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Genetic and Epigenetic Features in Uterine Smooth Muscle Tumors: An Update

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Abstract

Uterine Smooth Muscle Tumors (USMTs) can be either benign or malignant. The Uterine Leiomyoma (ULM) also called uterine fibroid is the most common benign USMT, but at least 4 other types of tumors are part of this classification: Mitotically Active Leiomyoma (MALM), Cellular Leiomyoma (CLM), Atypical Leiomyoma (ALM), and Uncertain Malignant Potential (STUMP). These tumors show high heterogeneity in several aspects such as size, location and symptoms and represent the current major cause of hysterectomy. In contrast, Uterine Leiomyosarcoma (ULMSs) occurs with lower frequency but higher recurrence, metastasis, and mortality rates. Although present the same cell pattern of differentiation, the origin and causes of these tumors are unknown. The diagnosis of these neoplasms is difficult by the symptoms overlapping, sharing of morphological and molecular characteristics, being possible to classify them only after the surgical procedure. In addition, despite of the MRI recommendation as better technique for LMS and LM differentiation, none image method still present sufficient sensitivity for their preoperative diagnosis. Some researchers believe that a degenerated ULM can turn into a ULMS; others claim that ULMSs can only arise *de novo*. Several studies have focused on the molecular mechanisms of these tumors; however, no specific marker or signaling has been defined for clinical and therapeutic applications. To help better understand their molecular biology, in this review, we assemble literature data from 2005 to 2019 that focuses on findings related to ULM and ULMS genetics and epigenetics.

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Introduction

Uterine smooth muscle tumors (USMTs)

USMTs are the most frequently occurring type of gynecological mesenchymal tumor and can be classified as benign or malignant based on their macro and microscopic features. Both benign (Uterine Leiomyoma, ULM) and malignant (Uterine Leiomyosarcoma, ULMS) neoplasms arise from myometrium, and a specific diagnosis is obtained only after a surgical procedure [1]. Sometimes, a correct diagnosis based on USMT features can be challenging. Besides non smooth muscle tumors that originate in the uterus showing overlapping histological and even immunohistochemical features with USTM, unusual figures may also occur in ULMs [2,3]. In the past, USMTs showing 10 or more mitoses per 10 High-Power Fields (HPFs) were sufficient for diagnosis. Presently, the mitotic index is an important feature in the assessment of malignancy, but several studies have shown that it alone is not predictive of a poor outcome [2,4]. Additionally, a large variety of features observed in USMTs, such as nuclear pleomorphism, hyperchromatism, irregularity in nuclear membranes, high nuclear size, and prominent nucleoli, are indicative of malignancy. However, the diagnostic criteria for the different subtypes of ULMS are not uniform [2]. Tumor biology forms the basis for outlining specific or targeted forms of treatment, which are currently under investigation for several cancer types. Much research is still needed on the subject, since to date there are no ancillaries to therapy against USMTs that can change the natural course of this disease [5]. So, in the last decades, focusing on the precise diagnosis of USMTs, several works were developed concerning their molecular features. The main studies and discoveries are addressed in this review.

Uterine leiomyoma

Uterine leiomyoma (fibroid) is the most common benign uterine smooth muscle neoplasm that affects women of reproductive age. Although many cases may be asymptomatic, the symptoms can include severe menstrual bleeding, pelvic pain, and infertility. Diagnosis is performed through medical imaging techniques such as trans abdominal or transvaginal ultrasound [6,7]. Hysterectomy

or myomectomy is the standard treatment for these neoplasms and the choice depends on the size, number, and extent of these tumors. Nonsurgical treatment may include Uterine Artery Embolization (UAE) and high-frequency MR-guided focused ultrasound surgery. The clinical management of ULMs consists of treatment of pain and bleeding and also the use of Gonadotropin-Releasing Hormone GnRH analogues. Moreover, recent studies have shown that in a hypoestrogenic state, the fibroids undergo shrinkage and blood loss attenuation [8]. Heterogeneity is a common feature of ULMs. Its histological variants may be associated with atypical elements known as Mitotically Active Leiomyoma (MALM), Atypical Leiomyoma (ALM), and Cellular Leiomyoma (CLM). ALMs and Smooth muscle tumors of Uncertain Malignant Potential (STUMPs) are two histologic variants of USMTs and have a more complex diagnosis. The potential for progression of these neoplasms to ULMSs requires careful exploration of the molecular link between ALMs, STUMPs, and ULMSs [9]. Some histological features may be important to differentiate the leiomyoma variants from uterine ULMSs: tumor size, cytological atypia, presence or absence of vascular invasion, coagulative necrosis, and tumor margin. However, there are no clinical findings that can clearly differentiate these neoplasms [10,11]. Studies using patient samples and cell cultures have shown that events such as gene mutations, histone acetylating, DNA methylation, as well as changes in microRNA (miRNA) expression profile appear to be frequent in ULMs and are commonly studied targets for therapy in several tumor types. Further research aimed at a more comprehensive understanding of the molecular aspects of ULMs may result in better prognosis as well as less invasive and equally effective therapeutic options for patients with symptomatic disease [12-15].

Aspects of ULM molecular signature

Knowledge of the genetic background of ULM tumorigenesis is considered quite unbalanced. There is a range of aberrantly expressed genes, among which are important oncogenes and tumor suppressor genes. However, even with the marked altered expression of these genes, they should not be used as a typical sign of tumorigenesis, since many other factors may influence this [16]. Approximately 40% of ULMs have nonrandom cytogenetic rearrangements that may lead to overexpression of $HMGA_2$. Other chromosomal alterations include, for example, 7q interstitial deletions, 6p21 rearrangements, and 12 trisomy. Around 70% of ULMs harbor specific mutations of mediator complex subunit 12 (MED12) [17]. Evidence indicates that ULMs present different genetic alterations among themselves. The clinical–pathological differences observed between ULM subtypes can be explained by the existence of different transcriptional patterns in key driver genes and pathways. Mehine et al. [18] pointed out the existence of specific conductive alterations, including HMGA2 rearrangements, MED12 mutations, balletic inactivation of FH, and COL4A5–COL4A6 deletions, as the main determinants for the molecular classification of these neoplasms. The authors reported that ULMs with aberrations in HMGA2 displayed highly significant up regulation of PLAG1, suggesting that HMGA2 promotes tumorigenesis through PLAG1 activation. Besides that, RAD51 paralog B (RAD51B) was upregulated in MED12 mutant lesions, suggesting a possible role of this gene in the development of ULMs. FH-deficient ULMs were characterized by activation of NRF2 target genes. This study highlighted the importance of the molecular stratification of ULMs in research and clinical practice. In addition to the genetic alterations found among the primary ULMs, Jiang et al. [19] showed molecular differences between primary and metastatic ULMs, which are a rare condition originating in women with a history of ULMs called pulmonary benign metastasizing leiomyoma (PBML). The authors revealed that mutations in BLMH, LRP2, MED12, SMAD2, and UGT1A8 were identified concomitantly in primary and metastatic ULMs. A missense mutation in PTEN (c. 492+1G>A) was identified only in the pulmonary metastasis of the patient. When investigating α-thalassemia/mental retardation syndrome X-linked (ATRX) and DAXX expression and the presence of Alternative Lengthening of Telomeres (ALT) in ULM subtypes, Ahvenainen et al. [20], identified the loss of ATRX or DAXX and/or ALT in 6.3% of histopathological atypical ULMs, while all conventional ULMs displayed normal ATRX, DAXX, and telomeres. Considering that the loss of ATRX and DAXX and the presence of ALT are characteristics frequently associated with the development of ULMS, some ULMs that cover these characteristics may harbor long-term malignant potential. The accumulation of Extracellular Matrix (ECM) components, including collagens, fibronectin, laminins, and proteoglycans, is a distinctive feature of ULMs. The accumulation of ECM is regulated by growth factors, cytokines, and steroid hormones. TGF-β, activin-A, PDGF, and tumor necrosis factor (TNF)-α enhances the synthesis of ECM components through the activation of signaling pathways such as Smad 2/3 and MEK/ERK. In addition, estrogen and progesterone are also responsible for the activation of signaling pathways, such as MEK/ERK, AKT, and PLCγ [21]. The consequences of this cascade are tumor growth and survival and increased secretion of ECM. Estrogen Receptors (ERs) and Progesterone Receptors (PRs) are abundantly expressed in ULMs. There is a tendency for increased PR expression according to the advancement of age and the number of tumors. The role of sex steroids is critical for leiomyoma development and maintenance, but autocrine/paracrine messengers are also involved in this process [22]. Growth factors, cytokines, and chemokines are major contributing factors in regulating cellular transformation, cell growth and apoptosis, angiogenesis, cellular hypertrophy, and excess tissue turnover. Among the major cytokines, the expression of Interleukin (IL)-1, IL-6, IL-11, IL-13, IL-15, Interferon (IFN)-γ, TNF-α, Granulocyte–Macrophage Colony-Stimulating Factor (GM-CSF), and erythropoietin has biological relevance for leiomyoma pathophysiology. The evaluation of chemokine expression indicates local production of Macrophage Inflammatory Protein (MIP)-lα, MIP-1β, eotaxin, IL-8, CCR1, CCR3, CCR5, CXCR1, and CXCR2 in both ULM and Myometrium (MM), with a lower content of eotaxin, MIP-1α, MIP-1β, and CCR5 mRNA in ULM [23].

Several karyotyping studies have identified deletions affecting the 7q22, 22q, and 1p regions in ULMs. The most common chromosomal aberration described in ULMs is the characteristic translocation t (12;14) (q15;q24) [24]. Other rearrangements involving 12q14–q15, such as paracentric inversions, have also been observed. In ULMs, normal karyotypes may have cryptic inversions of 12q. ULMs with chromosome 7 deletions or translocations are usually found in the mosaic state with 46, XX cells [25]. A specific region of 7q22 has been implicated as the region affected by deletions. This region codes a variety of genes related with cell growth [26]. Other cytogenetic abnormalities of lower frequency may include changes in the X chromosome: (X) (p11.2), t (X; 12) (p22.3; q15), -X, der (5) t (X; 5) (p11; p15)(q12), der (X) t (X; 3) (p22.3; q11.2) and inv (X) (p22q13) [25].

ULM pathogenesis is still not fully understood. Acquired factors such as obesity, hypertension, and early menarche increase the

risk for the development of these tumors. ULMs may be associated with epigenetic abnormalities which are caused by unfavorable environmental exposures. A range of tumor suppressor genes are shown to be abnormally hypermethylated in ULMs when compared with adjacent MM, collagen-forming and regulating genes, and a subset of ER genes [26-28]. Among 120 genes, the DNA methylation patterns of which differ between leiomyoma and adjacent myometrium, 22 genes including COL4A1, COL6A3, GSTM5, NUAK1, and DAPK1 have the consensus sequence of ER response elements [29]. Wei et al. [30] observed that the decrease of HDAC6 expression leads to low expression of ERα in ULM cells, resulting in inhibition of proliferation. Thus, the authors suggest that histone acetylation may be able to modulate estrogen receptors.

Many studies have used a variety of molecular methods to demonstrate differences between the gene expression of ULM and myometrial tissue. An irregular miRNA profile expression in uterine fibroids also has attracted interest in diagnostic and therapeutic applications [31]. Marsh et al. [32] indicated that 46 miRNAs were differentially expressed in ULM compared with normal MM. Of these, 19 were overexpressed and 27 were downregulated in ULM. The expression of miRNAs 21, 34a, 125b, 139, and 323 was confirmed using real- time PCR. The same group of researchers verified that members of the miRNA- 29 family (29a, 29b, and 29c) are all downregulated in ULM compared with MM *in vivo*. They asserted that this differential expression contributes to the excess extracellular matrix seen in ULM [33]. miRNAs have been intensively investigated in recent years. However, knowledge of the function and expression profile of other members of small noncoding RNAs (sncRNAs) is still quite limited. A network of interactions formed by sncRNA and lncRNA has been cited as a possible factor influencing cellular activity. Alteration in the expression of these molecules is associated with the development disorders, such as ULM, compared to normal tissue, however, future research will still be necessary to accurately infer the exact function of these molecules in the pathogenesis of these tumors With aim of determining the expression profile of these molecules in ULM, Chuang et al. [34] performed next- generation sequencing and screening of an sncRNA database. The results indicated upregulation of snoRNA (SNORD30, SNORD27, SNORA16A, SNORD46, and SNORD56) and downregulation of piRNA (piR1311, piR-16677, piR-20365, and piR-4153), tRNA (TRG-GCC5–1), and rRNA (RNA5SP202) expression in ULM compared with MM ($p < 0.05$).

Cao et al. [35] reported that the expression of H19 long noncoding RNA (lncRNA) is aberrantly increased in ULM. They demonstrated that, using cell culture and genome-wide transcriptome and methylation profiling analyses, H19 promotes the expression of MED12, HMGA2, and other ECM-related remodeling genes through mechanisms that include epigenetic modification by TET3. lncRNAs have gained much attention in recent years due to their potential for biological regulation, and for the first time, these data showed an example of evolutionarily conserved lncRNA in the pathogenesis of ULM together with the regulation of the expression of TET.

Uterine leiomyosarcoma

ULMSs comprise 60% to 70% of the Uterine Sarcoma (US) group and are considered the most prevalent histological type of this category of malignancies [36,37]. These tumors usually present as a large myometrial mass, with high rates of recurrence even in the early stage of the disease [36,38]. ULMSs occur at a median age of 50 years and patients usually present signs and symptoms such as abnormal vaginal bleeding (56%), palpable pelvic mass (54%), and pelvic pain (22%) similar to ULMs or STUMPs, making it difficult to clinically distinguish these tumors [36,39]. So, the differential diagnosis is determined only after surgical excision of the tumor. ULMS staging is based on the FIGO staging system for uterine sarcomas. In a recent SEER database research, half of patients with ULMSs were diagnosed as stage I, 14% as stage II or III, and 31% as stage IV disease [40]. For early stage disease (I/II), observation and surveillance are recommended, since data on the use of adjuvant chemotherapy are limited and often conflicting. There is no evidence of benefits regarding the use of radiotherapy in these patients. In advanced stage disease (III/IV), chemotherapy with Gemcitabine and Docetaxel should be considered. For patients who have recurrence of the disease, therapy should be chosen based on the patient's functional status and treatment-related toxicity [38]. There is growing interest in the research of genetic biomarkers that allow the development of new therapeutic strategies for patients with ULMSs, since the available options have limited efficacy or even high cytotoxicity [38,40,41].

Aspects of ULMS molecular signature

ULMSs exhibit a diverse genomic profile with chromosomal losses involving tumor suppressor genes or the hyper activation of pathways involved in cell proliferation [40-42]. Currently, two ULMS molecular subtypes have been defined based on their differences in gene expression signatures. Subtype I (low grade) presents standard gene expression similar to the normal cells of the smooth muscle which is characterized by the overexpression of genes such as LMOD1, SLMAP, MYLK, and MYH11. Subtype II (high grade) is characterized by the overexpression of genes involved in the Epithelial–Mesenchymal Transition (EMT) and tumorigenesis, such as CDK6, MAPK13, and HOXA1 [43]. Uterine sarcomas exhibit a variable rate of hormone receptor expression, and 25% to 60% and 35% to 60% of ULMSs are ER and PR positive, respectively [44]. The hormone therapy has been confirmed as effective for recurrent, metastatic, or unresectable Low-Grade Endometrial Stromal Sarcoma (LGESS) and hormone receptor positive (ER+/PR+) ULMSs, presenting favorable tolerance. However, such studies are limited because of the small sample number [45]. Studies have shown that high levels of Ki-67 (proliferation protein) are found in ULMSs compared with benign smooth muscle tumors. The overexpression of p53 and p16 (oncogenic proteins) has also been described in ULMSs and may be useful as an immunomarker for the distinction of benign and malignant USMTs. However, immunostains for p16, p53, and Ki-67 have a limited role in differentiating ULMSs from ALMs. [46]. PDGFRA, WT1, GNRHR, P53, BCL2, ESR, PGR, and LMP2 immunostaining has also been used to distinguish ULMs from ULMSs [47]. Cases of ULMSs from ULMs have been reported, suggesting that ULMSs may arise from pre-existing ULMs, but this hypothesis has not yet been proved [48-50]. Garcia et al. [51] analyzed the protein expression of components of the Sonic Hedgehog (SHH) signaling pathway. In this study, 176 samples (20 MM, 119 variants of ULM, and 37 ULMS) were used. This study showed that SMO, SUFU, GLI1, GLI3, and BMP4 expression gradually increased depending on tissue histology. Expression of SMO, SUFU, and GLI1 was shown to be increased in ULMS samples compared with MM. These data suggest that the expression of SHH pathway proteins may be useful for assessing the risk of malignancy of USMTs. In 2017, The Cancer Genome Atlas (TCGA) [52] confirmed the existence of mutations and deletions in RB1, TP53, and PTEN. The whole-exome sequencing of ULMS showed frequent alterations in TP53, RB1, ATRX, and

MED12 [45]. Tsuyoshi et al. [53] described MED12 as a biomarker useful for diagnosing tumors with a relatively favorable prognosis. The authors also correlated the mutations in TP53 and ATRX with more aggressive ULMSs. Studies associated the aggressive behavior of ULMSs towards deletions of 10q (which harbors the PTEN gene) with a gain of 5p (which harbors the CyclinA gene) [54-55]. ULMSs present genetic characteristics different from other LMSs.

Using the methods of genome-wide array-baseline Comparative Genomic Hybridization (CGH array) and Fluorescent in Situ Hybridization (FISH), it was found that the regions of high-level gains are 7q36.3, 7q33-q35, 12q13-q15, and 12q23.3, and the regions of homozygous losses are 1p21.1, 2p22.2, 6p11.2, 9p21.1, 9p22.1, 14q32.33, and 14q32.33 qter. The regions with high-level gains include HMGIC, SAS, MDM2, and TIM1 genes [55-56]. To date, molecular events of ULMS metastasis are largely unknown. Thus, for a better understanding, Davidson et al. [57] compared the global patterns of gene expression of 13 primary and 15 metastatic tumors. Genes overexpressed in primary ULMSs included OSTN, NLGN4X, NLGN1, SLITRK4, MASP1, XRN2, ASS1, RORB, HRASLS, and TSPAN7. Overexpressed genes in ULMS metastases included TNNT1, FOLR3, TDO2, CRYM, GJA1, TSPAN10, THBS1, SGK1, SHMT1, EGR2, and AGT. Real-time PCR reactions confirmed significant differences in the levels of FORL3, OSTN, and NLGN4X and immunohistochemistry showed significant differences in the expression of TDO2 [57]. Epigenetic events (histone acetylation, DNA methylation, or miRNA) in ULMSs have not been extensively studied so far. Changes in the pattern of DNA methylation and complex changes in chromatin structure contribute to tumor development, stimulating proliferation and metastasis from its initiation. The therapy by epigenetic regulators in sarcomas has been the subject of several researches because it concentrates the modifications in the hereditary genomic variations, not affecting the genetic code [58]. However, studies have shown that alterations in miRNA expression may be associated with malignant transformation in ULMSs [59-62]. Ravid et al. [63] compared the expression profiles of miRNAs in primary and metastatic ULMSs. Comparison of the two tumor groups showed lower miR-15a and miR-92a levels and higher miR-31 levels in primary ULMSs. These miRNAs control genes from the Wnt signaling pathway including FZD6, which was significantly more expressed in metastases compared with primary tumors [63].

De Almeida et al. [59] identified 24 miRNAs with altered expression in ULM and ULMS cells. In ULMS cells, five miRNAs exhibited overexpression and eight were repressed. Six miRNAs had the same expression pattern when compared to the cell line with patient samples. Among these molecules, only three had significant expression in ULMSs (miR-1-3p, miR-202-3p, and miR-7-5p). Already, Dos Anjos et al. [60], in a study associating miRNA expression with clinical–pathological data of patients with USs and uterine carcinosarcomas (UCSs), observed that in ULMSs, there is an association between lower cancer-specific survival (CSS) with the downregulation of miR-125a-5p and miR-10a-5p and the upregulation of miR-196a-5p and miR-34c-5p. In addition, the researchers found that two members of the miR-29 family (miR-29a-3p and miR-29b-3p) are associated with aggressive phenotypes in ULMSs. With aim of assessing the miRNA expression profiles of ULMS, ULM, and LM variants to identify a specific signature among these tumor types, Schiavon et al. [61] found 16 molecules differentially expressed. When comparing ULMSs and ULMs, five miRNAs were identified as differentially expressed, with miR-34a- 5p downregulated and miR-144-3p upregulated. Through this study, the group concluded that the expression profile of the 144-3p, 34a-5p and 206 miRNAs may be useful in characterizing uterine ULMS and distinguish it from benign tumors. The results indicate that deregulation of miRNAs 148a-3p, 27b-3p, 124-3p, 183- 5p and 135b-5p are associated with poor prognosis for ULMS patients [61]. A preliminary study that aimed to identify miRNA expression profiles in the main uterine sarcoma subtypes and mixed epithelial-mesenchymal tumors of the uterus evaluated the expression of 88 miRNAs in malignant and benign tissue samples. The tumor and control samples differed significantly in the expression of miR-23b, miR-1, let-7f, and let-7c in endometrial sarcomas and miR-1, let-7c, miR-133b, let- 143, let-7a, let-7d, let-7e, let-7g, miR-222, let-7i, and miR-214 in mixed epithelial mesenchymal tumors. No statistically significant changes were found in the expression levels of miRNAs between the ULMSs and controls, thus indicating that USs may present different gene signatures [62]. Lipogenic enzymes including fatty acid synthase FASN are upregulated in epithelial cancers, and correlate with poor prognosis. FASN has been indicated as a biomarker in Soft-Tissue Sarcomas (STS), being related both to the reduction of Disease-Free Survival (DFS) and Overall Survival (OS). Considering this, Guan et al. [64] developed a model of the "lipogenic phenotype" in ULMS (Ut-LMS) cells through FASN overexpression, which generated features of the malignant phenotype. The authors found that FASN induced histone 3 (H3) remodeling by altering H3-modifying enzymatic activities, thus demonstrating that FASN reprograms the Ut-LMS epigenome through histone modification and chromatin remodeling, promoting the "malignant phenotype" [64]. Regarding ULMS epigenetics, Fischer et al. [58] treated multiple LMS cell lines: (SK-UT1, SK-LMS1 and MES-SA) with various doses of the DNA methytransferase inhibitors (DNMTi) 5-azacitidine (Aza), 5-aza-2-deoxycytidine (DAC), and Guadecitabine (SGI-110). Guadecitabine was more effective in reducing cell survival. SK-UT1 was found to be the most sensitive to all three epigenetic modulators. The strains SK-LMS1 and MES-SA were more resistant. The group further found an apoptotic increase in treatment with Aza and Guadecitabine. Further it was still observed that Guadecitabine led to cell cycle arrest. ULMSs and soft tissue LMSs showed significantly different miRNA expression and methylation signatures, suggesting that the use of different therapeutic approaches should be considered. Advances in targeted therapy in ULMSs are of great interest among researchers and pharmaceutical companies. Pazopanib is a second-generation small molecule multiple Tyrosine Kinase Inhibitor (TKI) that targets several isoforms of VEGF, thus blocking tumor growth. In 2012, this treatment was licensed for use in advanced soft tissue sarcomas. Sorafenib and Sunitinib have shown limited benefits in ULMSs. Among immunotherapy strategies, Nivolumab, an anti-PD1 antibody, and Pembrolizumab, another anti-PD1 antibody, have been used in gynecological malignancies in recent years, the latter being approved for use in solid tumors in 2017 [36,40]. The PDFR antibody Olaratumab was studied in combination with doxorubicin versus doxorubicin alone, with the combination showing prolonged DFS and OS (11 months or more). Targeted therapies are currently promising for the future [37]. Literature search and data collection was performed using PubMed databases for articles dated from January 2005 to May 2019. The following keywords were used: uterine smooth muscle tumors, uterine leiomyoma, uterine leiomyosarcoma, molecular features, epigenetic features and genetic alterations.

Conclusion

Myometrial smooth muscle neoplasms constitute the most

frequently diagnosed group of gynecological neoplasms. Most of these tumor formations are considered as ULM, whereas less than 1% corresponds to ULMS. In the spectrum of uterine smooth muscle tumors, there are several leiomyoma variants, such as mitotically active, cellular, and atypical leiomyomas, as well as STUMPs. The origin of ULMSs still requires clarification considering its highly aggressive clinical behavior and high rates of recurrence and distant metastasis, even in early diagnosis. Presently, it is not known whether ULMSs develop from pre- existing ULMs or *de novo* as a result of myometrial cell malignancy. A range of genes and epigenetic factors have already been discovered as a means of differentiating between ULM and ULMS, but the high complexity of this group of tumors is still a barrier to properly diagnose and treat patients. This review provides insights into the specific molecular aspects of ULMs and ULMSs, highlighting the need for further studies aimed at delineating targeted treatment modalities and improving the available diagnostic methods.

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