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The Emerging Genomic Landscape of Endometrial Cancer

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Abstract

BACKGROUND—Endometrial cancer is responsible for ~74,000 deaths amongst women worldwide each year. It is a heterogeneous disease that consists of multiple different histological subtypes. In the United States, the majority of deaths from endometrial carcinoma are attributed to the serous and endometrioid subtypes. An understanding of the fundamental genomic alterations that drive serous and endometrioid endometrial carcinomas lays the foundation for the identification of molecular markers that could improve the clinical management of patients presenting with these tumors.

CONTENT—Herein we review the current state of knowledge of the somatic genomic alterations that are present in serous and endometrioid endometrial tumors. We present this knowledge in a historical context – reviewing the genomic alterations that have been identified over the past two decades or more, from studies of individual genes and proteins, followed by a review of very recent studies that have conducted comprehensive, systematic surveys of genomic, exomic, transcriptomic, epigenomic, and proteomic alterations in serous and endometrioid endometrial carcinomas.

SUMMARY—The recent mapping of the genomic landscape of serous and endometrioid endometrial carcinomas has resulted in the first comprehensive molecular classification of these tumors and has distinguished four molecular subgroups: a *POLE* ultramutated subgroup, a hypermutated/microsatellite unstable subgroup, a copy number low/microsatellite stable subgroup, and a copy number high subgroup. This molecular classification may ultimately serve to refine the diagnosis and treatment of women with endometrioid and serous endometrial tumors.

Introduction

Cancers that arise in the body (corpus) of the uterus represent the 8th leading cause of cancer-related death amongst American women, accounting for an estimated 8,190 deaths in 2013 (1). Worldwide, uterine corpus cancers caused approximately 74,000 deaths in 2008 (2). The majority of uterine corpus cancers are endometrial carcinomas, with the remaining cases (3%–5%) being sarcomas (stromal sarcomas, leiomyosarcomas, undifferentiated sarcomas, adenosarcomas) (3). Endometrial carcinomas can be further classified by histology as endometrioid adenocarcinoma, serous adenocarcinoma, clear cell adenocarcinoma, mixed cell carcinoma, mucinous adenocarcinoma, metaplastic carcinoma

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(carcinosarcoma), squamous cell carcinoma, transitional cell carcinoma, small cell carcinoma, undifferentiated carcinoma, and others (4). The classification of endometrial carcinomas by histological subtype, clinical stage, and grade, is important in assessing prognosis and in deciding the most appropriate treatment regimen (reviewed in (5)).

In the United States, there is a significant racial disparity in survival from uterine corpus cancer with 5-year relative survival rates of only 57%–63% for African American women compared to 84%–88% for white women (1). This difference in survival is explained at least in part by differences in socioeconomic status, access to health care, and by the fact that, compared with white women, African American women are more likely to be diagnosed with aggressive histological subtypes, including serous carcinomas, clear cell carcinomas, and sarcomas (reviewed in (6)).

The majority of endometrial carcinomas arise sporadically as a result of acquired somatic alterations. A large, population-based, case-control, genome wide association study has recently identified a locus (rs1202524) on 1q42.2, in the vicinity of the *CAPN9* gene, that may be associated with increased risk of endometrial cancer (7).

A small fraction of endometrial cancers are associated with autosomal dominant, inherited genetic susceptibility in the context of Lynch Syndrome (Hereditary Non-Polyposis Colorectal Cancer; HNPCC) and Cowden Syndrome (8–10). Lynch syndrome is attributed to germline mutations in mismatch repair genes (*MLH1, MSH2, MSH6, PMS2*), as well as germline deletions of *EPCAM* that result in transcriptional read-through leading to hypermethylation of the *MSH2* promoter, which is located adjacent to *EPCAM* on chromosome 2p21. In contrast, Cowden Syndrome is linked to germline mutations in the *PTEN* tumor suppressor gene. In a single institution study, the relative frequency at which endometrioid and non-endometrioid carcinomas occurred in endometrial cancer patients with Lynch Syndrome was similar to their relative frequency in the general population (11). Recently, whole genome sequencing of constitutional DNA from individuals diagnosed with multiple colorectal adenomas by age 60, revealed that a germline mutation ($POLD1^{Ser478Asn}$) in *POLD1*, which encodes the catalytic subunit of polymerase δ that promotes lagging strand synthesis during DNA replication, is linked to inherited predisposition to both colorectal cancer and endometrial cancer (12). Several studies have suggested that serous endometrial carcinoma may be a component tumor of Hereditary Breast Ovarian Cancer syndrome (reviewed in (13)). However, there is strong epidemiological evidence that the increased incidence of serous endometrial carcinoma in *BRCA1/BRCA2* mutation carriers is associated with prior tamoxifen treatment rather than an underlying genetic susceptibility (14). In this regard, it will be important to also ascertain whether tamoxifen use accounts for any of the documented increased risk to endometrial cancer associated with Cowden syndrome, which also includes breast cancer as a clinical manifestation.

A detailed discussion of the germline genomic alterations that confer susceptibility to endometrial cancer is the subject of another article in this *Special Issue*. Here, we will review both the traditional histological classification of endometrioid and serous

endometrial carcinomas and the molecular classification of these tumors, which has emerged from a new appreciation of their somatic genomic landscapes (15–20).

Histological Classification of Endometrial Carcinomas

Endometrioid endometrial carcinoma

Endometrioid endometrial carcinomas represent ~87–90% of all diagnosed endometrial carcinomas (21). They are frequently estrogen-dependent tumors associated with epidemiological risk factors that lead to unopposed estrogen exposure, including obesity, nulliparity, early age at menarche, and late age at menopause (22, 23). They may be preceded by hyperplasia, atypical hyperplasia, and endometrial intraepithelial neoplasia, which is a premalignant outgrowth from benign endometrial hyperplasia (reviewed in (24)). Most endometrioid tumors are diagnosed at an early clinical stage and are associated with an overall favorable prognosis (25). Treatment strategies for endometrioid endometrial carcinoma are guided not only by stage, but also by tumor grade and depth of myometrial invasion since high tumor grade (grade 3) and/or infiltration of more than 50% of the myometrium are predictors of increased risk of tumor recurrence (reviewed in (5)). Treatment for patients with advanced stage or recurrent disease is highly variable (26). The prognosis for advanced stage disease is relatively poor with 5-year overall survival rates of 36%–56% for stage III disease and 21%–22% for stage IV disease noted in one study (25). Although a number of molecularly targeted therapeutics are in clinical trials for endometrial carcinoma (reviewed in (5, 21)), there are currently no FDA-approved targeted therapies for this tumor type.

Over the past two or more decades, in the era preceding next generation sequencing, much has been done to understand the genetic etiology of endometrioid endometrial carcinomas (reviewed in (24)). Most endometrioid endometrial carcinomas tend to be chromosomally stable with diploid or near-diploid genomes (27). At the molecular level, they are characterized by high frequency genetic alterations in *PIK3CA*, *PIK3R1*, and *PTEN*, resulting in inappropriate activation of the PI3K pathway (28–32). *ARID1A*, which encodes the BAF250A tumor suppressor, is somatically mutated in 40% of low-grade endometrioid endometrial carcinomas (reviewed in (24)). Loss of BAF250A expression is likewise frequent and has been detected in 19%–34% of endometrioid endometrial carcinomas overall, 26%–29% of low-grade endometrioid endometrial carcinomas, 39% of high-grade endometrioid endometrial carcinomas, and in 16% of endometrial hyperplasias with atypia suggesting that this is an initiating event in endometrioid endometrial tumorigenesis ((33–35) and reviewed in (24)). Other signal transduction pathways that are frequently disrupted in endometrioid endometrial carcinomas include the *RAS-RAF-MEK-ERK* pathway, resulting from somatic mutations in *KRAS* (~18% of cases) or hypermethylation of the *RASSF1A* promoter (62–74% of cases) ((36) and reviewed in (24)). Somatic mutations in the *FGFR2* receptor tyrosine kinase occur in ~12% of endometrioid endometrial carcinomas and are mutually exclusive with *KRAS* mutations (36, 37). Although mutual exclusivity implies functional redundancy, the clinical correlates of *KRAS* and *FGFR2* mutations are different, indicating possible differences in their biological effects (36). The canonical WNT signaling pathway is often disrupted in endometrioid endometrial carcinomas, resulting from somatic

mutation of *CTNNB1* (2%–45% of cases) and stabilization of β-catenin (36, 38, 39). It has recently been shown that *CTNNB1* and *KRAS* mutations are mutually exclusive in endometrioid ECs, leading to the proposal that there may be functional cross-talk between the *RAS-RAF-MEK-ERK* and WNT/TCF signaling pathways in this cell type, or functional redundancy in the biological consequences of altered *RAS-RAF-MEK-ERK* and WNT/TCF signaling (36). Endometrioid tumors also often exhibit microsatellite instability (MSI) with an incidence of 34% MSI-positivity noted in a recent large single-institution study of 466 cases (36), and 40% MSI-positivity noted among endometrioid endometrial carcinomas selected for analysis by The Cancer Genome Atlas (15). The MSI phenotype in sporadic endometrial carcinomas is attributed to defective mismatch repair primarily resulting from hypermethylation of the *MLH1* promoter, as well as low frequency somatic mutations in *MSH6* and loss of MSH2 expression (40–42).

Serous endometrial carcinoma

Serous endometrial carcinomas are high-grade tumors that are often metastatic at presentation and have an associated 5-year relative survival rate of only 44.7%, compared to 91.2% for endometrioid endometrial carcinoma (43). Although they are rare at diagnosis, serous carcinomas are clinically aggressive and contribute substantially to mortality from endometrial cancer. In one study, serous tumors constituted only 10% of endometrial cancer diagnoses but accounted for 39% of deaths (44). Recent epidemiological evidence suggests that, similar to endometrioid endometrial carcinoma, increased body mass index may be a risk factor for serous endometrial carcinoma (23). Serous endometrial carcinomas may be preceded by precancerous cells with a so-called “p53 signature”, by endometrial glandular dysplasia, or by endometrial intraepithelial carcinoma (reviewed in (45)). Treatment approaches for serous endometrial carcinoma are variable but generally include surgical staging and cytoreduction followed by adjuvant chemotherapy and/or radiotherapy (reviewed in (46, 47)).

Although the genomic landscape of serous endometrial carcinoma has recently been deciphered (15–18), prior molecular studies of individual genes and pathways established that serous endometrial carcinomas are characterized by a high frequency (up to 90% of cases) of somatic mutations in *TP53* and/or p53 stabilization (48, 49). *TP53*/p53 abnormalities are believed to be initiating events in the development of serous endometrial cancer based on their occurrence in premalignant cells, in endometrial glandular dysplasia, and in endometrial intraepithelial carcinoma (reviewed in (24)). Consistent with the idea that p53 dysregulation is an initiating event in serous endometrial tumorigenesis, mice with conditional deletion of *Trp53* in the genitourinary tract develop non-endometrioid endometrial carcinomas including serous carcinomas (50). In addition to p53 alterations, human serous endometrial carcinomas also harbor frequent somatic mutations in *PPP2R1A*, which encodes a subunit of the PP2A phosphatase, and in *PIK3CA*, *PIK3R1* and *PTEN* within the PI3-kinase pathway (reviewed in (24)). Overexpression of the cell cycle proteins cyclin E and p16, amplification and overexpression of the *ERBB2* receptor tyrosine kinase, loss of expression of BAF250A, and altered expression of the cell adhesion proteins claudin-3, claudin-4, L1CAM, EpCAM, and E-cadherin have also been documented (reviewed in (24)).

High-grade endometrial carcinoma

A substantial proportion of high-grade endometrial carcinomas can be difficult to reproducibly classify according to histological subtype (reviewed in (51)). For example, one study noted discordant subtype classification in approximately one-third of high-grade endometrial tumors (52). The difficulty in unambiguously classifying some high-grade endometrial carcinomas is problematic because different histological subtypes have different clinical behaviors and different treatment considerations (reviewed in (53)). Immunochemical phenotyping for markers such as p53, ER, PR, PTEN, IMP3, and p16 may serve as informative adjuncts to traditional histopathology for the classification of high-grade endometrial tumors since unambiguously assigned histological subtypes tend to show characteristic differences in the expression patterns of these markers (54–56). In the future, mutational profiles may also be useful adjuncts to histopathological classification. For example, significant differences have been noted in the frequency of mutations among *ARID1A*, *PTEN*, *PIK3CA*, *PPP2R1A*, *TP53*, and *CTNNB1* in low-grade endometrioid endometrial carcinoma, high-grade endometrioid endometrial carcinoma, serous endometrial carcinoma, and endometrial carcinosarcomas, and the pattern of mutations in this six-gene set facilitated the histological reclassification of some endometrial tumors (57). In a combined analysis of immunohistochemical staining of grade 3 endometrioid endometrial carcinomas for MLH1, MSH2, p16, cyclin D1, ERBB2, WT1 and p53, 37% of cases had molecular profiles that resembled endometrioid carcinomas whereas 63% of cases resembled serous carcinomas at the molecular level (58). As we will discuss later in this review, the integrated genomic analysis of endometrioid and serous endometrial carcinomas by The Cancer Genome Atlas (TCGA) revealed that 19.6% of histologically classified high-grade (grade 3) endometrioid endometrial carcinomas in that study have genomic profiles that resemble those of serous carcinomas (15).

Molecular Classification of Endometrioid and Serous Endometrial Carcinomas

Although much has been done to understand the molecular etiology of endometrial carcinomas over the past several decades, the very recent application of next generation sequencing to comprehensively search for somatic alterations in endometrial carcinomas has resulted in a rapid, and significant shift in our understanding of the molecular events underlying these tumors. Beginning in 2012, a number of studies, including one from our own group, reported the results of systematic searches for somatic mutations among the ~22,000 protein-encoding genes that constitute the exome, in serous and endometrioid endometrial carcinomas (16–20). The first large-scale, fully integrated genomic analysis of endometrial carcinomas was reported in 2013 by TCGA (15) and employed whole exome resequencing, whole transcriptome sequencing, genome-wide copy number analysis, expression profiling, reverse phase protein array (RPPA), methylation profiling, and an assessment of microsatellite instability to interrogate 186 endometrioid, 42 serous, and 4 mixed histology endometrial carcinomas in an integrated manner (15). A subset of TCGA tumors (n=107) was also subjected to low-pass whole genome sequencing to identify structural variants. Together, these studies provided critical new insights into the molecular features of serous and endometrioid endometrial carcinomas including the first observation,

reported by TCGA, that endometrial carcinomas can be broadly classified into four distinct molecular subgroups based on an integrated analysis of somatic mutation rates, frequency of copy number alterations, and microsatellite instability status. In the following sections we provide an overview of the most salient features of the four molecular subgroups identified by TCGA, which are defined as "*POLE* ultramutated", "hypermutated/microsatellite unstable", "copy number low/microsatellite stable", and "copy number high (serous-like)".

POLE Ultramutated subgroup

As their name suggests, ultramutated tumors have an extraordinarily high mutation rate (232 $\times 10^{-6}$ mutations per Mb; 867 to 9,714 mutations per tumor), and an elevated incidence of C>A transversions (15). Overall, 6.4% of low-grade endometrioid endometrial carcinomas and 17.4% of high-grade endometrioid endometrial carcinomas, but none of the mixed histology or serous tumors in the TCGA study, were ultramutated. The ultramutated phenotype is attributed to somatic mutations in the exonuclease domain of *POLE* which encodes the catalytic and proof-reading subunit of the polymerase epsilon holoenzyme that catalyzes leading strand synthesis during DNA replication and regulates cell cycle progression, chromatin remodeling, and DNA repair (59). In an earlier study, Church et al., described somatic mutations in the exonuclease domain of *POLE* in 7% of endometrioid, 25% of serous, and 33% of mixed histology endometrial carcinomas, although it should be noted that the total number of serous and mixed histology tumors in that study was small (60). Church et al., further noted a significant increase in the incidence of *POLE* mutations with high tumor grade (4.7% grade 1 tumors *versus* 1.7% grade 2 tumors *versus* 22.2% grade 3 tumors; P=0.001) (60).

TCGA uncovered 190 significantly mutated genes (defined in that study as having a convolution test false discovery rate of 2% or less) among the *POLE*/ultramutated tumors. Significantly enriched pathways (p-value < 1×10^{-2}) associated with this subgroup involve gluconeogenesis, glycolysis, clathrin-mediated endocytosis signaling, tRNA charging, the TCA cycle II (eukaryotic), and actin cytoskeleton signaling. Although the number of ultramutated endometrial carcinomas that have been described thus far is small, it is noteworthy that the progression-free survival of patients in the ultramutated subgroup is more favorable than for other molecular subgroups (hypermutated/MSI, copy number low/MSS, or copy number high/serous-like) (15).

Hypermutated, microsatellite unstable subgroup

The so-called hypermutated/MSI endometrial cancer subgroup is composed of microsatellite unstable tumors that have low-level somatic copy number alterations (15). Consistent with their microsatellite instability phenotype, the hypermutated/MSI subgroup also displays frequent *MLH1* promoter methylation and reduced *MLH1* gene expression. Hypermutated/MSI tumors are also associated with a heavily methylated subgroup, suggestive of a CpG methylator phenotype (CIMP). In the TCGA tumor cohort, 28.6% of low-grade endometrioid endometrial carcinomas and 54.3% of high-grade endometrioid endometrial carcinomas were within the hypermutated/MSI subgroup. This observation is consistent with earlier reports that MSI-positivity occurs at significantly higher frequency in high-grade endometrioid ECs compared with low-grade endometrioid ECs (61–63). None of

the mixed histology or serous endometrial carcinomas in the TCGA cohort were within the hypermutated/MSI subgroup (15). The absence of serous ECs from the hypermutated/MSI subgroup is in accordance with the infrequent (0%–4%) occurrence of MSI documented in serous tumors by TCGA and in earlier analyses of other large cohorts of serous EC (15, 18, 57, 64).

Twenty-one significantly mutated genes (candidate pathogenic driver genes) have been identified in the hypermutated/MSI subgroup (Table 1), including 11 genes (*ARID5B, CSDE1, CTCF, GIGYF2, HIST1H2BD, LIMCH1, MIR1277, NKAP, RBMX, TNFAIP6, ZFHX3*) that were not previously known to be significantly mutated in endometrial carcinoma. Most of the remaining significantly mutated genes (*PTEN, PIK3CA, PIK3R1, ARID1A, RPL22, KRAS, CTNNB1, ATR, FGFR2, CCND1*) have well-documented roles in the endometrioid subtype as discussed earlier in this review and elsewhere (24, 65). *RPL22* has an emergent role in endometrioid endometrial carcinomas. Somatic mutations at a polynucleotide tract within *RPL22*, resulting in protein truncation, were previously demonstrated to occur in 52% of MSI-high endometrioid endometrial carcinomas, and to correlate with later age at diagnosis (67 versus 63 years, p=0.0005) (66). Although the functional effect of *RPL22* mutations in endometrial cancer remains to be determined, it is noteworthy that *RPL22* has been suggested to be a haploinsufficient tumor suppressor gene based on observations that 10% of primary T-ALLs exhibit monoallelic deletion of *RPL22* and that haploinsufficiency for *RPL22* accelerates tumorigenesis in a mouse model of T cell lymphoma (67).

In addition to significantly mutated genes, a number of significantly enriched pathways are recognized in the hypermutated/MSI subgroup including the threonine degradation II, glycine degradation, and anandamide degradation pathways. The RTK (Receptor Tyrosine Kinase)/RAS/β-catenin pathway is altered in 69.5% of hypermutated/MSI tumors and the *PIK3CA-PIK3R1-PTEN* axis is genomically altered in 95.5% of cases. As noted previously, targeted therapies directed against the PI3-kinase pathway are currently being evaluated in clinical trials for the treatment of endometrial cancer (reviewed in (21)). *KRAS* alterations, which may confer resistance to PI3K-pathway inhibitors (reviewed in (68)), is mutated or amplified in 35% of hypermutated/MSI endometrial tumors (15). An earlier large study of endometrioid endometrial carcinomas demonstrated that somatic mutations in *KRAS* and *FGFR2* were statistically significantly more frequent among MSI-positive than MSI-negative endometrioid tumors whereas mutations in *CTNNB1* were significantly more frequent among MSI-negative tumors (36).

Historically, there has been considerable interstudy variability regarding whether or not MSI status is associated with clinical outcome of endometrial cancer. Factors proposed to account for this variability include differences in the numbers of patients between studies was well as differences in the histopathological composition of study cohorts (61). However, a recent large single-institution study, exclusively composed of endometrioid endometrial cancers, observed no significant correlation between MSI status and either overall survival or disease-free survival (61). Moreover, a recently published meta-analysis of 23 studies, including the latter study (61), observed no significant correlation between MSI and clinical outcome for endometrial cancer (69).

Copy number-low, microsatellite stable (MSS) subgroup

The copy number-low/microsatellite stable subgroup described by TCGA included 60.0% of low-grade endometrioid carcinomas, 8.7% of high-grade endometrioid carcinomas, 2.3% of serous carcinomas, and 25% of mixed histology carcinomas. Sixteen significantly mutated genes were discerned in this molecular subgroup (Table 1), consisting of nine genes previously implicated in endometrial cancer (*PTEN, PIK3CA, CTNNB1, ARID1A, PIK3R1, KRAS, FGFR2, CHD4, SPOP*) by ourselves and others ((17, 18) and reviewed in (24)), and seven genes (*BCOR, CSMD3, CTCF, MECOM, METTL14, SGK1, SOX17*) that had not previously been recognized to have a role in endometrial tumorigenesis. However, even though significantly mutated genes are generally indicative of probable pathogenic driver genes, it is should be cautioned that the designation of *CSMD3* as a significantly mutated gene in endometrial cancer likely reflects the inadequacy of statistical algorithms to account for the observations that late-replicating genes and lowly-expressed genes, such as *CSMD3*, exhibit higher background mutation rates than early replicating genes or highly expressed genes (70). As such, the designation of *CSMD3* as a significantly mutated gene in endometrial cancer likely reflects an elevated background mutation rate rather than the accumulation of pathogenic driver mutations (70).

Almost all (92%) tumors in this subgroup have somatically altered the PI3K pathway. *KRAS* is altered in 16% of cases, which is considerably lower than the frequency of *KRAS* mutation in the MSI+/hypermutated ECs, in keeping with earlier observations that *KRAS* mutations are significantly more common in microsatellite-unstable versus microsatellite-stable EECs (36). The RTK/RAS/β-catenin pathway is also altered at high frequency (83%) among MSS/copy number low tumors and, within this pathway, somatic mutations in *CTNNB1* are particularly prevalent (52%). Mutations in *SOX17*, which regulates β-catenin levels, are observed exclusively in this subgroup.

Copy number-high subgroup

In the TCGA study, 5.0% of low-grade endometrioid carcinomas, 19.6% of high-grade endometrioid carcinomas, 97.7% of serous carcinomas, and 75% of mixed histology carcinomas were in the copy number-high tumor subgroup. That almost all serous ECs in the TCGA study are deemed copy number-high is consistent with previous reports that serous ECs are often aneuploid and chromosomally unstable (16, 17, 71, 72).

Eight significantly mutated genes have been described among the 60 copy number high/serous-like tumors in the TCGA study, including *CSMD3*, which, as discussed earlier in this review, probably reflects a statistical artifact rather than a *bona fide* driver gene (Table 1). The other significantly mutated genes in the serous-like subgroup were *TP53, PIK3CA, PTEN, PIK3R1*, and *PPP2R1A*, which have well-established roles in serous EC (reviewed in (24)), and *FBXW7* and *CHD4* which we and others previously identified as significantly mutated genes in serous endometrial carcinomas (16–18). With the exception of *CHD4*, each of the aforementioned genes is a *bona fide* cancer gene. As has previously been noted for *TP53*, the presence of somatic mutations within *FBXW7, PIK3CA*, and *PPP2R1A* in serous intraepithelial carcinoma and concurrent serous endometrial carcinomas implicates mutation of these genes as early events in the development of serous endometrial cancer

(16). The functional consequences of mutations in *CHD4*, which encodes the catalytic subunit of the NuRD chromatin-remodeling complex, remain to be elucidated. However, the designation of *CHD4* as a significantly mutated gene in serous and serous-like tumors (15, 17, 18), and the presence of mutation hotspots within this gene, strongly suggest that it is likely to be a causal driver gene.

Other genes that have emerged as significantly mutated genes in whole exome sequencing studies of serous endometrial carcinomas are *SPOP*, a putative tumor suppressor gene, *CDKN1A*, a *bona fide* cancer gene, *TAF1*, *HCFC1R1*, *CTDSPL*, *YIPF3*, and *FAM132A* (17,18). In terms of biological processes, our group has shown that genes that are involved in chromatin-remodeling and ubiquitin-mediated protein degradation are frequently mutated in serous endometrial tumors (18). That is not to say that chromatin-remodeling genes and ubiquitin ligase complex genes are not also perturbed in the endometrioid subtype; indeed, a number of chromatin-remodeling genes, such as *ARID1A*, *ARID5B*, *CTCF*, and *CHD4*, are also causal or candidate driver genes in molecular subgroups dominated by endometrioid endometrial tumors (Table 1).

Using statistical methods, a number of genomic regions of significant copy number alteration have been defined in serous-like tumors including regions of focal amplification involving the *MYC* oncogene, the *ERBB2* (*HER2*) receptor tyrosine kinase gene, and *CCNE1* (Cyclin E1), which are each focally amplified in 23%–25% of cases (15). The mutual exclusivity in serous EC of *CCNE1* amplification and somatic alterations affecting *FBXW7*, which normally mediates the ubiquitin-mediated degradation of Cyclin E, suggests that these genetic events are functionally redundant (16). The observation of frequent *MYC*, *ERBB2*, and *CCNE1* gene amplification in serous-like endometrial carcinomas is consistent with prior observations in serous endometrial carcinomas (16, 17, 24). Numerous additional genes of interest, including *PIK3CA*, *FBXW7*, *CHD4*, and *MBD3*, are located within larger regions of copy number alteration in serous and serous-like endometrial carcinomas (15–17).

Copy number-high endometrial tumors have a DNA methylation pattern similar to that of the normal endometrium. A large proportion (85%) of tumors in the copy number high subgroup are also within a so-called mitotic subgroup defined by altered mRNA expression of genes involved in cell cycle regulation (15). RNA sequencing has also revealed transcriptional differences that form significantly enriched pathways in the copy number high subgroup including G1/S checkpoint regulation, growth hormone signaling, Her-2 signaling in breast cancer, endothelin-1 signaling, cyclins and cell cycle regulation, and molecular mechanisms of cancer (15). Furthermore, in the serous-like molecular subgroup, increased levels of p53, and decreased levels of phospho-AKT have been noted by RPPA analysis (15).

The simultaneous assessment of the entire complement of protein-encoding genes by TCGA revealed that most of the *ERBB2*-amplified serous-like tumors also were *PIK3CA*-mutant (P=0.038). As noted (15), the co-occurrence of *ERBB2* amplification and *PIK3CA* mutation in serous-like tumors may be clinically relevant because in ERBB2-overexpressing breast cancer cell lines, activating mutations in *PIK3CA* are associated with decreased sensitivity to

trastuzumab and to lapatinib, therapeutic agents that target ERBB2 (73, 74). This illustrates the importance of evaluating the larger genomic context of druggable targets when, for example, considering the design and interpretation of clinical trials assessing targeted therapies. A small number of studies have assessed the clinical efficacy of trastuzumab for the treatment of ERBB2-positive advanced or recurrent endometrial cancer (reviewed in (75)) and additional clinical trials of trastuzumab or lapatinib in endometrial cancer are ongoing or planned (NCT01367002; NCT01454479). As these and other trials of targeted therapies directed against ERBB2 in endometrial cancer proceed, it may be useful to assess whether *PIK3CA* mutation status impacts clinical response. The *PIK3CA-PIK3R1-PTEN* axis itself is altered in 73% of copy number high/serous-like tumors whereas *KRAS* is mutated or amplified in 8% of serous-like tumors (15). The clinical efficacy of therapeutic agents targeting the PI3K/AKT/mTOR pathway in the treatment of endometrial cancer has recently been reviewed elsewhere (68).

One of the most interesting findings from the genomic analysis of endometrial tumors is that approximately one-fifth of tumors that were classified as grade 3 endometrioid endometrial carcinomas are “serous-like” at the molecular level. As noted in the TCGA study, the distinction between the histological and molecular classification of these cases has important clinical implications - suggesting that patients with grade 3 endometrioid endometrial carcinomas that have a serous-like genomic profile might be more appropriately treated with regimens that are used for serous carcinoma. As discussed earlier in this review, a subset of high-grade endometrial tumors are difficult to classify accurately by subtype at the histological level. The newfound realization that serous and endometrioid endometrial tumors can be molecularly classified into four distinct subgroupings may provide future opportunities to devise a panel of biomarkers, or indeed use integrated genomic profiling, to augment traditional histopathologic classification of endometrial carcinomas. In this regard, it is notable that 48 significantly mutated genes are altered at differential frequency across the four molecular subgroups of endometrial carcinoma reported by TCGA (Table 2). How the genomic profiles of endometrioid and serous endometrial carcinomas relate to the genomic profiles of other endometrial carcinoma subtypes remains to be determined.

Conclusions and future perspectives

In the past year, the pace of mutation discovery in endometrial cancer has been unprecedented. To date, the exomes of 96 serous and 233 endometrioid endometrial carcinomas have been deciphered (15–20). The integrated genomic analysis of these two subtypes of endometrial cancer by The Cancer Genome Atlas (15), as well as studies from individual laboratories (16–20), has provided unprecedented insights into the genomic, epigenomic, transcriptomic, and proteomic alterations that are present in serous and endometrioid endometrial tumors. Together these studies have given the endometrial cancer community the most comprehensive view of the genomic landscape of this disease thus far. It is likely that our view of this landscape, and the genetic and biological context of the alterations that shape it, will continue to be refined and defined by the functional annotation of candidate cancer genes that have emerged from these studies and by the sequencing of additional endometrial tumors, including rare histological subtypes. Prospective studies assessing the potential clinical utility of these findings will undoubtedly follow. One could

envision that the molecular classification of endometrial tumors might assist in guiding a determination of prognosis and treatment decisions, in the discovery of new druggable targets and pathways, and in implementing molecular diagnostics to detect endometrial cancers an earlier stage in their clinical course when prognosis is more favorable. In the latter case it is noteworthy that the genomic analysis of cells collected during Papanicolaou (PAP) tests holds promise for the early detection of endometrial carcinomas (19). In future studies it will also be important to decipher the genomic landscape of metastatic disease, and of precancerous lesions that precede endometrial carcinomas, as well as annotating and functionalizing somatic aberrations in the non-coding regions of the genome in endometrial carcinomas.

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Table 1

Significantly mutated genes (SMGs) in three molecular subgroups of endometrial cancer (15)

Molecular subgroup	No. of SMGs	Gene symbol	Gene name	Somatic mutation frequency
Hypermutated/ MSI	21	*PTEN*	Phosphatase and tensin homolog	87.7%
		PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha	53.8%
		PIK3R1	Phosphoinositide-3-kinase, regulatory subunit 1 (alpha)	41.5%
		ARID1A	AT rich interactive domain 1A (SWI-like)	36.9%
		RPL22	Rbosomal protein L22	36.9%
		KRAS	Kirsten rat sarcoma viral oncogene homolog	35.4%
		ZFHX3	Zinc finger homeobox 3	30.8%
		ARID5B	AT rich interactive domain 5B (MRF1-like)	23.1%
		CTCF	CCCTC-binding factor (zinc finger protein)	23.1%
		CTNNB1	Catenin (cadherin-associated protein), beta 1, 88kDa	20.0%
		ATR	Ataxia telangiectasia and Rad3 related	18.5%
		GIGYF2	GRB10 interacting GYF protein 2	16.9%
		CSDE1	Cold shock domain containing E1, RNA-binding	15.4%
		FGFR2	Fibroblast growth factor receptor 2	13.8%
		CCND1	Cyclin D1	12.3%
		LIMCH1	LIM and calponin homology domains 1	12.3%
		RBMX	RNA binding motif protein, X-linked	12.3%
		NKAP	NFKB activating protein	10.8%
		HIST1H2BD	Histone cluster 1, H2bd	7.7%
		TNFAIP6	Tumor necrosis factor, alpha-induced protein 6	7.7%
		MIR1277	microRNA 1277	6.2%
Copy number low/MSS	16	*PTEN*	Phosphatase and tensin homolog	76.7%
		PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha	53.3%
		CTNNB1	Catenin (cadherin-associated protein), beta 1, 88kDa	52.2%
		ARID1A	AT rich interactive domain 1A (SWI-like)	42.2%
		PIK3R1	Phosphoinositide-3-kinase, regulatory subunit 1 (alpha)	33.3%
		CTCF	CCCTC-binding factor (zinc finger protein)	21.1%
		KRAS	Kirsten rat sarcoma viral oncogene homolog	15.6%
		FGFR2	Fibroblast growth factor receptor 2	13.3%
		CHD4	Chromodomain helicase DNA binding protein 4	12.2%
		SPOP	Speckle-type POZ protein	10.0%
		CSMD3[§]	CUB and Sushi multiple domains 3	10.0%
		SOX17	SRY (sex determining region Y)-box 17	7.8%

Molecular subgroup	No. of SMGs	Gene symbol	Gene name	Somatic mutation frequency
		SGK1	Serum/glucocorticoid regulated kinase 1	6.7%
		BCOR	BCL6 corepressor	6.7%
		MECOM	MDS1 and EVI1 complex locus	4.4%
		METTL14	Methyltransferase like 14	3.3%
Copy number high/serous-like	8	*TP53*	Tumor protein p53	91.7%
		PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha	46.7%
		FBXW7	F-box and WD repeat domain containing 7, E3 ubiquitin protein ligase	21.7%
		PPP2R1A	Protein phosphatase 2, regulatory subunit A, alpha	21.7%
		PIK3R1	Phosphoinositide-3-kinase, regulatory subunit 1 (alpha)	13.3%
		CHD4	Chromodomain helicase DNA binding protein 4	13.3%
		PTEN	Phosphatase and tensin homolog	10.0%
		CSMD3[§]	CUB and Sushi multiple domains 3	10.0%

[§]Probable false-positive (70)

Table 2

48 SMGs mutated at differential frequency across four molecular subgroups of serous and endometrioid endometrial cancers (15)

Gene Symbol	Gene Name	Mutation Frequency POLE/ Ultramutated (n=17)	Mutation Frequency Hypermutated /MSI (n=65)	Mutation Frequency CN_Low/ MSS (n=90)	Mutation Frequency CN_High/ Serous-like (n=60)	Mutation Frequency All four subgroups (n=232)
TP53	Tumor protein p53	35%	8%	1%	92%	29%
PTEN	Phosphatase and tensin homolog	94%	88%	77%	10%	64%
POLE	Polymerase (DNA directed), epsilon, catalytic subunit	100%	8%	3%	2%	11%
MKI67	Antigen identified by monoclonal antibody Ki-67	94%	18%	2%	0%	13%
FAT3	FAT tumor suppressor homolog 3 (Drosophila)	76%	31%	1%	0%	15%
TAF1	TAF1 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 250kDa	82%	25%	1%	5%	15%
ZFHX3	Zinc finger homeobox 3	82%	31%	2%	7%	17%
RPL22	Ribosomal protein L22	29%	37%	0%	0%	13%
SPTA1	Spectrin, alpha, erythrocytic 1 (elliptocytosis 2)	76%	14%	6%	0%	12%
FAM135B	Family with sequence similarity 135, member B	76%	11%	4%	2%	11%
CSMD3[§]	CUB and Sushi multiple domains 3	94%	22%	10%	10%	19%
GIGYF2	GRB10 interacting GYF protein 2	59%	20%	0%	7%	12%
CSDE1	Cold shock domain containing E1, RNA-binding	59%	15%	1%	0%	9%
MLL4	Myeloid/Lymphoid Or Mixed-Lineage Leukemia Protein 4	65%	22%	4%	0%	13%
ATR	Ataxia telangiectasia and Rad3 related	65%	9%	0%	2%	8%
CTNNB1	Catenin (cadherin-associated protein), beta 1, 88kDa	41%	20%	52%	3%	30%
USH2A	Usher syndrome 2A (autosomal recessive, mild)	76%	18%	4%	5%	14%
LIMCH1	LIM and calponin homology domains 1	53%	12%	0%	0%	7%
RRN3P2	RNA Polymerase I Transcription Factor Homolog (S. Cerevisiae) Pseudogene	6%	0%	0%	0%	0%
FBXW7	F-box and WD repeat domain containing 7, E3 ubiquitin protein ligase	82%	9%	6%	22%	16%
CDH19	Cadherin 19, type 2	59%	5%	1%	5%	7%
USP9X	Ubiquitin specific peptidase 9, X-linked	59%	17%	1%	2%	10%
COL11A1	Collagen, type XI, alpha 1	71%	9%	2%	8%	11%

Gene Symbol	Gene Name	Mutation Frequency POLE/ Ultramutated (n=17)	Mutation Frequency Hypermutated /MSI (n=65)	Mutation Frequency CN_Low/ MSS (n=90)	Mutation Frequency CN_High/ Serous-like (n=60)	Mutation Frequency All four subgroups (n=232)
BCOR	BCL6 corepressor	65%	17%	7%	0%	12%
ARID1A	AT rich interactive domain 1A (SWI-like)	76%	37%	42%	5%	34%
ZNF770	Zinc finger protein 770	41%	5%	0%	0%	4%
ARID5B	AT rich interactive domain 5B (MRF1-like)	47%	23%	6%	0%	12%
SLC9C2	Solute carrier family 9, member C2 (putative)	53%	5%	2%	3%	7%
KRAS	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog	53%	35%	16%	3%	21%
PNN	Pinin, desmosome associated protein	35%	6%	0%	0%	4%
INPP4A	Inositol polyphosphate-4-phosphatase, type I, 107kDa	29%	9%	2%	0%	6%
CTCF	CCCTC-binding factor (zinc finger protein)	41%	23%	21%	0%	18%
CHD4	Chromodomain helicase DNA binding protein 4	65%	6%	12%	13%	15%
AMY2B	Amylase, alpha 2B (pancreatic)	29%	8%	0%	0%	4%
RBMX	RNA binding motif protein, X-linked	24%	12%	0%	0%	5%
PPP2R1A	Protein phosphatase 2, regulatory subunit A, alpha	29%	9%	1%	22%	11%
SIN3A	SIN3 transcription regulator homolog A (yeast)	35%	14%	4%	0%	8%
TNFAIP6	Tumor necrosis factor, alpha-induced protein 6	29%	2%	1%	0%	3%
PIK3R1	Phosphoinositide-3-kinase, regulatory subunit 1 (alpha)	65%	40%	33%	13%	32%
SGK1	Serum/glucocorticoid regulated kinase 1	35%	3%	6%	2%	6%
HOXA7	Homeobox A7	18%	6%	0%	0%	3%
METTL14	Methyltransferase like 14	24%	5%	3%	0%	4%
HPD	4-hydroxyphenylpyruvate dioxygenase	12%	6%	0%	0%	3%
MIR1277	MicroRNA 1277	12%	6%	0%	0%	3%
CCND1	Cyclin D1	18%	12%	4%	0%	6%
MECOM	MDS1 and EVI1 complex locus	24%	5%	4%	0%	5%
NFE2L2	Nuclear factor (erythroid-derived 2)-like 2	12%	11%	3%	0%	5%
ESR1	Estrogen receptor 1	24%	2%	6%	2%	5%

Mutation frequency of protein-encoding genes was retrieved using cBioPortal (URL: http://www.cbioportal.org/public-portal/); mutation frequency of *MIR1277* was retrieved using the TCGA data portal (URL: https://tcga-data.nci.nih.gov/tcga/).

[§] Probable false-positive (70)