Molecular pathogenesis of endometrial cancer

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Introduction.

Genetic changes which cause endometrial cancer may be discovered by simple comparison of tumor with normal tissues, and correlating clinicopathologic with genotypic features. More difficult is the specific elaboration of those interacting events which may transpire in a particular sequence during a protracted interval of carcinogenesis. A small burden of premalignant cells makes them elusive targets for study, and their histopathologic plasticity complicates achieving diagnostic consensus and reproducibility between laboratories. Despite these formidable obstacles, the last decade has seen an explosion of new data regarding endometrial carcinogenesis. Cancer subtypes have been clearly divided along genetic and clinical lines, and a flood of information about those genetic changes which cause endometrial cancer has been forthcoming from many sources, including non-gynecologic tumor systems. The diagnosis of premalignant endometrial lesions, long a confusing and contentious issue among pathologists, has achieved objectivity from biomarker studies and histomorphometric analysis. These data have yielded a scientific basis for standardization and revision of endometrial precancer diagnosis in a routine diagnostic setting. Lastly, experimental access to preclinical stages of premalignant endometrial disease, a phase of tumorigenesis which is the probable mediator of endocrine risk factors, affords an opportunity for cancer chemoprevention.

Genetic Subgroups of Endometrial cancer.

Sporadic endometrial adenocarcinoma may be classified into dichotomous genotypic classes defined by polarized frequencies of inactivation of specific genes (Table I). These genetic pathways of endometrial carcinogenesis are generally paralleled by endometrioid (Type 1) and non-endometrioid (Type 2) subtypes that comprise distinct clinicopathologic entities. Approximately 70-80% of newly diagnosed cases of endometrial cancer in the U.S. are of endometrioid histology. Type 1 cancers have been associated with unopposed estrogen exposure, and are often preceded by premalignant disease. Progression to carcinoma is highly inefficient, involving complex interactions between multiple genetic events (PTEN, KRAS, microsatellite instability) and ambient hormonal selection factors. In contrast, Type 2 endometrial cancers have papillary serous or clear cell histology with a very aggressive clinical course. Hormonal risk factors have not been identified, nor is there a readily observed premalignant phase. Type 2 tumors characteristically present as fully developed malignancies and have P53 tumor suppressor gene defects. For purposes of discussion Type 1 and Type 2 sporadic endometrial adenocarcinoma might just as well be considered separate diseases.

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A third group are those extremely rare endometrial adenocarcinomas which present as a manifestation of multi-cancer heritable syndromes (Table II)\(^{10,11}\). The low frequency with which these are encountered in clinical practice belies their high level of scientific interest, as familial presentation affords unique opportunities to dissect those causal genetic events which may also be effective in a sporadic setting. The PTEN inactivation seen in Cowden’s syndrome\(^3,12\), and DNA mismatch repair defects of Hereditary Nonpolyposis Colon Cancer\(^1,15\), are frequent accompaniments to sporadic endometrial carcinogenesis\(^{16}\).

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<table>
<thead>
<tr>
<th>Gene</th>
<th>Alteration</th>
<th>Endometrioid</th>
<th>Non-Endometrioid</th>
<th>Refs</th>
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<tr>
<td>p53</td>
<td>mutation</td>
<td>5-10%</td>
<td>80-90%</td>
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<tr>
<td>PTEN</td>
<td>loss of function</td>
<td>55%</td>
<td>11%</td>
<td>3,5,6</td>
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<td>25-38%</td>
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<td>MLH1</td>
<td>Microsatellite Instability (epigenetic silencing)</td>
<td>17%</td>
<td>5%</td>
<td>4,19-21</td>
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<td>loss of function</td>
<td>68-81%</td>
<td>76%</td>
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<td>loss of function</td>
<td>20-34%</td>
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<td>65%</td>
<td>67%</td>
<td>15,28</td>
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<td>Bax</td>
<td>loss of function</td>
<td>48%</td>
<td>43%</td>
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<td>Estrogen &amp; Progesterone receptors</td>
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<td>70-73%</td>
<td>19-24%</td>
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<tr>
<td>Hereditary Nonpolyposis Colon Cancer</td>
<td>Mismatch Repair MLH1, MSH2, MSH6</td>
<td>colon, endometrial cancer</td>
<td>4</td>
</tr>
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</table>

An overview of the most prevalent genetic changes in endometrial carcinoma can be obtained by detailed review of a relatively small number of individual genetic changes.

**P53.**

p53 is a tumor suppressor gene that is inactivated in half of all human tumors\(^{17}\). As a multifunctional transcription factor p53 plays a central role in cell cycle regulation and apoptosis pathways. Despite substantial effort it has not always been possible to link p53 mutations with a
particular histologic pattern or clinical outcome in many tumor types. Endometrial cancer is one of the exceptions, in which p53 mutations are almost exclusively associated with a specific histological subtype, and not distributed stochastically among half of the cases. Type 2 tumors, which are generally of serous papillary or clear cell histology frequently (>90%) harbor p53 mutations 18. A much lower p53 mutational rate in Type 1 tumors (<10%) makes p53 a useful diagnostic marker in distinguishing type 1 from 2 endometrial cancers 22.

In most studies, p53 mutations have been detected by immunohistochemical staining of paraffin sections from endometrial cancers. Since wild-type p53 is below detection levels and most mutations stabilize the protein causing its accumulation to a detectible level, positive staining has been used as synonymous with a p53 mutation. However, this interpretation is complicated by a few biological factors.

While most p53 mutations are missense mutations that lead to accumulation of the mutant protein, a distinct subset are nonsense mutations or deletions that will be missed by this approach. In addition, wild type p53 can be induced to a detectable level in the absence of a mutation. For example, DNA damage in the case of radiation therapy can induce expression24. Several genes including mdm2 and p14 ARF that regulate p53 levels have been shown to cause detectable levels of p53 in the absence of a mutation 23;25.

Moreover, descriptive reporting of scattered positive p53 immunostaining has been misleading, in that the clonal nature of the p53 mutation is not considered in interpreting the results. Only diffuse and uniform (meaning an early mutation present in all tumor cells), or geographic focal clonal staining (meaning a second clonal event within the tumor) is biologically meaningful and useful in distinguishing the two endometrial cancer types (Figure 1). Therefore, a conventional descriptive scoring method used for most other immuno stains in pathology (mild, moderate, severe etc.) is inappropriate for p53.
For the above reasons some of the earlier reports on p53 found a less distinct difference between type 1 and 2 endometrial carcinomas. However, it is becoming evident now that this gene is almost exclusively mutated in type 2 endometrial cancers. In rare cases when p53 protein is detected in type 1 cancers it is generally not due to mutation.

**PTEN.**

Inactivation of the PTEN tumor suppressor gene (formerly known as “MMAC1”) is the most common genetic defect in endometrial carcinoma. The PTEN protein product is a dual specificity phosphatase which acts to suppress cell division and enable apoptosis via an AKT-dependent pathway. PTEN inactivation may be caused by a variety of mechanisms including mutation or deletion. Reported rates of PTEN inactivation in individual patient series are highly affected by the mix of tumor subtypes assembled and whether gene function is assessed by deletion (loss of heterozygosity) mutation, or presence of PTEN protein. Loss of PTEN function is most prevalent in the endometrioid subtype of endometrial cancers, reaching a peak rate of 83% in those tumors preceded by a histologically discrete premalignant phase.

Additional support for PTEN inactivation in genesis of endometrial cancers has been forthcoming from PTEN knockout mice and human syndromes caused by germline PTEN inactivation. Heterozygous PTEN inactivation produces an endometrial phenotype in mice, with 100% development of hyperplastic lesions, and 20% of animals progressing to endometrial carcinoma. Humans with constitutive germline PTEN mutations may present with the heritable cancer syndrome of Cowden’s disease, which includes high rates of breast, thyroid, and other cancers in conjunction with hamartomas of multiple organs. There appears to be an increased risk of endometrial cancer in women with Cowden’s syndrome, but only small numbers of these patients have been available for study, and the magnitude of increased risk is modest. It is reasonable to conclude that in humans, nongenetic factors combined with additional (non-PTEN) gene inactivation events are co-determinants of endometrial cancer risk.

Approximately a third of inactivated PTEN alleles in sporadic endometrial cancer are deletions which include the chromosomal location of the PTEN gene, 10q23. Detailed mapping of the long arm of chromosome 10 in endometrial cancers suggested the possibility that additional closely linked tumor suppressors might be co-inactivated by deletion with PTEN. The homeodomain containing gene EMX2 is a strong candidate for just such a gene. Increased native EMX2 expression is associated with diminished endometrial proliferative activity, a pattern that might be predicted for a tumor suppressor. Deletion of EMX2, and commensurate decline in expression, is seen in some endometrial adenocarcinomas.

**Microsatellite Instability.**

Female carriers of the hereditary nonpolyposis colon cancer (HNPCC) syndrome have an extremely high rate of endometrial cancer, estimated at 22-43%. Patients with HNPCC have destabilization of small tandem repeats, referred to as microsatellite instability. This is caused by structural defects in DNA mismatch repair genes such as MLH1, MSH2, and MSH6 that prevent replication repair of hairpin loops that form preferentially within palindromic or repetitive DNA sequences. The microsatellite instability phenotype, manifest as a change in the number of repeat units within individual microsatellites, is seen in benign and malignant tissues, including resultant endometrial cancers of HNPCC women.

Microsatellite instability is not specific to familial forms of endometrial cancer, but also accompanies 17-23% of sporadic endometrial carcinomas. The cause of instability differs, however, as sporadic endometrial cancers with microsatellite instability infrequently contains those mutations of mismatch repair genes which had been seen in hereditary (HNPCC) endometrial cancer patients.
cancers. Rather, sporadic endometrial cancers acquire microsatellite instability through epigenetic inactivation of the MLH1 gene - a change not evident in the usual mutational screens initially used to query the functional integrity of MLH1.

The manner in which microsatellite instability influences cellular function is complex. It is a widespread process that affects a large number of DNA motifs widely distributed throughout the genome. Secondary inactivation of specific genes may be accomplished by alteration of repeat sequences in coding regions, epigenetic inactivation of expanded microsatellites in regulatory domains, or a hypermutable state in non-repeat areas. The effects of microsatellite instability in endometrial carcinoma are not mediated by P53, KRAS, and PTEN inactivation, as changes in these genes are comparable in microsatellite unstable compared to stable cancers.

Microsatellite instability is more common in endometrioid endometrial adenocarcinomas (17-19%) compared to non-endometrioid carcinomas (5-8%) . Population specific or inter-study differences in the microsatellite instability rates of endometrial cancer are thus expected when the compared groups do not have the same mix of histologic types, confounding attempts to correlate this phenotype with overall survival. In general, larger studies have not confirmed survival predictive value of microsatellite instability.

Premalignant phases of (Type 1) endometrioid endometrial carcinogenesis.

Premalignant endometrial lesions are genetically altered bona fide neoplasms. They contain acquired monoclonal genetic features (mutations, non-random X chromosome inactivation, altered microsatellites) which offsets them from source polyclonal tissues, yet upon detailed analysis are seen to have incremental changes less than that of resultant cancers (Figure 2). The monoclonal properties of histologically diagnosable precancers is a generalizable

Figure 2: Clonal model of endometrial carcinogenesis.

Endometrioid endometrial (Type 1) adenocarcinomas arise by successive genetic events which accumulate within nested hierarchical subclones of mutant cells. Starting from a polyclonal field of cells with a wild type genotype (left, open circles) initiation by inactivation of the PTEN tumor suppressor gene is not accompanied by any change in light microscopic histology. Patches of sparsely distributed PTEN-mutant glands are indistinguishable from those morphologically identical wild type glands with which they are intermingled. This “latent,” or subclinical, precancer phase converts to a clinically detectible stage when additional mutations produce a change in cytology and gland architecture diagnostic of EIN. Contiguous growth of closely packed glands in EIN lesions is due to an expansile localized geometry of mutant glands derived from a common progenitor (monoclonal). The number and specific identity of genetic changes necessary for progression to carcinoma are unknown, arbitrarily shown as “Genes A-C”. Early events preceding morphologic change include microsatellite instability and PTEN inactivation. Less is known about subsequent events, which may include KRAS inactivation.
phenomenon, having been confirmed in premalignant tissues at a wide variety of tissue sites, including vulva\textsuperscript{57}, cervix\textsuperscript{58}, oral mucosa\textsuperscript{59}, and esophagus\textsuperscript{60}.

The high frequency and protracted course of premalignant disease which occurs in endometrioid adenocarcinomas is not seen in non-endometrioid endometrial cancers. Rarely, serous Endometrial Intraepithelial Carcinoma is seen as an isolated finding, but much more common in non-endometrioid tumors is secondary surface spread of malignant cells (Figure 3)\textsuperscript{61}. It is a condition which should not be construed as a premalignant state because it is not genetically different from the co-existing carcinomas, and rarely occurs in the absence of a frank carcinoma elsewhere in the uterus.

Loss of PTEN function through mutation and/or deletion is the earliest known event in endometrial carcinogenesis\textsuperscript{31,62}, a biomarker informative for detection of affected glands. In the manner of a true “gatekeeper”\textsuperscript{63}, PTEN expression is lost at the inception of clonal outgrowth, in cells which are histologically indistinguishable from their normal companions, and are dispersed in small patches within the polyclonal source field. Immunohistochemical staining for PTEN protein in archival paraffin embedded endometrial tissues\textsuperscript{64} is a highly sensitive method to identify these patches in routine pathologic materials. A surprisingly high fraction, 43\%, of endogenously cycling premenopausal women with a normal proliferative endometrium have acquired small numbers of PTEN-defective endometrial glands which upon genetic analysis bear sequence-confirmed PTEN mutations or deletions of 10q23 (Figure 4)\textsuperscript{62}. These PTEN-defective endometrial glands are incompletely shed during menses, growing out as morphologically unremarkable glands with each subsequent cycle. Exposure to estrogens unopposed by progestins produces a characteristic series of histologic changes in the endometrium, ranging from occasional glandular cystic dilatation to gland branching and thrombosis-induced foci of stromal breakdown. These endometria which are variably diagnosed by pathologists as “anovulatory”, “disordered proliferative” or “simple non-atypical hyperplasias,” have architectural changes uniformly distributed throughout in a non-localizing

**Figure 3: Surface spread of p53 mutant non-endometrioid type endometrial adenocarcinoma.**

Clear cell endometrial adenocarcinoma with nuclear p53 staining (Panel A). Adjacent to invasive tumor, the uterine luminal surface has been overrun by malignant cells that stand out from subjacent benign glands (Panel B). Surface spread is common in patients with invasive non-endometrioid endometrial carcinomas, and does not necessarily represent an earlier stage of tumorigenesis. P53 immunohistochemistry with monoclonal antibody (murine monoclonal P53-1801) diaminobenzidine detection, and methyl green counterstain. Scale bar is 100µm.
manner. Approximately half of these endometria have scattered rare PTEN-null glands, presumably having been present prior to onset of the hormonal imbalance. PTEN-null glands of anovulatory endometria have a cytology and architecture which exactly matches that of their PTEN-expressing companion glands, including a similar extent of dilatation, branching, and tubal change. These preclinical phases of carcinogenesis are so frequent that they can be construed as a normal background event.

Progression of subclinical, or “latent”, precancers is highly inefficient, and involves successive accumulation of additional genetic damage that culminates in an altered subclone with aberrant histomorphology and growth (Figures 2,4). The point of origin of this subclone becomes the epicenter of an expanding localizing endometrial lesion which may be recognized by its altered cytology and crowded architecture. This is the stage at which pathologists are able to diagnose an atypical endometrial hyperplasia, and clonal analysis of physically contiguous glands confirms them to be derived from a common progenitor. Atypical endometrial hyperplasias have many of the genetic features seen in subsequent carcinomas including KRAS mutation, microsatellite instability, and β-catenin mutations. Over half of atypical hyperplasias are PTEN-null, and in informative cases the immunohistochemical staining pattern shows tight clusters of PTEN null glands with an abnormal cytology.

Clinical implications of a revised carcinogenesis model.
The current WHO endometrial hyperplasia diagnostic schema\textsuperscript{70} was developed at a time when the clonal origin of premalignant disease was unappreciated, and the only method to experimentally demonstrate a premalignant phenotype was to follow groups of patients and measure cancer incidence. Histopathologic correlation with cancer outcome was a statistical process that failed to provide definitive classification of individual cases. With the advent of reliable markers for those features which characterize premalignant disease (presence of mutations, clonal pattern of growth), it became possible to resolve individual cases and assemble prototypical collections of genetically defined precancers\textsuperscript{71}. These are a valuable resource for \textit{de novo} discovery of those histopathologic features which are pathognomonic of endometrial precancers.

Monoclonal growth of precancers explains why the first histopathologic changes present in localizing fashion. This contrasts with the global field effects of unopposed estrogens, and the diffuse intermingling of patches of mutant cells with those normal tissues from which they are indistinguishable. Monoclonal putative endometrial precancers with acquired genetic changes that can be matched (in the same patient) to subsequent endometrial cancers have undergone objective computerized morphometry to define their structural characteristics\textsuperscript{53}. This disclosed that a very specific architectural change was highly associated with premalignant disease: glandular crowding to the extent that gland area exceeds that of stroma. Cytology in the crowded focus always differs from that of the uncrowded background, suggesting that a relative internal comparison standard for judging cytologic “atypia” may be more reliable than a fixed or stereotypical cytologic standard. The idea that lesion architecture may be a cardinal determinate of premalignant behavior is quite contrary to the previous emphasis on cytology as the dominant predictor of endometrial cancer risk\textsuperscript{72}.

A pitfall in using laboratory endpoints alone to define premalignant disease is that they may quickly become self-serving, and fail to provide compelling evidence of increased cancer risk. There is an established body of histomorphometric data which has established those objectively measurable features of routine hematoxylin and eosin stained endometrial histology that increase prospective clinical endometrial cancer risk \textsuperscript{73-75}. Three features measured by computerized image analysis when algorithmically reduced to a “D-Score” are highly sensitive and specific in prediction of future or concurrent endometrial cancer. Application of this objective image analysis procedure

<table>
<thead>
<tr>
<th>EIN Diagnostic Criterion</th>
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<tbody>
<tr>
<td>1. Architecture</td>
<td>Area of glands exceeds that of stroma. Most often focal.</td>
</tr>
<tr>
<td>2. Cytologic Change</td>
<td>Cytology is different in focus of crowded glands compared to background.</td>
</tr>
<tr>
<td>3. Size</td>
<td>Maximum dimension should exceed 1mm. Smaller lesions have unknown clinical course.</td>
</tr>
<tr>
<td>4. Exclude benign mimics</td>
<td>Normal secretory, basalis, lower uterine segment, endometrial polyps, reparative changes, cystic atrophy, tangential sections, disruption artifact, etc.</td>
</tr>
<tr>
<td>5. Exclude Cancer</td>
<td>Carcinoma if: there are solid areas of epithelial growth, glands are maze like and “rambling, or there is significant cribriforming.</td>
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to a series of endometrial tissues of known clonal composition has confirmed that monoclonal putative endometrial precancers have a histopathology identical to that known to increase endometrial cancer risk. These lesions have been designated Endometrial Intraepithelial Neoplasia or “EIN” and criteria for their routine diagnosis by practicing pathologists clearly specified (Table 3). This is a group of lesions that should be met with hormonal or surgical therapeutic ablation, along the lines of therapeutic responses previously applied to diagnoses of atypical endometrial hyperplasia.

Genetically altered endometrial cells which have not yet progressed to the point where they demonstrate the histopathologic features of EIN have an undefined clinical outcome, and thus no current basis to justify therapeutic intervention. Generally, this phase of disease is only discernible with specialized studies such as PTEN immunohistochemistry, which as stated previously will disclose PTEN-null glands in almost half of normal women. Monitoring of this preclinical interval is of great interest in a research setting, where protective effects of experimental therapies might be detected by changes in the prevalence or physical configuration of mutant cells.

**Endocrine modifiers.**

Estrogens which are not opposed by the counterbalancing effects of progestins confer an increased risk of endometrioid (Type 1) endometrial adenocarcinoma. Relevant exposures include hormonal replacement therapy, excessive peripheral conversion in obesity, and endogenous production by estrogenic ovarian tumors or polycystic ovarian disease. The level of increased cancer risk is estrogen dose and duration dependent, ranging from 3-10 fold. Estrogen risks are obviated by addition of progestins such as medroxyprogesterone acetate, which protects against development of endometrial hyperplasia, and when administered in a combined low dose oral contraceptive formulation may reduce endometrial cancer risk below that of the population background.

![Figure 5. Hormonal regulation of endometrial glandular PTEN expression.](image)

**Figure 5. Hormonal regulation of endometrial glandular PTEN expression.**

PTEN protein (brown) is abundant under the dominant influence of estrogens, in normal proliferative endometrial glands (Panel A). After several days of progesterone exposure mid-secretory endometrial glands demonstrate a decline in PTEN abundance (Panel B). P53 immunohistochemistry with monoclonal antibody (murine monoclonal P53-1801), diaminobenzidine detection, and methyl green counterstain. Scale bar is 100µm.

Despite extensive epidemiologic data linking estrogens to increased endometrial cancer rates, there is surprisingly little evidence of those specific cellular mechanisms which are responsible. In
some models estrogens are thought to increase the rate of mutagenesis, but this is probably a very small effect\textsuperscript{86}. Estrogens may indirectly elevate endometrial mutational rate by increasing proliferative activity in general. The basal frequency with which new mutations arise through random mutagenesis is a combined function of field size and cell division rate\textsuperscript{87,88}. Given a random mutagenesis rate of $10^{-7}$ per gene per cell division\textsuperscript{87}, and an average menstrual cycle which regenerates over $10^9$ cells (several grams at $10^9$ cells/gram) each cycle produces hundreds of cells mutated for any selected gene. Limiting conditions are those which define an advantage for a particular mutation, thereby allowing proliferation to a sufficient cell number that a superimposed second hit can occur\textsuperscript{89,90}. Estrogens may define just such an advantage for the PTEN gene, where physiologic expression in endometrial glands is high under estrogen dominated conditions (Figure 5)\textsuperscript{91}. PTEN-null endometrial cells would be unable to exert the tumor suppressor functions normally required in such a proliferative estrogenic state, thereby defining a growth advantage. In contrast, loss of PTEN function in a progesterone rich environment may have few effects, as normal genetically intact endometrial glands shut down expression of PTEN in that circumstance.

Large scale expression profiling of endometrial tissue RNAs has enabled global comparisons of hormonal changes to those of malignant transformation\textsuperscript{92}. Malignant (Type I endometrioid) endometrial tissues most closely mimic the expression profile of estrogen-driven normal proliferative endometrium, and specifically fail to express most genes which increase in activity in normal secretory endometrium upon progesterone exposure. Overall, loss of gene expression in cancers is the predominant alteration of neoplastic transformation, accounting for 8 of 10 discriminating changes in RNA abundance. This is to be expected from a model of transformation which is primarily driven by inactivation of tumor suppressors. Only a minute fraction of gene expression changes of cancers, however, are caused by primary mutational events\textsuperscript{93}. Most are the downstream effects of a causal event within a pathway cascade.

Persistence of premalignant disease and its progression to carcinoma are heavily modified by endometrial tissue shedding and competitive remodeling. Precancers located within a non-cycling endometrial compartment such as the endometrial basalis, or a hormonally non responsive endometrial polyp are unlikely to be shed during a regular menstrual cycle. Correspondingly, unopposed estrogens prolong the interval between shedding episodes, and do so under conditions that favor outgrowth of precancers. These considerations must be taken into account in devising a comprehensive picture of the evolution of what is an inherently unstable process. While it is tempting to believe that the secrets of carcinogenesis will be discovered using high resolution molecular tools, the regional context of complex tissue interactions should not be overlooked.

References

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