out of the 80 endometrial tumor samples [86]. All of these changed genes identified in endometrial tumors are listed in Table 1.

3. Summary

Although morphological basis and several molecular indicators of clinic diagnosis are widely used for endometrial cancer, but we are still in a stage of “blind people touch elephant” to endometrial carcinogenesis even other cancers, all of the molecular evidence of signaling pathways identified to be involved in the carcinogenesis
### Table 1. Genetic/Epigenetic alterations in endometrial cancer.

<table>
<thead>
<tr>
<th>Gene/Protein</th>
<th>Genetic Alterations</th>
<th>Epigenetic Alterations</th>
<th>Expression/Distribution</th>
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<td>Deactivation/Downregulation</td>
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<td>Abnormal accumulations</td>
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<tr>
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<td>MSI (Microsatellite instability)</td>
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Caution: Hypermethylation indicates the modification is on the Promoter region.

of EC are dispersion and disorder, in this paper we try to establish a clear and concise model to show the bird version for carcinogenesis of endometrial tissue based on the discovered proteins and pathways, and we successfully connected the pathological functions from different signaling pathways to four hallmarks of cancer (Figure 7); this model enable us to easily understand the molecular mechanisms for carcinogenesis of EC, and
will be helpful to design treatment targets and may give some directions to search new treatment strategies for this type of cancer in the future, and this model of EC carcinogenesis may be similar with that of other cancers.

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References


PloS One of Primary and Metastatic Endometrial Cancers Identifies KRAS, FGFR2 and PIK3CA to Be Frequently Mutated.


[http://dx.doi.org/10.1093/jnci/82.1.4](http://dx.doi.org/10.1093/jnci/82.1.4)

[http://dx.doi.org/10.1038/376066a0](http://dx.doi.org/10.1038/376066a0)

[http://dx.doi.org/10.1126/science.286.5449.2511](http://dx.doi.org/10.1126/science.286.5449.2511)

[http://dx.doi.org/10.1038/sj.bjc.6601194](http://dx.doi.org/10.1038/sj.bjc.6601194)


[http://dx.doi.org/10.1016/S1096-9896(03)00350-2](http://dx.doi.org/10.1016/S1096-9896(03)00350-2)

[http://dx.doi.org/10.1172/JCI32278](http://dx.doi.org/10.1172/JCI32278)

[http://dx.doi.org/10.1074/jbc.270.25.14863](http://dx.doi.org/10.1074/jbc.270.25.14863)

[http://dx.doi.org/10.1038/35052073](http://dx.doi.org/10.1038/35052073)

[http://dx.doi.org/10.1074/jbc.M100556200](http://dx.doi.org/10.1074/jbc.M100556200)

[http://dx.doi.org/10.1074/jbc.M109.085696](http://dx.doi.org/10.1074/jbc.M109.085696)

[http://dx.doi.org/10.1038/ncponc0195](http://dx.doi.org/10.1038/ncponc0195)


[http://dx.doi.org/10.1002/jcp.21622](http://dx.doi.org/10.1002/jcp.21622)

[http://dx.doi.org/10.1007/s10585-004-2873-4](http://dx.doi.org/10.1007/s10585-004-2873-4)

[http://dx.doi.org/10.1158/1078-0432.CCR-05-2692](http://dx.doi.org/10.1158/1078-0432.CCR-05-2692)

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