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Reviews

The Emerging Genomic Landscape of Endometrial Cancer

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BACKGROUND: Endometrial cancer is responsible for approximately 74 000 deaths annually among women worldwide. It is a heterogeneous disease comprising multiple histologic subtypes. In the US, 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: We review the current state of knowledge regarding somatic genomic alterations that occur in serous and endometrioid endometrial tumors. We present this knowledge in a historical context by reviewing the genomic alterations that studies of individual genes and proteins have identified over the past 2 decades or so. We then review very recent comprehensive and 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 produced the first comprehensive molecular classification of these tumors, which has distinguished 4 molecular subgroups: a *POLE* [polymerase (DNA directed), ε, catalytic subunit] 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.

Cancers that arise in the body (corpus) of the uterus represent the eighth leading cause of cancer-related death among American women, accounting for an estimated 8190 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 (carcinosarcoma), squamous cell carcinoma, transitional cell carcinoma, small cell carcinoma, undifferentiated carcinoma, and others *(4)*. The classification of endometrial carcinomas by histologic subtype, clinical stage, and grade is important in assessing prognosis and in deciding the most appropriate treatment regimen [reviewed in *(5)*].

In the US, the survival rates for uterine corpus cancer show substantial racial disparity, with 5-year relative survival rates of only 57%–63% for African American women, compared with 84%–88% for white women *(1)*. This difference in survival is explained at least in part by differences in socioeconomic status, access to healthcare, and the fact that compared with white women, African American women are more likely to be diagnosed with aggressive histologic subtypes, including serous carcinomas, clear cell carcinomas, and sarcomas [reviewed in *(6)*].

The majority of endometrial carcinomas arise sporadically via 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*[2] (calpain 9)

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[2] Human genes: *CAPN9*, calpain 9; *MLH1*, mutL homolog 1; *MSH2*, mutS homolog 2; *MSH6*, mutS homolog 6; *PMS2*, PMS2 postmeiotic segregation increased 2 (*S. cerevisiae*); *EPCAM*, epithelial cell adhesion molecule; *PTEN*, phosphatase and tensin homolog; *POLD1*, polymerase (DNA directed), delta 1, catalytic subunit; *BRCA1*, breast cancer 1, early onset; *BRCA2*, breast cancer 2, early onset; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; *PIK3R1*, phosphoinositide-3-kinase, regulatory subunit 1 (alpha); *ARID1A*, AT rich interactive domain 1A (SWI-like); *KRAS*, Kirsten rat sarcoma viral oncogene homolog; *RASSF1*, Ras association (RalGDS/AF-6) domain family member 1; alias, RASSF1A; *FGFR2*, fibroblast growth factor receptor 2; *CTNNB1*, catenin (cadherin-associated protein), beta 1, 88kDa; *TP53*, tumor protein p53; *ERBB2*, v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2; *PPP2R1A*, protein phosphatase 2, regulatory subunit A, alpha; *POLE*, polymerase (DNA directed), epsilon, catalytic subunit; *ARID5B*, AT rich interactive domain 5B (MRF1-like); *CSDE1*, cold shock domain containing E1, RNA-binding; *CTCF*, CCCTC-binding factor (zinc finger protein); *GIGYF2*, GRB10 interacting GYF protein 2; *HIST1H2BD*, histone cluster 1, H2bd; *LIMCH1*, LIM and calponin homology domains 1; *MIR1277*, microRNA 1277; *NKAP*, NFKB activating

gene—that may be associated with an increased risk of endometrial cancer *(7)*.

A small fraction of endometrial cancers are associated with an autosomal dominant inherited genetic susceptibility in the context of Lynch syndrome (hereditary nonpolyposis colorectal cancer) and Cowden syndrome *(8–10)*. Lynch syndrome is attributed to germline mutations in mismatch-repair genes—*MLH1* (mutL homolog 1), *MSH2* (mutS homolog 2), *MSH6* (mutS homolog 6), *PMS2* [PMS2 postmeiotic segregation increased 2 (*S. cerevisiae*)]—as well as germline deletions of *EPCAM* (epithelial cell adhesion molecule) that produce 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*[3] tumor suppressor gene. A single-institution study found that the relative frequency of endometrioid and nonendometrioid carcinomas 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 years revealed that a germline mutation (Ser478Asn) in the *POLD1* [polymerase (DNA directed), delta 1, catalytic subunit] gene, which encodes the catalytic subunit of polymerase δ that promotes lagging-strand synthesis during DNA replication, is linked to an 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)*]. Strong epidemiologic evidence has shown that the increased incidence of serous endometrial carcinoma in carriers of *BRCA1* (breast cancer 1, early onset) or *BRCA2* (breast cancer 2, early onset) mutations is associated with prior tamoxifen treatment, rather than with 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 for 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. In the present article, we review both the traditional histologic 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)*.

Histologic Classification of Endometrial Carcinomas

ENDOMETRIOID ENDOMETRIAL CARCINOMA

Endometrioid endometrial carcinomas represent approximately 87%–90% of all diagnosed endometrial carcinomas *(21)*. They are frequently estrogen-dependent tumors associated with epidemiologic 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, because a high tumor grade (grade 3) and/or infiltration of >50% of the myometrium are predictors of an increased risk for tumor recurrence [reviewed in *(5)*]. The treatment for patients with advanced-stage or recurrent disease is highly variable *(26)*. The prognosis for advanced-stage disease is relatively poor, with one study noting 5-year overall-survival rates of 36%–56% for stage III disease and 21%–22% for stage IV disease *(25)*. Although a number of molecularly targeted therapeutics are in clinical trials for endometrial carcinoma [reviewed in

protein; *RBMX*, RNA binding motif protein, X-linked; *TNFAIP6*, tumor necrosis factor, alpha-induced protein 6; *ZFHX3*, zinc finger homeobox 3; *RPL22*, ribosomal protein L22; *ATR*, ataxia telangiectasia and Rad3 related; *CCND1*, cyclin D1; *CHD4*, chromodomain helicase DNA binding protein 4; *SPOP*, speckle-type POZ protein; *BCOR*, BCL6 corepressor; *CSMD3*, CUB and Sushi multiple domains 3; *MECOM*, MDS1 and EVI1 complex locus; *METTL14*, methyltransferase like 14; *SGK1*, serum/glucocorticoid regulated kinase 1; *SOX17*, SRY (sex determining region Y)-box 17; *FBXW7*, F-box and WD repeat domain containing 7, E3 ubiquitin protein ligase; *CDKN1A*, cyclin-dependent kinase inhibitor 1A (p21, Cip1); *TAF1*, TAF1 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 250kDa; *HCFC1R1*, host cell factor C1 regulator 1 (XPO1 dependent); *CTDSPL*, CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) small phosphatase-like; *YIPF3*, Yip1 domain family, member 3; *FAM132A*, family with sequence similarity 132, member A; *CCNE1*, cyclin E1; *MYC*, v-myc avian myelocytomatosis viral oncogene homolog; *MBD3*, methyl-CpG binding domain protein 3; *MKI67*, antigen identified by monoclonal antibody Ki-67; *FAT3*, FAT atypical cadherin 3; *SPTA1*, spectrin, alpha, erythrocytic 1 (elliptocytosis 2); *FAM135B*, family with sequence similarity 135, member B; *KMT2B*, lysine (K)-specific methyltransferase 2B (also known as: *MLL4*, myeloid/lymphoid or mixed-lineage leukemia protein 4); *USH2A*, Usher syndrome 2A (autosomal recessive, mild); *RRN3P2*, RNA polymerase I transcription factor homolog (*S. cerevisiae*) pseudogene 2; *CDH19*, cadherin 19, type 2; *USP9X*, ubiquitin specific peptidase 9, X-linked; *COL11A1*, collagen, type XI, alpha 1; *ZNF770*, zinc finger protein 770; *SLC9C2*, solute carrier family 9, member C2 (putative); *PNN*, pinin, desmosome associated protein; *INPP4A*, inositol polyphosphate-4-phosphatase, type I, 107kDa; *AMY2B*, amylase, alpha 2B (pancreatic); *SIN3A*, SIN3 transcription regulator family member A; *HOXA7*, homeobox A7; *HPD*, 4-hydroxyphenylpyruvate dioxygenase; *NFE2L2*, nuclear factor, erythroid 2-like 2; *ESR1*, estrogen receptor 1.

[3] See Tables 1 and 2 for the gene names for symbols not expanded on their first appearance in the text.

(5, 21)], there are currently no targeted therapies approved by the US Food and Drug Administration for this tumor type.

Over the past 2 decades in the era preceding next-generation sequencing, much effort was devoted to understanding 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, these carcinomas are characterized by high-frequency genetic alterations in the *PIK3CA*, *PIK3R1*, and *PTEN* genes that produce inappropriate activation of the PI3K (phosphoinositide 3-kinase)[4] 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 protein is likewise frequent and has been detected in 19% to 34% of endometrioid endometrial carcinomas overall, 26% to 29% of low-grade endometrioid endometrial carcinomas, 39% of high-grade endometrioid endometrial carcinomas, and 16% of endometrial hyperplasias with atypia suggesting that this phenomenon is an initiating event in endometrioid endometrial tumorigenesis [*(33–35)*; reviewed in *(24)*]. Other signal transduction pathways that are frequently disrupted in endometrioid endometrial carcinomas include the RAS-RAF-MEK-ERK pathway, which is disrupted by somatic mutations in *KRAS* (approximately 18% of cases) or by hypermethylation of the *RASSF1* [Ras association (RalGDS/AF-6) domain family member 1; alias, RASSF1A] promoter (62%–74% of cases) [*(36)*; reviewed in *(24)*]. Somatic mutations in the *FGFR2* receptor tyrosine kinase occur in approximately 12% of endometrioid endometrial carcinomas *(36, 37)*. *FGFR2* mutations and *KRAS* mutations are mutually exclusive *(36)*. Although mutual exclusivity implies functional redundancy, the clinical correlates of *KRAS* and *FGFR2* mutations are different, indicating possible differences in their biological effects *(36)*. Endometrioid endometrial carcinomas often show disruption of the canonical WNT signaling pathway owing to somatic mutation of the *CTNNB1* gene (2%–45% of cases) and stabilization of β-catenin *(36, 38, 39)*. Recent findings that *CTNNB1* and *KRAS* mutations are mutually exclusive in endometrioid endometrial carcinomas have led to the proposal that functional cross talk between the RAS-RAF-MEK-ERK and WNT/TCF signaling pathways may occur in this cell type or that functional redundancy exists in the biological consequences of altered RAS-RAF-MEK-ERK and WNT/TCF signaling *(36)*. In addition, endometrioid tumors 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 (TCGA) *(15)*. The MSI phenotype in sporadic endometrial carcinomas has been attributed to defective mismatch repair, primarily due to hypermethylation of the *MLH1* promoter, as well as to low-frequency somatic mutations in *MSH6* and loss of *MSH2* expression *(40–42)*.

SEROUS ENDOMETRIAL CARCINOMA

Serous endometrial carcinomas, high-grade tumors that are often metastatic at presentation, have an associated 5-year relative survival rate of only 44.7%, compared with 91.2% for endometrioid endometrial carcinoma *(43)*. Although they are rare at diagnosis, serous carcinomas are clinically aggressive and contribute substantially to the mortality from endometrial cancer. In one study, serous tumors constituted only 10% of endometrial cancer diagnoses but accounted for 39% of the deaths *(44)*. Recent epidemiologic evidence suggests that, similar to endometrioid endometrial carcinoma, an 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 have 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 on the basis of 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 *TP53* in the genitourinary tract develop non-endometrioid endometrial carcinomas, including serous carcinomas *(50)*. In addition to p53 alterations, human serous endometrial carcinomas also harbor fre-

[4] Nonstandard abbreviations: PI3K, phosphoinositide 3-kinase; MSI, microsatellite instability; TCGA, The Cancer Genome Atlas; L1CAM, L1 cell adhesion molecule; EpCAM, epithelial cell adhesion molecule; IMP3, insulin-like growth factor 2 mRNA-binding protein 3; RTK, receptor tyrosine kinase.

quent somatic mutations in the *PPP2R1A* gene (which encodes a subunit of the PP2A phosphatase) and in the *PIK3CA*, *PIK3R1*, and *PTEN* genes within the PI3K pathway [reviewed in *(24)*]. Increased amounts of the cell cycle proteins cyclin E and p16, amplification and overexpression of the *ERBB2* [v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2] gene (which encodes the ERBB2 receptor tyrosine kinase), loss of BAF250A production, and altered amounts of the cell adhesion proteins claudin-3, claudin-4, L1CAM (L1 cell adhesion molecule), EpCAM (epithelial cell adhesion molecule), 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 classify reproducibly according to histologic 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 histologic subtypes have different clinical behaviors and different treatment considerations [reviewed in *(53)*]. Immunochemical phenotyping for markers such as p53, estrogen receptor, progesterone receptor, PTEN, IMP3 (insulin-like growth factor 2 mRNA-binding protein 3), and p16 may serve as informative adjuncts to traditional histopathology for the classification of high-grade endometrial tumors, because unambiguously assigned histologic subtypes tend to show characteristic differences in the expression patterns of genes encoding these markers *(54–56)*. 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, and the other 63% of cases resembled serous carcinomas at the molecular level *(57)*. In the future, mutational profiles may also be useful adjuncts to histopathologic classification. For example, significant differences have been noted in the frequencies of mutations among the *ARID1A*, *PTEN*, *PIK3CA*, *PPP2R1A* (protein phosphatase 2, regulatory subunit A, alpha), *TP53*, and *CTNNB1* genes in low-grade endometrioid endometrial carcinoma, high-grade endometrioid endometrial carcinoma, serous endometrial carcinoma, and endometrial carcinosarcomas, and the pattern of mutations in this 6-gene set has facilitated the histologic reclassification of some endometrial tumors *(58)*. As we discuss later in this review, an integrated genomic analysis of endometrioid and serous endometrial carcinomas by TCGA has 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 progress has been made over the past several decades toward understanding the molecular etiology of endometrial carcinomas, the very recent application of next-generation sequencing to comprehensively search for somatic alterations in endometrial carcinomas has led to a rapid and substantial shift in our understanding of the molecular events underlying these tumors. Beginning in 2012, several studies, including one from our own group, reported the results of systematic searches for somatic mutations in serous and endometrioid endometrial carcinomas in the approximately 22 000 protein-encoding genes that constitute the exome *(16–20)*. The first large-scale, fully integrated genomic analysis of endometrial carcinomas, which was reported in 2013 by TCGA *(15)*, used whole-exome sequencing, whole-transcriptome sequencing, genome-wide copy number analysis, expression profiling, reverse-phase protein array, methylation profiling, and MSI assessment 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 have provided critical new insights into the molecular features of serous and endometrioid endometrial carcinomas, including the first observation (reported by TCGA)—based on an integrated analysis of somatic mutation rates, frequency of copy number alterations, and MSI status—that endometrial carcinomas can be broadly classified into 4 distinct molecular subgroups. The following sections provide an overview of the most salient features of the 4 molecular subgroups identified by TCGA. These subgroups are termed "*POLE* ultramutated," "hypermutated/microsatellite-unstable," "copy number low/microsatellite-stable" "copy number high (serous-like)."

POLE ULTRAMUTATED SUBGROUP

As the name suggests, ultramutated tumors have an extraordinarily high mutation rate (232×10^{-6} mutations/Mb; 867–9714 mutations/tumor) and an increased 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 proofreading subunit of the polymerase ε 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 is important to note that the total number of serous and mixed-histology tumors in that study was small *(60)*. Church et al. also noted a significant increase in the incidence of *POLE* mutations with high tumor grade (4.7% grade 1 tumors vs. 1.7% grade 2 tumors vs. 22.2% grade 3 tumors; $P = 0.001$) *(60)*.

TCGA uncovered 190 significantly mutated genes (defined in that study as having a false-discovery rate in the convolution test of ≤2%) among *POLE* ultramutated tumors. Significantly enriched pathways (P values <0.01) associated with this subgroup involve gluconeogenesis, glycolysis, clathrin-mediated endocytosis signaling, tRNA charging, tricarboxylic acid 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 are more favorable than for other molecular subgroups [hypermutated/microsatellite-unstable, copy number low/microsatellite-stable, or copy number high (serous-like)] *(15)*.

HYPERMUTATED/MICROSATELLITE-UNSTABLE SUBGROUP

The so-called hypermutated/microsatellite-unstable endometrial cancer subgroup is composed of microsatellite-unstable tumors that have low-level somatic copy number alterations *(15)*. Consistent with their MSI phenotype, the hypermutated/microsatellite-unstable subgroup also displays frequent *MLH1* promoter methylation and reduced *MLH1* gene expression. Hypermutated/microsatellite-unstable tumors are also associated with a heavily methylated subgroup suggestive of a CpG methylator phenotype. 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/microsatellite-unstable subgroup. This observation is consistent with earlier reports that MSI positivity occurs at a significantly higher frequency in high-grade endometrioid endometrial carcinomas than in low-grade endometrioid endometrial carcinomas *(61–63)*. None of the mixed-histology or serous endometrial carcinomas in the TCGA cohort were within the hypermutated/microsatellite-unstable subgroup *(15)*. The absence of serous endometrial carcinomas from the hypermutated/microsatellite-unstable subgroup is in accord with the infrequent (0%–4%) occurrence of MSI documented in serous tumors by TCGA and in earlier analyses of other large cohorts of serous endometrial carcinoma *(15, 18, 58, 64)*.

Twenty-one significantly mutated genes (candidate pathogenic driver genes) have been identified in the hypermutated/microsatellite-unstable 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)*. The role of *RPL22* in endometrioid endometrial carcinomas is emerging. Somatic mutations at a polynucleotide tract within *RPL22*, which lead to protein truncation, were previously demonstrated to occur in 52% of MSI-high endometrioid endometrial carcinomas and to correlate with a later age at diagnosis (67 vs. 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-cell acute lymphoblastic leukemias 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 have been recognized in the hypermutated/microsatellite-unstable 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/microsatellite-unstable tumors and the *PIK3CA-PIK3R1-PTEN* axis is genomically altered in 95.5% of cases. As noted previously, targeted therapies directed against the PI3K 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)*], were observed in 35% of hypermutated/microsatellite-unstable endometrial tumors *(15)*. An earlier, large study of endometrioid endometrial carcinomas demonstrated that somatic mutations in *KRAS* and *FGFR2* were significantly more frequent among MSI-positive than MSI-negative endometrioid tumors, whereas *CTNNB1* mutations were significantly more frequent among MSI-negative tumors *(36)*.

Table 1. Significantly mutated genes (SMGs) in 3 molecular subgroups of endometrial cancer.[a]

Molecular subgroup	No. of SMGs	Gene symbol	Gene name	Somatic-mutation frequency
Hypermutated/microsatellite-unstable	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	Ribosomal 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/ microsatellite-stable	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[b]	CUB and Sushi multiple domains 3	10.0%
		SOX17	SRY (sex determining region Y)-box 17	7.8%
		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[b]	CUB and Sushi multiple domains 3	10.0%

[a] The Cancer Genome Atlas Research Network et al. *(15)*.
[b] Probable false positive [Lawrence et al. *(70)*].

Historically, there has been considerable inter-study variability regarding whether MSI status is associated with the clinical outcome of endometrial cancer. Factors proposed to account for this variability include differences in the numbers of patients between studies, as well as differences in the histopathologic composition of study cohorts *(61)*. A recent large single-institution study of endometrioid endometrial cancer cases observed no significant correlation between MSI status and either overall survival or disease-free survival *(61)*. Moreover, a recently published metaanalysis of 23 studies, including the aforementioned study *(61)*, also observed no significant correlation between MSI and clinical outcome for endometrial cancer *(69)*.

COPY NUMBER–LOW/MICROSATELLITE-STABLE 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): 9 genes previously implicated in endometrial cancer (*PTEN*, *PIK3CA*, *CTNNB1*, *ARID1A*, *PIK3R1*, *KRAS*, *FGFR2*, *CHD4*, *SPOP*) by us and others [*(17, 18)*; reviewed in *(24)*], and 7 genes (*BCOR*, *CSMD3*, *CTCF*, *MECOM*, *METTL14*, *SGK1*, *SOX17*) not previously recognized to have a role in endometrial tumorigenesis. Although significantly mutated genes are generally indicative of probable pathogenic driver genes, 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 low-expressed genes, such as *CSMD3*, exhibit higher background mutation rates than early-replicating genes or highly expressed genes *(70)*. Therefore, the designation of *CSMD3* as a significantly mutated gene in endometrial cancer likely reflects an increased background mutation rate rather than the accumulation of pathogenic driver mutations *(70)*.

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

COPY NUMBER–HIGH (SEROUS-LIKE) 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 endometrial carcinomas in the TCGA study are deemed copy number high is consistent with previous reports that serous endometrial carcinomas are often aneuploid and chromosomally unstable *(16, 17, 71, 72)*.

The TCGA study described 8 significantly mutated genes, including *CSMD3*, among the 60 copy number–high (serous-like) tumors (Table 1). The inclusion of *CSMD3*, as discussed earlier in this review, probably reflects a statistical artifact rather than *CSMD3* being a bona fide driver gene. The other significantly mutated genes in the serous-like subgroup were *TP53*, *PIK3CA*, *PTEN*, *PIK3R1*, and *PPP2R1A*, which have well-established roles in serous endometrial tumors [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 hot spots within this gene strongly suggest 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* [cyclin-dependent kinase inhibitor 1A (p21, Cip1)], a bona fide cancer gene; *TAF1*; *HCFC1R1* [host cell factor C1 regulator 1 (XPO1 dependent)]; *CTDSPL* [CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) small phosphatase-like]; *YIPF3* (Yip1 domain family, member 3); and *FAM132A* (family with sequence similarity 132, member A) *(17, 18)*. In terms of biological processes, 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 genes of the ubiquitin ligase complex 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).

Statistical methods have been used to define a number of genomic regions of significant copy number alteration in serous-like tumors, including regions of focal amplification involving the *MYC* (v-myc avian myelocytomatosis viral oncogene homolog) 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 tumors 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 of serous endometrial carcinomas [*(16, 17)*; reviewed in *(24)*]. Numerous additional genes of interest, including *PIK3CA*, *FBXW7*, *CHD4*, and *MBD3* (methyl-CpG binding domain protein 3), are located within larger regions of copy number alteration in serous and serous-like endometrial carcinomas *(15–17)*.

Copy number–high (serous-like) 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 (serous-like) subgroup are also within a so-called mitotic subgroup, defined by altered mRNA production for genes involved in cell cycle regulation *(15)*. RNA sequencing has also revealed transcriptional differences that form significantly enriched pathways in the copy number–high (serous-like) subgroup, including G_1/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 p53 protein levels and decreased phospho-AKT protein levels have been noted by reverse-phase protein array 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* mutated ($P = 0.038$). 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 lapatinib, therapeutic agents that target ERBB2 *(73, 74)*. This observation 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 for treating 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 has an effect on 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 classified as grade 3 endometrioid endometrial carcinomas are "serous-like" at the molecular level. As noted in the TCGA study, the distinction between the histologic and molecular classification of these cases has important clinical implications—suggesting that patients who have grade 3 endometrioid endometrial carcinomas with a serous-like genomic profile might be treated more appropriately with regimens that are used for serous carcinoma. As is discussed earlier in this review, a subset of high-grade endometrial tumors is difficult to classify accurately by subtype at the histologic level. The newfound realization that serous and endometrioid endometrial tumors can be molecularly classified into 4 distinct subgroupings may provide future opportunities to devise a panel of biomarkers, or indeed use integrated genomic profiling, to augment the traditional histopathologic classification of endometrial carcinomas. In this regard, it is notable that 48 significantly mutated genes are altered at different frequencies across the 4 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

Table 2. Forty-eight SMGs mutated at different frequencies across 4 molecular subgroups of serous and endometrioid endometrial cancers.[a]

Gene Symbol	Gene Name	Mutation frequency				
		POLE ultramutated (n = 17)	Hypermutated/ microsatellite unstable (n = 65)	Copy number low/microsatellite stable (n = 90)	Copy number high (serous-like) (n = 60)	All 4 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[b]	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%
KMT2B[c]	Lysine (K)-specific methyltransferase 2B	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 2	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%
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%

Continued on page 107

Table 2. Forty-eight SMGs mutated at different frequencies across 4 molecular subgroups of serous and endometrioid endometrial cancers.[a] *(Continued from page 106)*

Gene Symbol	Gene Name	Mutation frequency				
		POLE ultramutated (n = 17)	Hypermutated/ microsatellite unstable (n = 65)	Copy number low/microsatellite stable (n = 90)	Copy number high (serous-like) (n = 60)	All 4 subgroups (n = 232)
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 family member A	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 2-like 2	12%	11%	3%	0%	5%
ESR1	Estrogen receptor 1	24%	2%	6%	2%	5%

[a] The Cancer Genome Atlas Research Network et al. *(15)*. Mutation frequencies of protein-encoding genes were retrieved via cBioPortal (http://www.cbioportal.org/public-portal/). The mutation frequency of *MIR1277* was retrieved via the TCGA data portal (https://tcga-data.nci.nih.gov/tcga/).
[b] Probable false positive [Lawrence et al. *(70)*].
[c] HUGO-approved gene symbol and name. Also known as *MLL4* (myeloid/lymphoid or mixed-lineage leukemia protein 4).

integrated genomic analysis of these 2 subtypes of endometrial cancer by TCGA *(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 histologic subtypes. Prospective studies assessing the potential clinical utility of these findings will undoubtedly follow. One can 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 at an earlier stage in their clinical course, when the prognosis is more favorable. In the latter case, it is noteworthy that the genomic analysis of cells collected during Papanicolaou 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 the precancerous lesions that precede endometrial carcinomas, as well as annotating and functionalizing somatic aberrations in the noncoding regions of the genome in endometrial carcinomas.

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