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The genomics and genetics of endometrial cancer

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Abstract

Most sporadic endometrial cancers (ECs) can be histologically classified as endometrioid, serous, or clear cell. Each histotype has a distinct natural history, clinical behavior, and genetic etiology. Endometrioid ECs have an overall favorable prognosis. They are typified by high frequency genomic alterations affecting *PIK3CA*, *PIK3R1*, *PTEN*, *KRAS*, *FGFR2*, *ARID1A* (BAF250a), and *CTNNB1* (β-catenin), as well as epigenetic silencing of *MLH1* resulting in microsatellite instability. Serous and clear cell ECs are clinically aggressive tumors that are rare at presentation but account for a disproportionate fraction of all endometrial cancer deaths. Serous ECs tend to be aneuploid and are typified by frequent genomic alterations affecting *TP53* (p53), *PPP2R1A*, *HER-2/ERBB2*, *PIK3CA*, and *PTEN*; additionally, they display dysregulation of E-cadherin, p16, cyclin E, and BAF250a. The genetic etiology of clear cell ECs resembles that of serous ECs, but it remains relatively poorly defined. A detailed discussion of the characteristic patterns of genomic alterations that distinguish the three major histotypes of endometrial cancer is reviewed herein.

Keywords

endometrial; cancer; genomics; genetics; sporadic

Introduction

Endometrial cancer (EC) is the sixth most commonly diagnosed cancer among women worldwide, causing ~74,000 deaths in 2008.[1] Most ECs are sporadic but 2%–5% are familial. Familial EC is linked to germline mutations in the mismatch repair genes *MLH1*, *MSH2*, *MSH6*, or *PMS2*, and to certain germline deletions in *EPCAM*, in families with Lynch syndrome (reviewed by Meyer et al),[2] or to germline mutations in *PTEN* associated with Cowden Syndrome.[2–4]

ECs can be classified into a number of distinct histological subtypes. Endometrioid, serous, and clear cell ECs represent the three major histological subtypes, each with a distinct natural history, genetic etiology, and associated clinical outcome.[5,6] Other rare histological subtypes of EC include carcinosarcomas, also known as malignant mixed Müllerian tumors, mucinous carcinomas, squamous cell carcinomas, and transitional cell carcinomas.[7,8] In the clinical setting, endometrial tumors can be comprised of a single histology or an admixture of two or more distinct histotypes, in which each component represents at least 10% of the

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tumor volume (reviewed by Acharya et al).[7] In cases of mixed histology, clinical treatment is generally based on the most aggressive component (reviewed by Acharya et al).[7] This review will focus on endometrioid, serous, and clear cell ECs because, collectively, they comprise the majority of endometrial carcinomas.

Endometrioid ECs (EECs) represent the most common histological subtype at presentation. They are estrogen-dependent tumors that may be preceded by hyperplasia, atypical hyperplasia, and endometrial intraepithelial neoplasia, a premalignant outgrowth from hormonally-induced, benign endometrial hyperplasia.[9–11] Epidemiological risk factors leading to unopposed estrogen exposure including obesity, nulliparity, early age at menarche, late age at menopause, and unopposed estrogen therapy in post-menopausal women, are established risk factors for EEC (reviewed by Mahboubi et al).[12] Most EECs are low-grade (G1 or G2) tumors that are diagnosed at an early stage, before extra-uterine spread.[6] Consequently, surgical intervention is curative in many cases, and contributes to an overall favorable prognosis for EEC, as evidenced by a 5-year relative survival rate of ~90%.[6] However, the prognosis is markedly less favorable for advanced stage disease and high-grade (G3) EECs.[5,6,13]

Serous and clear cell ECs are high-grade, estrogen-independent tumors that generally arise from the atrophic endometrium in postmenopausal women, although there are examples of serous EC in a non-atrophic background.[14] They have no known epidemiological risk factors other than increasing age. Serous ECs can be preceded by precancerous cells that exhibit a "p53 signature," endometrial glandular dysplasia (EmGD), and endometrial intra-epithelial carcinoma (EIC).[15–22] Serous EC is frequently diagnosed at an advanced stage and has a significantly poorer prognosis than EEC, with an overall 5-year relative survival rate of only 44%.[6] Clear cell EmGD has been suggested to precede clear cell EC.[23] The overall 5-year relative survival rate for clear cell ECs is 65%, intermediate to serous and EECs.[6] Together, serous and clear cell tumors represent only ~13% of diagnosed tumors, but they contribute disproportionately to mortality and account for more than half of all deaths from EC.[13,24] Even when corrected for stage, patients with serous and clear cell EC have a much worse prognosis than those with EEC, pointing to differences in the underlying biology of these subtypes.[13]

Historically, most genetic studies have focused on EEC. There have been few systematic studies of serous EC, and even fewer on clear cell EC. Thus, the genetic etiology of the most clinically aggressive subtypes remains relatively poorly defined. Nonetheless, it is clear that there are important genetic distinctions between the three subtypes, both from mutational analyses and gene expression profiling.[25] In this review, we will highlight the somatic genetic alterations that distinguish sporadic endometrioid and non-endometrioid (serous and clear cell) tumors.

The genetic etiology of endometrioid endometrial cancers

EECs are typified by frequent microsatellite instability (MSI), and somatic alterations within the PI3K pathway, the MAPK pathway, *CTNNB1*(β-Catenin), and *ARID1A* (BAF250a) (Table 1 and Figure 1).

Microsatellite instability (MSI)

A MSI phenotype is marked by a high frequency of mutations at sites of short nucleotide repeats (microsatellites) within the genome. MSI is the result of unrepaired errors that arise during DNA replication. It is detectable in ~20% of unselected endometrial tumors,[26–28] and is more frequent among EECs than non-EECs (NEECs).[29,30] In sporadic endometrial tumors, MSI-positivity reflects an increased mutation rate resulting from somatic alterations

in DNA mismatch repair genes. Most presumed sporadic, MSI-positive EECs are associated with epigenetic silencing of *MLH1,* via promoter hypermethylation.[31–34] This occurs early in EEC progression; *MLH1* promoter hypermethylation has been documented in 3% of complex endometrial hyperplasias, and 33% of atypical hyperplasias.[29]

A smaller fraction of MSI-positive EECs have somatic mutations in *MSH6*,[30,33] or loss of MSH2 protein expression.[35,36] Somatic mutations in *MSH3* have also been described in sporadic EC but, because they occur within a mononucleotide repeat tract, it has been suggested that they may be a consequence, rather than a cause, of defective mismatch repair.[37] Likewise, certain *MSH6* mutations have recently been proposed to occur secondarily to MSI.[38]

MLH1 and other mismatch repair genes are among the so-called "caretaker genes" that normally function to preserve genomic stability; loss of their function leads to the accumulation of mutations in other target genes that drive tumorigenesis.[39] A number of target genes have been described in EC, although it is worth noting that most studies do not state whether the tumors occurred sporadically or in the context of Lynch syndrome. Within MSI-high EECs, the presence of somatic mutations involving simple nucleotide repeats in *BHD* (13%),[40] *BAX* (29%–53%),[33,41–43] *IGFIIR* (14%–21%),[33,41] *TGFβ-RII* (10%–37%),[38,41,44,45] *E2F4* (21%),[33] *MLH3* (21%),[42] *MSH3* (14%–33%),[37,41,42] *MHS6* (7%–36%),[33,38,41,42] *CDC25C* (7%),[42] *DNAPKcs* (34%),[46] *RAD50* (17%),[46] *MRE11* (15%–50%),[46,47] *ATR* (14%–15%),[42,46] *BRCA1* (15%),[46] *CtIP* (12%),[46] *CHK1* (7%–28%),[41,42] and *MCPH1* (12%),[46] implicates these genes as targets of MSI and potential drivers of MSI-positive endometrial tumorigenesis. Many of these genes, including *ATR*, are involved in the DNA damage response. MSI-associated truncating mutations in *ATR* are loss-of-function mutations that are significantly associated with both disease-free survival and overall survival in multivariate analyses.[48,49]

Early-stage EECs with and without MSI exhibit distinct gene expression profiles.[50] It has been suggested that this might be either a direct effect of their differing MSI status, or alternatively, it might result from differences in the global methylation status of MSI+ and MSI− tumor subgroups, and therefore be indirectly associated with MSI caused by *MLH1* hypermethylation.[50]

The PI3K pathway

The most frequently altered biochemical pathway in EECs is the PI3K-PTEN-AKT signal transduction pathway, which regulates numerous cellular processes including proliferation, growth, and survival.[51] In the most comprehensive evaluation of PI3K pathway alterations in EECs to date, more than 80% of tumors had one or more somatic alterations affecting the pathway.[52] These alterations consist of high frequency mutations in *PIK3R1* (p85α), *PIK3CA* (p110α), and *PTEN; PIK3CA* amplification (7%–33% of EECs)*; PTEN* promoter methylation or loss of PTEN expression; as well as rare mutations in *AKT1* (2%) and *PIK3R2* (p85β) (5%).[52–64] In EEC, an additional level of dysregulation of mTOR is achieved by loss of expression of TSC2 and LKB1, which have been documented in 13% and 21% of EECs, respectively.[65]

The interplay between the various PI3K pathway alterations in EECs is complex. *PIK3R1* and *PIK3CA* mutations are generally mutually exclusive, suggesting functional redundancy.[52,58] In contrast, *PTEN* mutations frequently coexist, and can functionally cooperate, with *PIK3R1* and *PIK3CA* mutations.[52,54,58] Although PTEN is an important regulator of the PI3K-AKT pathway, it also has PI3K-independent functions. For example, PTEN plays an important role in the maintenance of genomic integrity.[66] Recent work

revealed that PTEN-deficient EC cell lines are sensitive to PARP inhibitors, pointing to a potential Achille's heel for targeted therapy in EC.[67]

Endometrial tumors have a tissue specific pattern of *PIK3CA* mutations, with a significantly higher frequency of mutations in the ABD and C2 domains of p110α than any other tumor type that has been comprehensively evaluated.[52,57,62] The reason for this tissue specificity is unclear but it is intriguing that p85α, which binds the ABD and C2 domains of p110α, is somatically mutated at high frequency in EC but only rarely in other tumors. Together, these observations suggest that disrupting the p85α-p110α interaction may confer a tissue specific selective advantage in endometrial tumorigenesis.

PTEN mutation is one of the earliest known events in the genesis of EEC, occurring in 20%–27% of endometrial hyperplasias,[68,69] and in 55% of endometrial intraepithelial neoplasias.[70] *PTEN* mutations are believed to precede mismatch repair defects in the progression of sporadic EECs.[71] In contrast to *PTEN*, *PIK3CA* mutations are rare in complex atypical hyperplasia, and appear to be later events in the progression of EEC.[72]

The RAS-RAF-MEK-ERK pathway

The RAS family of oncogenes are frequently activated in a variety of human cancers. RAS proteins mediate signal transduction via both the RAF-MEK-ERK and PI3K-PTEN-AKT pathways, and thus regulate numerous processes including cell proliferation and cell survival.[73]

Somatic mutations in *KRAS* were first described in EC over two decades ago, and were subsequently found to be significantly more frequent in EEC than in serous EC.[74–80] On average, *KRAS* is mutated in 18% of EECs compared with 3% of serous ECs (Figure 1).[81] *KRAS* mutations occur early in the genesis of EECs, having been documented in atypical endometrial hyperplasia.[82–84] However, MSI appears to precede *KRAS* mutation in the progression of EEC.[82]

In EC, *KRAS* mutations can coexist with mutations in *PTEN*, *PIK3CA*, and *PIK3R1*, suggesting that *KRAS* mutations are not functionally redundant with PI3K pathway mutations.[52,57,58,85] This is supported by the results of a recent comprehensive genomics and proteomics analysis of the RAS-RAF-MEK-ERK and PI3K-PTEN-AKT pathways in EC in which Cheung et al showed that *KRAS* mutations were associated with increased phosphorylation of MEK1/2, ERK1/2, and p38MAPK.[52] Oda et al have also shown functional synergy between mutant *KRAS* and mutant *PIK3CA* in the transformation of HMLE cells.[85] Finally, a conditional mouse model of EC in which *PTEN* was ablated and *KRAS* was activated in the reproductive tract, showed an acceleration in the development of EC as compared to mice with only a single lesion.[86]

In contrast to *KRAS* mutations, somatic mutations in codons 11 and 15 of *BRAF*, the sites of hotspot mutations in other cancers, are infrequent in EECs,[38,87–91] and are mutually exclusive with *KRAS* mutations and hypermethylation of *RASSF1A.*[89] The overall *BRAF* mutation frequency in ECs is 1%.[81] Only one study noted a high frequency (21%) of *BRAF* mutations in EC.[92] It has been suggested that this high frequency of mutations might reflect ethnic differences between study populations,[91] although this has not yet been verified.

RASSF1A is a multifunctional tumor suppressor that has been implicated in the regulation of numerous cellular processes and pathways, including the RAS signal transduction pathway.[93] Hypermethylation of the *RASSF1A* promoter is frequent in EECs (62%–74%) and correlates with reduced expression of RASSF1A.[94–96] *RASSF1A* promoter methylation

has been documented in histologically normal tissue adjacent to EEC, and in complex hyperplasia with and without atypia.[95,97]

In EECs, methylation of the *RASSF1A* promoter is significantly associated with advanced stage disease.[94] *RASSF1A* promoter hypermethylation is significantly more frequent in microsatellite unstable tumors than in microsatellite stable tumors, leading to the proposal that this reflects an underlying methylator phenotype that targets the *MLH1* mismatch repair gene and other genes, including *RASSF1A*.[89] *RASSF1A* methylation is also more frequent in tumors lacking a *KRAS* mutation than in tumors with mutant *KRAS* (38% vs 14%), although the difference did not achieve statistical significance.[89]

Several other genes that modulate the activity of the RAS-RAF-MAPK pathway are also subjected to aberrant methylation in EECs. These include *RASSF2A*, *HDAB2IP*, *BLU*, *SPROUTY-2*, and *RSP6KA6* (*RSK4*).[94,98,99]

FGFR2

Somatic mutations in the *FGFR2* receptor tyrosine kinase have been described in 12% of EECs.[52,100,101] *FGFR2* mutations are mutually exclusive with *KRAS* mutations, indicating functional redundancy, whereas most (77%) *FGFR2*-mutant ECs are *PTEN*-mutant.[102] In EC, the vast majority of *FGFR2* mutations are missense mutations within the extracellular, transmembrane, and kinase domains of the protein. Codon 252 (S252) forms a prominent mutation hotspot within a region of the extracellular domain that mediates ligand binding.[101] The S252W mutant is oncogenic and accounts for ~41% of all mutations reported in EC to date.[81,100] EC cell lines that harbor the FGFR2-S252W mutant appear to be dependent upon expression of the mutant protein for their survival.[100,102] Importantly, EC cell lines with an activating mutation in *FGFR2* are more sensitive to killing by PD173074, a pan-FGFR inhibitor, than *FGFR2*-wildtype EC cell lines, thus pointing to mutant FGFR2 as a potential therapeutic target.[100,102]

CTNNB1(β-Catenin)

CTNNB1 encodes β-catenin, an integral member of the canonical WNT signaling pathway. Somatic mutations in *CTNNB1* and stabilization of β-catenin are common features of EEC.[103,104] *CTNNB1* mutations occur in up to 45% of EECs; they have not been found in NEECs, but only a small number of tumors have been evaluated (Table 1). Similarly, nuclear expression of β-catenin has been observed in 31%–47% of EECs, compared with 0%–3% of NEECs.[104] A significant correlation between β-catenin accumulation and *CTNNB1* mutations has been noted ($P < 0.0001$).[105] Dysregulation of *CTNNB1*/β-catenin occurs early in the pathogenesis of EEC; it has been observed in atypical hyperplasias, in the squamous component of complex endometrial hyperplasia with atypia, and in endometrial intraepithelial neoplasia.[106–110]

ARID1A (BAF250a)

ARID1A is a recently described tumor suppressor gene that encodes BAF250a, a component of the SWI/SNF chromatin-remodeling complex.[111] Dysregulation of *ARID1A* and BAF250a has been implicated in a large fraction of EECs. Loss of BAF250a expression has been observed by immunohistochemistry (IHC) in 26%–29% of low-grade (G1 or G2) EECs, and in 39% of high-grade (G3) EECs.[112,113] Consistent with this observation, somatic mutations in *ARID1A* were detected among 40% of low-grade EECs; 50% of mutated tumors showed loss of BAF250a expression.[113]

The genetic etiology of serous and clear cell ECs

In contrast to EECs, serous ECs are often aneuploid,[114–120] and are typified by frequent stabilization or mutation of *p53*, overexpression of cyclin E and ERBB2, p16 dysregulation, mutations in *PPP2R1A*, and a moderate frequency of alterations within the PI3K pathway (Table 1 and Figure 1).

TP53 (p53)

The most frequently altered cancer gene in serous EC is the *TP53* tumor suppressor gene. In early landmark studies, 80%–86% of serous tumors showed positive immunostaining for p53, and 53%–90% of tumors had somatic *TP53* mutations.[80,121–125] *TP53*/p53 aberrations occur very early in the genesis of serous EC. They are present in morphologically benign endometrial glands or epithelium adjacent to serous EC, the so-called "p53 signature", as well as in EmGD, and EIC.[18,22,122,124] In 50% of uteri with coexisting "p53 signatures," EmGD, EIC, and serous EC, identical *p53* mutations were observed in all four entities.[22] An increasing frequency of *TP53* mutations has also been noted between the normal endometrium (0%), EmGD (43%), EIC (72%), and serous-EC (96%).[18] These observations, coupled with detailed pathologic descriptions of "p53 signatures," EmGD, and EIC, present a new model for the evolution of serous EC. This model posits a transition from the normal resting epithelium, to latent precancerous "p53 signatures," to precancerous EmGD, to EIC, and finally to serous EC.[18,22]

In contrast to serous ECs, EECs have a significantly lower overall incidence of p53 positivity (3%–52%) and *TP53* mutation (12%–23%).[80,92,123,124,126–129] The incidence of *TP53* mutations is greater in high-grade (G3) EECs than in low-grade EECs (43% of G3, 8% of G2, 0% of G1).[80] However the incidence of p53 positivity and *TP53* mutation in high-grade EECs is still subject to interpretation, as some of the reported high-grade EEC cases may actually be serous EC, due to the occasional histological ambiguity between these two subtypes.[130] The frequency of *TP53* mutations in clear cell EC has not been well defined although one study noted mutations in 9% of tumors.[131]

PPP2R1A

The PP2A serine-threonine phosphatase is a trimeric holoenzyme composed of a catalytic subunit (PP2Ac; subunit C), a scaffolding subunit (PR65; subunit A) and one of a number of variable regulatory (B) subunits (reviewed by Eichhorn et al).[132] The scaffolding subunits are encoded by *PPP2R1A* (PR65α) or *PPP2R1B* (PR65β). They contain 15 HEAT (Huntington/elongation/A-subunit/TOR) motifs; HEAT motifs 2–7 mediate binding to the regulatory subunits, whereas HEAT motifs 11–15 mediate binding to the catalytic subunit of the holoenzyme.

Somatic mutations in *PPP2R1A* (PR65α) occur at very high frequency (17%–41%) in serous EC.[133–135] In contrast, *PPP2R1A* is infrequently (5%–7%) mutated in EECs.[133–135] It remains to be determined whether *PPP2R1A* is mutated in pure clear cell ECs; only five primary tumors of this subtype have been sequenced and no mutations were detected.[133,134]

Resequencing of *PPP2R1A* in ECs has thus far been confined to exons 5 and 6, based on earlier observations that *PPP2R1A* mutations in ovarian cancer localized exclusively within these two exons.[135] Interestingly, the distribution of *PPP2R1A* mutations within exons 5 and 6 differs between endometrial and ovarian cancers. The majority (72%, 18 of 25 mutations) of mutations in ovarian cancer involve codons 182 and 183 whereas the majority of mutations in EC (77%, 30 of 39) involve codons 179, 256, and 257. The significance of this tissue-specific difference is currently unclear but has been suggested to possibly reflect different underlying mechanisms of mutagenesis, or perhaps tissue-specific functional

effects.[135] Only a small number of mutations in *PPP2R1A* have been described in EECs, but it is noteworthy that they were more frequent in codons 182/183 than in codons 256/257.[133–135]

The mechanism whereby *PPP2R1A* mutations contribute to tumorigenesis is currently unclear. The clustering of mutations to the 5th and 7th HEAT motifs of PR65α which interface with the regulatory subunits of PP2A, has led to speculation that the mutant scaffolding proteins might have an impaired interaction with the regulatory subunits, thus resulting in altered substrate recognition and/or altered phosphatase activity.[133,135] Because the majority of *PPP2R1A* mutations are heterozygous, and PP2A has been ascribed tumor suppressor properties (reviewed by Eichhorn et al),[132] it has been proposed that mutant *PPP2R1A* might function either as a haploinsufficient tumor suppressor gene, or by exerting a dominant negative effect on the protein encoded by retained wild type allele.[135]

HER-2/ERBB2

Protein overexpression and genomic amplification of the HER-2/ERBB2 receptor tyrosine kinase are significantly more frequent among serous ECs than among EECs.[136–138] In serous EC, overexpression of HER-2/ERBB2 by IHC has been noted in 17%–80% of cases.[119,136,137,139–147] *HER-2/ERBB2* amplification, determined by FISH, has been noted in 17%–68% of serous tumors that overexpress the protein,[141,148] and in 17%–42% of serous tumors overall.[136,138,143,148] A number of factors have been suggested to account for the inter-study variability in the frequency of HER-2/ERBB2 overexpression, including the small number of samples in some studies, differences in study populations, and variability in IHC, including inconsistencies in scoring HER-2/ERBB2 positivity.[141]

Several studies have observed correlations between HER-2/ERBB2 status and clinicopathological characteristics of serous ECs. HER-2/ERBB2-overexpressing serous ECs were associated with significantly shorter survival times (overall, 2-year, and 5-year) than HER-2/ERBB2-negative serous ECs, suggesting that HER-2/ERBB2 overexpression may be of prognostic value.[136,141,142,145] Higher frequencies of HER-2/ERBB2 overexpression and amplification have been noted in serous ECs from African Americans compared with Caucasians, although the basis for this difference remains unexplained.[140,149] Finally, two studies noted that patients with HER-2/ERBB2-positive serous ECs were more likely to have had a personal history of breast cancer than those who were HER-2/ERBB2-negative.[141,144] The role of HER-2/ERBB2 perturbations in clear cell EC remains poorly defined due to the limited number of tumors analyzed.

The PI3K pathway

Somatic alterations in the PI3K pathway are significantly less frequent in serous EC than EEC. Nonetheless, the combined frequency of PI3K pathway alterations in serous EC is appreciable (39%), resulting from mutations in *PTEN* (13%), *PIK3CA* (35%), and *PIK3R1* (8%).[57,58,150,151] Compared to serous ECs, clear cell ECs do not show a statistically significant difference in the mutation frequency of *PTEN* (5%), *PIK3CA* (30%), and *PIK3R1* (20%), although only a small number of clear cell tumors have been analyzed.[57,58] Overall, 35% of clear cell ECs had a PI3K pathway mutation in one series.[58]

The spectrum of *PIK3R1* mutations in NEECs differs somewhat from that of EECs.[58] Most *PIK3R1* mutants found in NEECs are truncation mutations, which preferentially co-occur with *PIK3CA* mutations and are currently of unknown functional significance. This is in contrast to *PIK3R1* mutations in EECs, which tend to be small in-frame deletions that are mutually exclusive with *PIK3CA* mutations and, in some cases, have an impaired ability to inhibit AKT activation.[52,58]

ARID1A (BAF250a)

Loss of BAF250a expression has recently been reported in 18% of serous ECs and in 26% of clear cell ECs.[112] The frequency of BAF250a loss is significantly lower in serous ECs than in high-grade endometrioid carcinomas ($P < 0.001$).[112] No mutations in *ARID1A* have been reported in either serous or clear cell ECs but only a limited number of these tumors have been sequenced.[113] Given the strong correlation between mutations in *ARID1A* and loss of BAF250a expression in other tumors,[113] it seems likely that *ARID1A* mutations are also present within NEECs.

CCNE (cyclin E)

High levels of cyclin E, measured by IHC staining, have been reported in 51%–80% of poorly differentiated ECs, compared with 31%–45% of well- to moderately-differentiated ECs; in some studies, this difference attained statistical significance.[152–154] Cyclin E overexpression is also statistically significantly more frequent among NEECs than EECs (54.5% vs 27.5%; $P = 0.035$).[154]

There are at least two underlying molecular mechanisms that account for high levels of cyclin E in EC. The first mechanism is amplification of *CCNE*, which is present in 16% of ECs overall, and in 30% of ECs that over express cyclin E.[154] The second mechanism is loss-of-function mutations within the *FBXW7/CDC4/hAGO* tumor suppressor gene.[154,155] *FBXW7* encodes the substrate recognition component of an SCF-ubiquitin ligase complex that targets cyclin E for ubiquitin-mediated proteosomal degradation.[156,157] Somatic mutations within *FBXW7* have been reported at variable frequency among endometrial carcinomas. Two studies found *FBXW7* mutations only rarely (~3%) in endometrial carcinomas, though neither specified the histology of tumors analyzed for mutations.[100,154] In contrast, Suehiro et al identified a high frequency of *FBXW7* mutations in EECs (46.8%).[158] Spruck et al reported a moderate frequency (16%) of *FBXW7* mutations in endometrial tumors that had elevated levels of cyclin E or phosphorylated cyclin E, although the tumor histotype was not specified.[155] Thus, the frequency of *FBXW7* mutations in NEECs remains to be elucidated.

CDKN2A (p16)

The CDKN2A/p16 tumor suppressor is a negative regulator of G1/S cell cycle progression. Recent studies on large tumor panels have revealed that serous ECs nearly uniformly show strong diffuse staining of p16, indicative of high expression.[159–162] This is in stark contrast to the weak focal staining of endometrioid tumors of all grades. Though the prognostic significance and molecular basis for p16 overexpression has yet to be determined, it has been suggested that p16 expression may serve as a potent biomarker that might be useful in the molecular classification of ECs, particularly for high-grade tumors.[161–163] In addition, *CDKN2A* is mutated in 10%–28% of EECs compared with 44% of NEECs, although the latter observation is based on a small sample size.[163–165]

Claudins and other cellular adhesion proteins

In 2005, Santin et al noted differential expression of numerous genes by microarray analysis between primary short-term cultures of serous ECs and normal endometrial cells, including several genes that regulate cell adhesion.[166] Among these genes, claudins-3 and -4, which encode cell adhesion proteins present at tight junctions, were upregulated in serous EC. RT-PCR confirmed the upregulation of claudin-3 (8-fold) and claudin-4 (12-fold) in serous cultures compared with normal endometrial cell cultures. Immunohistochemistry for claudin-4 on corresponding primary tumor specimens, as well as a small number of additional serous tumors, revealed stronger staining for claudin-4 in serous EC compared

with normal endometrial cells. In a subsequent study of a large number of endometrial tumors, Konecny et al showed that positive immunohistochemical staining for claudins-3 and -4 is significantly more frequent among serous (78% and 56%) and clear cell (61% and 44%) ECs than among EECs (38% and 9%).[167] In multivariate analyses, claudin expression was not a significant independent prognostic indicator. In contrast, Sobel et al failed to find an association between claudin-3 and -4 levels and histotype of EC in a small series of tumors.[168] One possible reason for the variability between studies might be the differences in sample sizes. The observation that claudins-3 and -4 are upregulated in serous EC holds promise for the development of targeted therapy, since *Clostridium perfringens* enterotoxin (CPE) targets claudins-3 and -4 and causes cytolysis upon binding.[169]

The original study that uncovered upregulation of claudins-3 and -4 in serous EC, compared with normal endometrium, also noted upregulation of several other genes that encode cell adhesion proteins, including *L1CAM* (*L1 cellular adhesion molecule*), and *EpCAM* (*Epithelial Cell Adhesion Molecule*).[166] The observation of *L1CAM* upregulation was consistent with an earlier report that immunohistochemical expression of L1CAM was more frequent among serous ECs than EECs (75% vs 16%), although the number of serous tumors evaluated was small.[170] The upregulation of *EpCAM* expression in serous EC has also been verified immunohistochemically; in one study, EpCAM staining was shown to be significantly higher in serous ECs than in normal endometrium.[171] Serous EC cell lines that were positive for EpCAM were sensitive to MT201 (adecatumumab), a human monoclonal antibody against EpCAM, suggesting that high EpCAM levels may represent a druggable target for serous ECs.[171] As discussed below, E-cadherin, another cell adhesion molecule, has a well-established role in serous EC.

E-cadherin

The *CDH1* tumor suppressor gene encodes E-cadherin, a calcium-dependent cell adhesion molecule. Loss of E-cadherin expression is a characteristic feature of the epithelial to mesenchymal transition.[172] Negative or reduced expression of E-cadherin has been described in ECs, and is significantly more frequent among serous and clear cell endometrial tumors than among EECs [83% vs 53%; $P = 0.002$],[173] [62% vs 5%; $P < 0.001$],[174] [87.1% vs 50%; $P = 0.001$],[175] [75% vs 43%; $P = 0.04$].[176] In stage I–III EC, multivariate Cox regression analysis showed that high E-cadherin expression was associated with decreased overall mortality, and was statistically significantly associated with decreases in EC mortality, disease progression, and extra pelvic recurrence.[177] In a recent multicenter Phase II trial (GOG-119) that examined prognostic factors in stage IV or recurrent ECs, high expression of E-cadherin was associated with longer median survival, and reduced risks of disease progression and death.[178]

The molecular mechanisms accounting for reduced E-cadherin expression in EC are not fully elucidated. Somatic mutations in *CDH1* are rare in EC.[179] Loss of heterozygosity encompassing the gene has been reported at higher frequency in NEECs than EECs (57% vs 22.5%).[176] *CDH1* promoter hypermethylation is also common among ECs (21%–40%) but does not always correlate with reduced protein expression.[176,180,181]

Other mechanisms that may contribute to decreased E-cadherin expression in EC include dysregulation of certain transcriptional repressors of E-cadherin. Transcriptional repressors of E-cadherin include SNAI1 (Snail), SNAI2 (Slug), ZEB1, HMGA2, and TWIST.[182] In stage IC EECs, each of these repressors is significantly overexpressed at the mRNA level, compared with normal endometrium, with a tendency towards associated lower E-cadherin levels, although this was not statistically significant.[182] Other studies have reported a statistically significant inverse correlation between Snail and E-cadherin expression in

metastatic EECs.[183] Similarly, an inverse correlation between ZEB1 expression and E-cadherin expression has been noted in EC cell lines.[184]

Therapeutic targets for EC

Uncovering the genetic etiology of EC has provided not only new insights into the biology of the disease, but has also revealed molecular alterations that may be exploited for targeted therapy (Table 2).

The frequent mutational disruption of the PI3K-PTEN-AKT axis in EEC prompted clinical trials of drugs that target this pathway. Among these agents are the mTOR inhibitors temsirolimus (CC1-779), everolimus (RAD001), and ridaforolimus (AP23573). Encouraging results of a Phase II trial of temsirolimus in chemotherapy-naïve and chemotherapy-treated patients, with recurrent or metastatic EC, have recently been reported.[185] In the chemotherapy-naïve group, 14% of evaluable patients had a partial response and 69% had stable disease (mean duration 9.7 months; range 2.1 to 14.6 months). In the chemotherapy-treated group, partial responses were achieved in 4% of patients, while 48% of patients had stable disease (mean duration 3.8 months; range 2.4 to 23.2 months). Interestingly, the *PTEN* mutational status of archival tumor tissue was not predictive of response but, as noted in the study, this may not reflect the mutational status of the recurrent tumor.[185] A Phase II trial of everolimus in previously treated, progressive, or recurrent EEC also reported encouraging results.[186] Although there were no cases of complete or partial response, 43% of evaluable patients had stable disease at the time of first evaluation (8 weeks); the confirmed clinical benefit rate was 21% at 20 weeks. No significant molecular correlates of response were detected.[187] The interim results of a Phase II trial of ridaforolimus (AP23573) as a single agent in advanced EC patients with disease progression, revealed that 33% of evaluable patients had clinical benefit response, including two partial responses, one of which was serous EC.[188] Importantly, preclinical studies have shown that inhibition of mTOR can lead to activation of MAPK, while pharmacological inhibition of MAPK enhances the anti-tumor effect of rapamycin, both in vitro and in vivo.[189] These observations have led to clinical trials using combinatorial approaches to target both the PI3K and MEK pathways in EC and other cancers.

The recent identification of activating *FGFR2* mutations in a subset of EECs, and subsequent preclinical studies, have highlighted mutant FGFR2 as a potentially druggable target. A Phase II clinical trial to access safety, tolerability, and pharmacokinetics of FP-1039, a soluble fusion protein designed to bind FGFR ligands, for patients with metastatic or locally advanced EC and a somatic $FGFR2^{S252W}$ or $FGFR2^{P243R}$ mutation, is currently recruiting patients (NCT01244438). A Phase II study (NCT01379534) evaluating the efficacy of TKI258 (dovitinib), a multitargeted receptor tyrosine kinase inhibitor, for treatment of *FGFR2*-mutated or -wildtype, advanced or metastatic EC, is also recruiting patients.

Recent preclinical evidence has indicated that PTEN deficiency sensitizes EC cells to PARP inhibitors.[67] Encouragingly, a recent case report of an EC patient with a PTEN-deficient, presumed BRCA-intact, metastatic endometrioid endometrial tumor reported clinical benefit following treatment with olaparib, a PARP inhibitor.[190] NCI clinical trial #NCT01237067 is a study for refractory or recurrent women's cancers, including EC, which is designed to determine the safety and efficacy of olaparib, a PARP inhibitor, in combination with carboplatin.

HER-2 amplification and overexpression in NEECs also presents a druggable target. Individual case reports have documented clinical responses in advanced or recurrent EC patients following treatment with trastuzumab, an anti-HER-2 monoclonal antibody.[191,192]

However, a Phase II trial of trastuzumab in a small cohort of recurrent or advanced stage, HER2-positive EC patients documented stable disease in 40% of evaluable cases, with no reports of partial or complete response.[193]

Additional targeted therapies being evaluated for the treatment of EC include pharmacological inhibitors of VEGF, HIF1a, EphA2, and EGFR, as reviewed in detail elsewhere.[8,194]

Conclusion and future prospects

In conclusion, our understanding of the genetic etiology of EECs and serous ECs has advanced considerably over the past 20 years, and reflects a large body of research on individual genes, gene families, and pathways, as reviewed herein. As for most cancers, the rate-limiting step in dissecting the genetic alterations that underlie EC has been the availability of sufficiently high-resolution genomic technologies.[195] However, within the past 5 years, the development and implementation of so-called next generation sequencing has resulted in a massive paradigm shift in cancer genomics because it provides the tools to systematically interrogate cancer genomes, exomes, and transcriptomes, nucleotide by nucleotide, for somatic alterations in gene sequence, structure, and copy number.[195]

The Cancer Genome Atlas is currently conducting large-scale, integrated genomic and epigenomic analyses of low-grade EECs, high-grade EECs, and serous ECs using massively parallel sequencing and other high resolution genomic and epigenomic approaches. The resulting catalogs of somatic alterations are eagerly awaited because they will reveal, for the first time, the most comprehensive view of the genomic, transcriptomic, and epigenomic landscape of ECs. This will provide a solid foundation for future studies to determine whether the altered genes are relevant to the biology and clinical management of women with EC.

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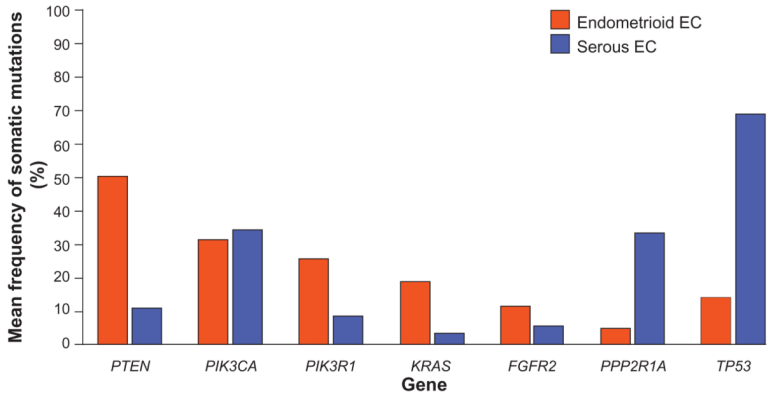

Figure 1.

Mean frequency of somatic mutations in cancer genes in endometrioid and serous ECs. The data were derived for genes that have been evaluated in at least 40 tumors of each subtype: *FGFR2*,[52,100,101] *KRAS*,[38,52,53,57,63,77,78,80,87,88,90,92,100,102,105] *PIK3CA*,[52,57] *PIK3R1*,[52,58] *PPP2R1A*,[133–135] *PTEN*,[52,53,56,57,59,60,62,72,102,196–198] *TP53*.[52,60,80,92,122,128,129,131,196]

Table 1

Frequency range of genomic and proteomic aberrations among endometrioid and non-endometrioid endometrial cancers

Tumor characteristic	Frequency (range)		References
	EECs (%)	NEECs (%)	
Aneuploidy	10–50	70–95	116,118–120
MSI+	20–23	15	26–28,30
AKT1 mutation	2–3	13	53,199
ARID1A mutation	40	0	113
BRAF mutation	0–23	11	88,92
CDKN2A mutation	10–30	44*	163–165
CTNNB1 mutation	2–45	0**	52,103,110
FBXW7 mutation	2–16	0	154,155
FGFR2 mutation	5–16	2–3	100,101
KRAS mutation	8–43	2	57,80,88
PIK3CA mutation	20–52	33	57,62
PIK3R1 mutation	21–43	12	52,58
PPP2R1A mutation	3–7	17–41	133–135
PTEN mutation	26–79	13–19	57,198
TP53 mutation	5–20	53–90	60,122,125,129
CCNE1 amplification	5	42	154
ERBB2 amplification	1–63	17–42	137,138,200
E-Cadherin negative expression	5–53	62–88	173,174,176
Claudin-3 positive expression	38	74	167
Claudin-4 positive expression	9	63	167
p16 positive expression	5–38	63–100	160,161

Notes:

* Based on an analysis of twelve tumors;

** based on an analysis of nine tumors.

Table 2

Ongoing clinical trials of targeted therapies for endometrial cancer (ClinicalTrials.gov)

Inhibitor	Molecular target	Phase	Monotherapy/combination therapy	Trial identifier
Temsirolimus	mTOR	II	Combination	NCT01010126
Temsirolimus	mTOR	II	Combination	NCT00977574
Temsirolimus	mTOR	I	Combination	NCT00982631
Ridaforolimus	mTOR	I	Combination	NCT01256268
Everolimus	mTOR	I	Combination	NCT00703807
MK2206	AKT	II	Monotherapy	NCT01307631
BKM120	PI3K	II	Monotherapy	NCT01397877
XL147	PI3K	II	Monotherapy	NCT01013324
XL147	PI3K	I	Combination	NCT00756847
GDC-0980	PI3K	II	Monotherapy	NCT01455493
BKM120	Pan-PI3K	II	Monotherapy	NCT01289041
DS-7423	PI3K/mTOR	I	Monotherapy	NCT01364844
BEZ235	PI3K/mTOR	II	Monotherapy	NCT01290406
PF-04691502/PF-05212384	PI3K-mTOR/PI3K-mTOR	II	Combination	NCT01420081
XL147/MSC1936369B	PI3K/MEK	I	Combination	NCT01357330
GSK1120212/GSK2110183	MEK/AKT	I	Combination	NCT01476137
MSC1936369B/SAR245409	MEK/PI3K-mTOR	I	Combination	NCT01390818
FP-1039	FGF	II	Monotherapy	NCT01244438
Trastuzumab	HER-2	II	Combination	NCT01367002
ARRY-380	HER-2	I	Monotherapy	NCT00650572
BIBF 1120	VEGFR/FGFR/PDGFR	II	Monotherapy	NCT01225887
TKI258	RTKs	II	Monotherapy	NCT01379534
Sunitinib or temsirolimus	RTKs/mTOR	II	Monotherapy	NCT01396408
GSK2636771	PTEN-deficiency	I/IIa	Monotherapy	NCT01458067
ARRY-382	CSF-1 receptor	I	Monotherapy	NCT01316822
RO4929097/temsirolimus	Gamma-secretase/mTOR	I	Combination	NCT01198184
Olaparib	PARP	I	Combination	NCT01237067