2 Molecular Pathology and Cytogenetics of Endometrial Carcinoma, Carcinosarcoma, and Uterine Sarcomas

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Introduction

Uterine neoplasms include epithelial cancers (endometrial carcinomas and carcinosarcomas) and mesenchymal neoplasms (leiomyosarcomas and endometrial stromal sarcomas). The epithelial cancers occur much more frequently than uterine mesenchymal tumors, and hence more information is available on their molecular pathology. Carcinosarcoma of the uterus previously considered as mixed neoplasms with stromal and epithelial elements is now classified as high-grade endometrial carcinoma on the basis of genetic and molecular characteristics. This chapter will describe the molecular and cytogenetic features of uterine cancers.

Molecular Pathology and Cytogenetics of Endometrial Carcinoma

In 1983 Bokhman proposed that there are two different pathogenetic types of endometrial carcinoma that require different approaches to detection and treatment [1]. Type I tumors, which account for 70–80 % of endometrial cancers, follow the estrogen-related pathway. They arise in a background of unopposed estrogen stimulation, coexist with complex and atypical hyperplasia, and express estrogen (ER) and progesterone receptors (PR) [2]. These tumors occur in premenopausal and perimenopausal women and histologically show low-grade endometrioid differentiation. Mucinous adenocarcinomas are also included under type I as they are of low grade and express ER and PR receptors.

Type II tumors in contrast are more aggressive and mostly include the high-grade serous and clear cell subtypes. These tumors arise in a background of atrophic endometrium unrelated to estrogen stimulation [3]. ER and PR receptor expression is negative or sometimes weakly positive in these tumors. Type II tumors occur at an older age, roughly 5–10 years later than type I tumors [2]. It has now been proved that both these types of tumors are caused by different molecular alterations [4, 5]. Main molecular alterations seen in type I endometrial cancers are MSI (microsatellite instability) and mutations affecting the PTEN, KRAS, PIK3CA, and CTNNB1 genes. Type II cancers on the other hand commonly exhibit P53 alterations, LOH (loss of heterozygosity) on several chromosomes, and molecular alterations affecting p16, STK15, E-cadherin, and c-erb-B2 [6].

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The integrated proteomic, transcriptomic, and genomic analysis of endometrial cancers by The Cancer Genome Atlas (TCGA) Research Network has shown that endometrial cancers can be subdivided into four different clusters based on these characteristics [7]. Progression-free survival analysis has shown significant survival differences between the groups with cluster 1 having the best and cluster 4 having the worst outcome. This genomic-based classification may lead to changes in the management of endometrial cancers as we need to consider whether endometrioid tumors belonging to cluster 4 may have improved survival with addition of chemotherapy or patients belonging to cluster 1 can be left alone without any adjuvant treatment [7].

Microsatellite Instability (MSI)

The genes responsible for microsatellite instability (MSI) encode proteins involved in DNA mismatch repair (MMR). The ability of cells to repair defects produced during DNA replication is affected when a mutation affects these genes. Hence, cells with defective MMR genes replicate DNA mistakes more frequently than others [8]. These faulty mutations can accumulate in the coding and noncoding DNA sequences, including microsatellites, which are short tandem repeats. Some mononucleotide repeats are located within the coding sequences of important genes (BAX, IGFIIR, hMSH3, hMSH6, MBD4, CHK-1, Caspase-5, ATR, ATM, BML, RAD-50, BCL-10, and Apaf-1) [6].

Seventy five percent of endometrial cancers associated with Lynch syndrome and 25–30 % of sporadic endometrial cancers demonstrate MSI [8]. In sporadic endometrial cancers, MSI is due to MLH-1 promoter hypermethylation and is associated with type I endometrioid cancers rather than type II. The presence of MSI is associated with a higher histological grade [6]. In Lynch syndrome, MSI arises due to mutations arising in MSH2, MH6, MLH1, or PMS2.

Phosphatase and Tensin Homolog (PTEN)

PTEN is a tumor suppressor gene, which has important functions in the regulation of cell cycle and apoptosis [9, 10]. This gene is located on chromosome 10q23 and encodes for a protein – phosphatase and tensin homolog (PTEN) – with tyrosine kinase function. The PTEN gene product regulates many key processes in cell such as proliferation, adhesion, migration, and apoptosis and is also a suppressor of tumor growth [11]. PTEN also exerts its effect on cell survival and proliferation through the phosphatidylinositol 3-kinase (PI3K)/Akt pathway [12]. It inhibits PI3K-Akt pathway inducing apoptosis and/or cell cycle arrest [12]. Hence, loss of PTEN function causes aberrant cell proliferation and escape from apoptosis.

The expression of PTEN in the endometrium is controlled by estrogen and progesterone and is expressed more in the proliferative phase than in the secretory [12]. PTEN gene inactivation can occur by point mutation, promoter hypermethylation, or deletion (loss of heterozygosity (LOH)) at 10q23 [6]. PTEN inactivation is seen in 60–80 % of endometrioid cancers and in only less than 10 % of non-endometrioid endometrial cancers [12–15]. The authors have shown loss of PTEN expression in endometrial hyperplasia with and without atypia, and hence, it is thought to play an important role in endometrial cancer tumorigenesis [16]. Altered PTEN expression has been reported in up to 55 % of precancerous lesions of the endometrium, and this is thought to be initiated in response to known hormonal risk factors. Progesterone has shown to promote involution of PTEN-mutated tumor cells [13]. PTEN mutations can coexist with MSI with 60–86 % of MSI-positive endometrial cancers showing PTEN mutations [6]. Data regarding the prognostic significance of PTEN mutations are controversial [17], but Salveston et al. showed correlation between PTEN mutations, low FIGO stages, and favorable prognosis [18]. In this study patients with PTEN mutations had better 5-year survival compared with those with no mutations.

PTEN-deficient cells are sensitive to mammalian target of rapamycin (mTOR) inhibitors in vitro since loss of PTEN leads to activation of Akt which upregulates mTOR activity [19]. mTOR inhibitor temsirolimus showed a response rate of 26 % in endometrial cancer patients [20].

RAS-RAF-MEK-ERK Signaling Pathway

This pathway plays an important role in tumorigenesis. Mutations in KRAS proto-oncogene is not present in the normal endometrium but is seen in 6–16 % of atypical hyperplasia and 10–30 % of endometrial carcinomas [13, 21]. It has been shown that as the endometrium changes from normal to varying degrees of hyperplasia, there is an increase in KRAS point mutations [22]. Increased frequency of KRAS mutations is reported in endometrial cancers associated with MSI [23]. BRAF, another member of the RAS-RAF-MEK-ERK pathway, is mutated very infrequently in endometrial cancer [24]. Activated RAS is associated with enhanced cell proliferation, transformation, and cell survival. RAS effectors like RASSF1A (RAS association domain family member 1) are thought to have an inhibitory signal, which needs to be inactivated during tumorigenesis [6]. The increased activity of the RAS-RAF-MEK-ERK pathway can also be due to RASSF1A inactivation by promoter hypermethylation [25].

PIK3CA

PI3K (phosphatidylinositol 3-kinase) is a heterodimeric enzyme with a catalytic (p110) and regulatory (p85) subunit. The PIK3CA gene codes the p110α catalytic subunit of this enzyme, which is located on chromosome 3q26.32 [6]. Mutations affecting this subunit have been implicated in many malignancies and may contribute to the alteration of PI3K/AKT signaling pathway in endometrial cancer [13]. Mutations affecting the PIK3CA gene are located mainly in the helical (exon 9) and kinase (exon 20) domains, but mutations can also occur in exons1–7 [6]. In 24–39 % of endometrial cancers, PIK3CA mutations occur, and they coexist frequently with PTEN mutations [26]. PIK3CA mutations affecting exon 20 have been associated with high histological grade and myometrial invasion. Though initially described in endometrioid carcinomas, PIK3CA mutations can also occur in non-endometrioid endometrial carcinomas and mixed tumors. Mutation affecting the p85a inhibitory subunit of PI3K has also been detected in 43 % of endometrioid carcinomas and 12 % of non-endometrioid cancers [6].

β-Catenin

Studies have shown elevation of beta-catenin in several cancers including endometrial carcinoma and atypical endometrial hyperplasia [27, 28]. The increased beta-catenin levels occur due to mutation of the beta-catenin gene (CTNNB1) located in chromosome 3p21. Beta-catenin is a part of the E-cadherin-catenin complex, which has a role in cell differentiation and maintenance of normal tissue architecture. When mutation occurs in the exon gene of CTNNB1, there is stabilization of beta-catenin protein leading to its cytoplasmic and nuclear accumulation. It also forms complexes with the DNA-binding proteins and participates in the signal transduction [6]. These mutations are seen in 14–44 % of endometrial cancer and are independent of the presence of MSI, PTEN, or KRAS mutation. Beta-catenin mutations are distributed homogenously in different areas of the tumors suggesting that they play a role in the early steps of endometrial tumorigenesis [13]. There are controversial data regarding the prognostic significance of beta-catenin, but they probably occur in tumors with good prognosis [6].

Fibroblast Growth Factor Signaling Pathway

Studies have indicated that fibroblast growth factor (FGF) signaling pathway is important in

endometrial cancer. FGF receptor (FGFR) is downregulated by a protein SPRY-2 that is found inactivated in endometrial cancer [6]. Inactivation of SPRY-2 causes increased cell proliferation. Almost 20 % of endometrial cancers have reduced SPRY-2 immunoexpression. In 6–12 % of endometrial carcinomas, especially in endometrioid types, somatic mutations affecting the receptor tyrosine kinase FGFR2 have been detected [29]. It is of interest to note that FGFR mutations and PTEN mutations often coexist, whereas FGFR mutations and KRAS mutations are mutually exclusive [6]. FGRF2 receptor antibodies are currently considered as targeted therapy agents in endometrial carcinoma.

TP53

TP53 mutations are mainly seen in non-endometrioid endometrial cancers (90 %). 10–20 % of endometrioid cancers (mainly grade 3) also exhibit these mutations [3, 30]. TP53 is a tumor suppressor gene located in chromosome 17 (locus 17p13.1). This gene encodes a phosphoprotein called TP53, which participates in cell cycle regulation, DNA repair systems, and apoptosis [11]. Loss of its normal activity prevents apoptosis and promotes tumor progression [31]. An increase in P53 expression from the normal endometrium to hyperplasia through to endometrial carcinoma has been demonstrated by Horee et al., suggesting a possible role in disease progression [32]. Overexpression of TP53 was found to be correlated with advanced stage, lymph node metastases, and high-grade endometrial cancers [33].

HER2/neu

HER2/neu receptor is a membrane-bound tyrosine kinase receptor, which belongs to the epidermal growth factor receptor family. It plays a role in regulating cell growth and differentiation. HER2/neu gene amplification results in overexpression of the receptors resulting in increasing cell proliferation. The amplification of HER2/neu is seen in a wide variety of malignancies including breast, ovarian, and endometrial [34–36]. In endometrial cancers HER2/neu overexpression is associated with reduced disease-free and overall survival [37]. Increased expression of HER2/neu is found in about 30 % of uterine serous cancers and 10–20 % of high-grade endometrioid cancers. Well-differentiated endometrioid cancers rarely exhibit HER2/neu positivity [12, 38]. Trastuzumab is a monoclonal antibody, which has targeted action against the HER2/neu protein and is being used widely in breast cancer patients who are HER2/neu positive. But trials using trastuzumab in advanced or recurrent HER2-positive endometrial cancers have failed to show benefit [39].

E-cadherin

E-cadherin is a transmembrane glycoprotein of the cadherin family, which promotes and maintains cell adhesion. Cadherins are tissue specific and are required for the assembly of cells into solid tissues [12]. Epithelial cells express E-cadherin and its levels are reduced in many carcinomas including breast, lung, prostate, and also endometrial [12, 40]. Reduced E-cadherin expression was more seen in type 2 endometrial cancers and also in those carcinomas with advanced stage [41]. Fifty seven percent of type 2 endometrial cancers demonstrated loss of heterozygosity of E-cadherin gene at 16q22.1 compared to 22 % of type 1 carcinomas [6].

P16

P16 tumor suppressor gene is located on chromosome 9p21 and this encodes for a cell cycle regulatory protein. Inactivation of p16 leads to uncontrolled cell growth. P16 inactivation was seen in 45 % of serous carcinomas and some clear cell cancers [42].

EGFR

EGFR is a transmembrane tyrosine kinase receptor, whose mutation has been identified in many

malignancies. EGFR overexpression has also been identified in uterine serous carcinomas [43]. Overexpression of EGFR is associated with advanced stage and poor prognosis [44]. EGFR antagonists include tyrosine kinase inhibitors like gefitinib, erlotinib, and lapatinib and anti-EGFR monoclonal antibody cetuximab[42].

Other Molecular Alterations in Non-endometrioid Malignancies

The molecular feature that has been described as most typical of non-endometrioid cancer is the widespread chromosome gains and losses, which reflect aneuploidy [45]. The mitotic spindle checkpoint genes STK15, BUB1, and CCNB2 are upregulated in non-endometrioid endometrial cancers [6]. STK 15 is the gene essential for chromosome segregation and centrosome functions and it is frequently amplified in non-endometrioid endometrial cancers. Serous carcinoma has other documented potential biomarkers like epithelial cell adhesion molecule (EpCAM), claudin-3 and claudin-4 receptors, serum amyloid A, folate-binding protein, mesothelin, and insulin-like growth factor II mRNA-binding protein 2 (IMP2) [6].

Clear cell carcinomas of the endometrium appear to arise from a different pathogenetic pathway. There are morphological similarities between the ovarian and endometrial clear cell carcinomas and both exhibit PIK3CA and PTEN mutations. The ARID1A gene mutation and loss of corresponding protein BAF250a that is seen in clear cell and endometrioid carcinomas of the ovary are also seen in 26 % of clear cell endometrial cancers [6].

Non-endometrioid endometrial carcinomas differ from endometrioid carcinomas in expression profiling as shown by cDNA array studies [46]. In endometrioid carcinomas TFF3, FOXA2, and MSX2 genes are upregulated, whereas in serous carcinomas IGF2, PTGS1, FOLR, and p16 are increased. When the expression profiles of similar histological types of ovarian and endometrial carcinomas were compared, it was found that there were striking differences in the endometrioid and serous carcinomas, whereas clear cell carcinomas, regardless of the organ of origin, had a similar profile [6].

MicroRNAs (miRNAs) are 20–25 nucleotide noncoding RNAs regulating the expression of target genes. Aberrant expression of miRNA is associated with malignant behavior and specific miRNAs are associated with each cancer types. MiRNA profiling has been shown to differentiate tumors better than traditional gene expression analysis [6]. In endometrial cancer miR-185, miR106a, miR-210, miR-423, miR-103, miR-107, miR-Let7c, miR-205, miR-200c, miR-449, miR-429, miR-650, miR-183, miR-572, miR-200a, miR-182, miR-622, miR-34a, and miR-205 were shown to be upregulated, and miR-Let7e, miR-221, miR-30c, miR-152, miR-193, miR-204, miR-99b, miR-193b, miR-204, miR-99b, miR-193b, miR-411, miR-133, miR-203, miR-10a, miR-31, miR-141, miR-155, miR-200b, and miR-487b were downregulated [6]. The miRNA signatures of serous carcinomas differed from that of endometrioid endometrial carcinoma.

Integrated Genomic Characterization by the TCGA Network

The Cancer Genome Atlas (TCGA) network did molecular analysis of 373 patients with endometrial cancer (307 endometrioid and 66 serous) and found MSI in 40 % endometrioid and 2 % serous tumors. They subclassified endometrial carcinomas into four clusters based on (i) MSI status, (ii) copy number clusters, and (iii) nucleotide substitution frequencies and patterns [7]. Cluster 1 was the ultra-mutated group with very high mutation rates, and this group had mutations in the exonuclease domain of POLE (catalytic subunit of DNA polymerase epsilon involved in DNA replication and repair). Cluster 2 had hypermutated tumors showing increased MSI and most of them with promotor 1 hypermethylation. Cluster 3 was microsatellite stable (MSS) and had a lower mutation frequency and most of the tumors were endometrioid. Cluster 4 had a low

mutation frequency but a high rate of somatic copy number alterations (SCNAs), and the group contained most of the serous and mixed histology tumors with frequent TP53 mutations. When the progression-free survival was analyzed after a median follow-up of 32 months, it was found that cluster 1 had a significantly better progression-free survival (PFS) compared to other clusters with cluster 2 having better PFS than cluster 3 and cluster 4 having significantly worse PFS than others [7].

Thus, the integrated molecular analysis of endometrial carcinomas by TCGA led to the identification of four different groups of endometrial carcinomas as opposed to the traditional classification of type I and type II tumors. The new POLE subtype (cluster 1) comprised about 10 % of the endometrioid tumors. This group is characterized by hotspot mutations in the exonuclease domain of POLE, ultrahigh somatic mutation frequency, and MSS. The survival analysis showed a significantly high progression-free survival for this group. The analysis of SCNAs also added new information about endometrial cancers showing that the extent of SCNAs correlated with the progression-free survival [7]. Twenty-five percent of high-grade endometrioid carcinomas had extensive SCNAs and increased TP53 similar to that of uterine serous carcinomas.

Therapeutic Implications

The improved knowledge about the molecular characteristics of endometrial carcinoma should ideally translate into targeted therapy offering better survival with less treatment-related toxicity to the patient. Gynecologic Oncology Group (GOG) had conducted phase II trials for trastuzumab, bevacizumab, lapatinib, and gefitinib in the treatment of endometrial cancers.

Trastuzumab is a monoclonal antibody directed against HER2 receptor and has proven survival advantage in HER2-positive women affected with breast cancer. GOG 181-B looked into treating patients with advanced or recurrent HER2-positive endometrial carcinoma with trastuzumab [39]. Trastuzumab did not show any activity against HER2-positive endometrial cancer in this phase II trial. Serous tumors have high frequency of HER2 amplification, and trials have shown that uterine serous carcinoma may respond to HER2 inhibition [47]. Further research is warranted in this area.

Bevacizumab is a recombinant humanized monoclonal antibody against vascular endothelial growth factor A (VEGF-A). It is used in the treatment of many malignancies including ovarian and cervical malignancies. The GOG 229-E phase II trial assessed the activity of bevacizumab in recurrent or persistent endometrial cancer and found that 40 % of patients survived progression free for 6 months and 13.5 % of patients had objective clinical response [48]. The results were similar across all histologies. The results of GOG 086-P, a randomized phase II trial combining bevacizumab with chemotherapy, is awaited.

Lapatinib is a member of the 4-anilinoquinazoline class of kinase inhibitors and acts as a dual inhibitor of both EGFR and HER2 tyrosine kinase activity [49]. GOG 229-D assessed the efficacy of lapatinib in endometrial cancer and found that it had insufficient activity to warrant its use as a single agent in endometrial cancer [50]. The GOG 229-C trial involving gefitinib, yet another tyrosine kinase inhibitor, did not show improved response rates for patients with persistent or recurrent endometrial cancer [51].

Konency et al. assessed the activity of fibroblast growth factor receptor (FGFR) inhibitors Dovitinib and NVP-BGJ398 in human endometrial cancer cells and found that both molecules had significant antitumor activity in FGFR2-mutated endometrial cancer xenograft models [52]. The antiproliferative effect of metformin in obese endometrioid endometrial cancer patients was analyzed by Schuler et al. who found that 65 % of patients responded to metformin and it reduced proliferation by 11.75 % supporting further therapeutic clinical trials using metformin [53].

Molecular Pathology of Carcinosarcoma

Carcinosarcoma comprises of 2–5 % of all endometrial cancers. Morphologically these tumors contain admixed carcinomatous and sarcomatous components. But the epithelial and stromal components of carcinosarcomas show identical patterns of X chromosome inactivation, indicating their origin from a single stem cell clone [54]. Studies have shown that both the epithelial and mesenchymal elements show immunohistochemical expression of p53, MSH2, and MSH6 confirming the monoclonal origin [13]. In carcinosarcomas the malignant epithelial cells which express E-cadherin transdifferentiate into malignant mesenchymal cells that express N-cadherin and cadherin-11. This epithelial mesenchymal transition (EMT) promotes the tumor cell interaction with the stroma, promoting invasion and metastasis [55]. On the basis of mutations, carcinosarcomas have been subclassified into endometrioid type with mutations involving PTEN and ARID1A and serous type with TP53 and PPP2R1A mutations [56]. Another important feature noted is the downregulation of miR-200 family of miRNAs and overexpression of miR-214 in the mesenchymal component of carcinosarcoma [57].

Molecular Pathology and Cytogenetics of Leiomyosarcomas

Leiomyosarcomas (LMS) comprise approximately 1–3 % of all uterine malignancies and about 40–50 % of all uterine sarcomas [58]. They are clinically aggressive and have an overall poor prognosis [59]. Majority of them arise de novo, while a small subset is associated with benign leiomyoma. Studies have shown that loss of heterozygosity, overexpression, amplification, and mutations can contribute to the development of LMS [60]. In LMS, LOH at chromosome 10 was more frequently seen when compared to leiomyoma and may contribute to sarcomagenesis [60]. Mittal et al. [61] showed that chromosomal gains and losses in the benign leiomyomatous areas were retained in the sarcomatous areas with additional gains and losses occurring in the sarcomatous areas.

LMS show differential expression of many genes involved in cell proliferation and cell cycle regulation unlike benign leiomyomas. CDKIN2A that codes for p16 is upregulated enabling the immunohistochemical detection of p16 in LMS [62].

Mutation in p53 was noted in 24 % of LMS [60]. In LMS the expression of Ki-67, p53, and p16 was substantially higher, and the expression of tumor suppressor genes PTEN, RASSF1A, and DAP (death-associated protein) was downregulated compared to benign leiomyoma. The downregulation is caused by promotor hypermethylation of the genes [60]. Increased expression of twist homolog 1 (TWIST 1) and fascin homolog 1(FSCN 1) is associated with tumor progression and metastases. Other poor prognostic factors are strong expression of Ki-67, p53, p16, ESR 1(estrogen receptor 1), PGR (progesterone receptor), cyclin D1, and phospholipase D1 as well as low expression of BCL-2 [60]. Loss of BRCA 1 is also said to be involved in the progression of LMS.

Mutations in MED12 gene (mediator complex subunit 12) were identified in 50–80 % of conventional leiomyomas. These mutations are specific to uterine smooth muscle tumors but are less common in leiomyosarcomas [60–65]. Gene products which regulate mitotic centrosome and spindle functions like UBE2C, Aurora A and B kinases, TPX2, and Polo-like kinase 1 are overexpressed in LMSs. Targeting Aurora A has been shown to induce apoptosis and decrease proliferation in uterine LMSs [57]. Increased tyrosine kinase receptor activity and enhanced mTOR signaling have also been demonstrated in uterine LMSs [59].

MiRNAs are important in smooth muscle cell differentiation of uterine LMSs. The miRNA signature of LMS is more similar to bone marrow-derived human mesenchymal cells, whereas the miRNAs of benign leiomyomas are

linked with more mature smooth muscle cells and myometrium [66]. But it is unclear as to whether the LMS cells are derived from the differentiation blockade of smooth muscle progenitor cells or de-differentiation of mature smooth muscle cells [66].

Molecular Pathology and Cytogenetics of Endometrial Stromal Tumors

Endometrial stromal tumors (EST) are rare uterine neoplasms comprising about 1 % of all uterine malignancies [67]. According to the World Health Organization, these tumors are classified into three categories: endometrial stromal nodule (ESN), low-grade endometrial stromal sarcoma (ESS), and undifferentiated endometrial sarcoma (UES) [68]. Low-grade ESS is a tumor with low malignant potential and a favorable prognosis, whereas UES is relatively uncommon and has got a poor prognosis.

ESTs are genetically heterogeneous group of tumors and have distinct cytogenetic abnormalities [69]. It was in 1988 that Dal Cin et al. published the first cytogenetic change in ESS, the insertion of chromosome 19 into chromosome 10 [70]. Three years later, the now hallmark mutation of ESTs, t(7;17)(p21;q12), was reported by Sreekantiah et al. [71]. Since the publication of these results, there have been numerous reports of chromosomal translocations in ESTs, but they are all primarily on low-grade ESS.

The most common and extensively studied translocation in ESTs is that of JAZF1-SUZ12 gene fusion. In this the first three exons of JAZF1 on chromosome 7p15 join the last 15 exons of SUZ12 on chromosome 17q21 [59]. This translocation is very specific to ESTs and has not been noticed in other uterine mesenchymal neoplasms. The JAZF1-SUZ12 gene fusion has been demonstrated in 65 % of ESNs, 48 % of ESSs, and 12 % of UESs [59, 69]. The presence of these mutations in ESNs and ESSs suggests that the chromosomal translocation and gene rearrangement is an early event in the pathogenesis of ESS. It is postulated that ESNs develop from normal endometrial stroma by acquiring the t(7;17) translocation and later transform into ESS by genetic or epigenetic silencing of the unrearranged JAZF1 allele [72]. The small percentage of UESs showing this translocation suggests that they may be developing from ESSs or ESNs via dedifferentiation [73]. But majority of the UESs seem to develop by genetic pathways, which are different from that of ESNs and ESSs [69].

Other less commonly seen gene fusions in ESTs are PHF1-JAZF1, EPC1-PHF1, and MEAF6-PHF1 [59]. MiRNAs also seem to contribute to the pathogenesis of ESTs. Studies have shown similar miRNA profiles in ESSs with or without gene rearrangements. Also several miRNAs altered in ESSs and UESs are involved in Wnt, VEGF, and EGFR signaling pathways suggesting a common pathogenesis [74].

Conclusions

Endometrial carcinomas were traditionally classified as the histologically low-grade type I tumors and type II tumors with high-grade histologies including papillary serous and clear cell types. Mutations differ between these two types with type I tumors showing more PTEN, PIK3CA, β-catenin, RAS-RAF-MEK-ERK pathway mutations, and MSI. Type II tumors have overexpression of P53, HER2/neu, and EGFR and inactivation of E-cadherin and P16. The recent work by TCGA research network has subclassified endometrial cancers into four different types based on proteomic, transcriptomic, and genomic analysis. Survival analysis also showed distinctive progression-free survival curves for these groups. This classification may lead to changes in the management of endometrial cancers in the future.

Molecular studies of carcinosarcomas have confirmed their monoclonal origin, there is transdifferentiation of the malignant epithelial cells into malignant mesenchymal cells, and this epithelial mesenchymal transition promotes invasion and metastases. Loss of heterozygosity, gene amplification, and mutations contribute to the development of leiomyosarcomas. Endometrial stromal sarcomas have characteristic translocations, the most common one being JAZF1-SUZ12 gene fusion.

Key Points

1. Endometrial carcinomas are broadly divided into type I and type II which are caused by different molecular alterations.
2. Main molecular alterations seen in type I endometrial cancers are MSI (microsatellite instability) and mutations affecting the PTEN, KRAS, PIK3CA, and CTNNB1 genes.
3. Type II cancers commonly exhibit P53 alterations, LOH (loss of heterozygosity) on several chromosomes, as well as molecular alterations affecting p16, STK15, E-cadherin, and c-erb-B2.
4. TCGA has reclassified endometrial carcinoma into four groups based on molecular characteristics, with the POLE-mutated group having very good survival rates.
5. Both the epithelial and mesenchymal elements of carcinosarcoma show immunohistochemical expression of p53, MSH2, and MSH6 confirming the monoclonal origin.
6. On the basis of mutations, carcinosarcomas have been subclassified into endometrioid type with mutations involving PTEN and ARID1A and serous type with TP53 and PPP2R1A mutations.
7. LOH at chromosome 10 was more frequently seen in LMS when compared to leiomyoma and may contribute to sarcomagenesis.
8. In LMS the expression of Ki-67, p53, and p16 was substantially higher, and the expression of tumor suppressor genes PTEN, RASSF1A, and DAP (death-associated protein) was downregulated compared to benign leiomyoma.
9. t(7;17)(p21;q12) is the hallmark mutation of endometrial stromal tumors.
10. JAZF1-SUZ12 gene fusion is very specific to endometrial stromal tumors.

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