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Mini-review

Molecular mechanisms of endometrial stromal sarcoma and undifferentiated endometrial sarcoma as premises for new therapeutic strategies

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ABSTRACT

Endometrial stromal sarcoma (ESS) and undifferentiated endometrial sarcoma (UES) are very rare gynecologic malignancies. Due to the rarity and heterogeneity of these tumors, little is known about their epidemiology, pathogenesis, and molecular pathology. Our previous studies have described deregulation of histone deacetylases expression in ESS/UES samples. Some of these enzymes can be inhibited by substances which are already approved for treatment of cutaneous T-cell lymphoma. On the basis of published data, they may also provide a therapeutic option for ESS/UES patients. Our review focuses on molecular mechanisms of ESS/UES. It describes various aspects with special emphasis on alteration of histone deacetylation and its possible relevance for novel therapies.

Pathophysiology

Endometrial stromal tumors belong to the rarest uterine neoplasms. Uterine mesenchymal tumors comprise less than 5% of all primary uterine malignancies with endometrial stromal tumors accounting for less than 10% thereof [1].

According to the 2003 WHO classification, endometrial stromal tumors are divided into (i) non-invasive endometrial stromal nodule (ESN), a well-circumscribed benign mesenchymal tumor consisting of uniform cells closely resembling the uterine stromal cells of normal proliferative-phase endometrium; (ii) low-grade endometrial stromal sarcoma (ESS), an infiltrative tumor with stromal cells cytologically almost identical to those observed in the ESN but associated with low aggressive malignant behavior, and (iii) undifferentiated endometrial sarcomas (UES) [2]. In this classification the differentiation between low-grade and undifferentiated tumors is not made on mitotic count, but on the basis of nuclear pleomorphism and necrosis [3]. Strictly defined microscopic criteria (as nuclear atypia) support the WHO 2003 classification of ESS and UES [4] and are helpful in predicting recurrence [5]. Prognostic factors in uterine sarcomas have recently also been summarized by Gadducci [6]. These changes in definition and diagnostic criteria of ESS and UES make the interpretation of studies on biologic and prognostic features in low-grade ESS and UES particularly hazardous and require careful verification.

The heterogeneous group of undifferentiated sarcomas often lacks specific differentiation and usually bears no morphological resemblance to endometrial sarcoma. They can be subdivided into groups with either uniform or pleomorphic nuclei [7]. The overall 5-year survival rate of patients with low-grade ESS ranges from 68% to 100%, whereas the 5-year survival rate of UES patients is markedly lower. Due to the rarity and heterogeneity of endometrial stromal neoplasms, little is known about their epidemiology, pathogenesis, and molecular pathology. These circumstances make investigations of their various aspects difficult, which is also reflected by the lack of efficient therapy.

Recent therapeutic options for ESS/UES

Therapeutic options for ESS/UES have been summarized in-depth in previous reviews [8–10]. Current primary therapy for endometrial stromal sarcoma is surgery, mainly abdominal hysterectomy. The role of bilateral salpingo-oophorectomy and ovary preservation remain controversial [11–14]. Lymphadenectomy does not have an effect on survival [12]. Surgical removal of the primary

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tumor is frequently combined with subsequent adjuvant treatment involving radio- and/or chemotherapy. However, in most cases chemotherapy is moderately active and has palliative character only. Standardized systemic therapy in ESS/UES is not established yet.

The expression of molecular targets for tyrosine kinase inhibitors (TKI) in ESS and UES was reported [15–17]. However, only a few cases of responses to imatinib in patients with uterine sarcomas expressing at least one target of TKI have been described. A single case of UES with EGFR expression temporarily responded to imatinib [18]. Furthermore, a complete metabolic response to imatinib mesylate in a patient with a low-grade ESS has been reported [19]. In contrast, a retrospective immunohistochemical and molecular analysis of potential targets of TKI in 52 ESS and 13 UES highly question the use of TKI in endometrial stromal tumors [20].

In some studies, a therapeutic use of progestins and aromatase inhibitors in the treatment of low-grade ESS has been shown. Aromatase inhibitors block the enzyme aromatase, which turns androgen into estrogen, thus reducing estrogen production in postmenopausal women. As a consequence, the amount of body estrogen for stimulation of estrogen-receptor positive tumor cells is decreased. Progestins bind to progesterone receptors and downregulate gene transcription. This is especially true for estrogen receptors, leading to the reduction of circulating estrogens and decrease in endometrial gland and stromal proliferation [3]. In their review, Thanopolou et al. summarized, among other results, data of 18 patients with recurrent/metastatic ESS treated with aromatase inhibitors. Five complete responses and 11 partial responses were seen. In addition, a negative impact of hormonal replacement therapy in ESS was demonstrated [10]. A high percentage of ESS cases express hormone receptors, especially estrogen (40–100%) and progesterone (60–100%) receptors [10,21,22]. On the other hand, contradictory data were published regarding the expression of androgen receptors in uterine sarcomas [23,24]. Hormonal therapies seem to have differential efficacy in ESS and UES. ESS tumors frequently express estrogen and progesterone receptors and usually show better response to hormonal therapies. Although hormonal therapy has been shown to be able to stabilize disease or to induce a remission, it must be stressed that this effect depends on the receptor status [8]. On the other side, UES tumors usually do not express hormone receptors and, therefore, are not susceptible to hormonal therapy. Aromatase inhibitors, including letrozole, seem to be promising agents which can be used either as adjuvant or as first-line treatment [10].

Because of tumor rarity, one can hardly expect that novel molecularly targeted therapies will be specifically developed against endometrial stromal sarcoma. Therefore, therapies used for other solid tumors, might be investigated with regard to their efficacy for treatment of endometrial stromal sarcomas. However, to establish the basis for such studies, molecular pathophysiology of ESS/UES has to be elucidated in more detail.

Genetic alterations in ESS/UES

Chromosomal and cytogenetic studies have shown some heterogeneous genetic aberrations in ESS and UES. One of the most frequent genetic aberrations found is the t(7;17) (p15;q21) chromosomal translocation, first described by Hennig et al. [25]. This non-random chromosomal change is mainly present in endometrial stromal sarcomas [26,27]. At the sites of the 7p15 and 17q21 breakpoints Koontz et al. found fusion of two zinc-finger proteins, the so-called *JAZF1/JJAZ1* gene fusion [28]. The JAZF1/JJAZ1 gene fusion seems to be quite distinctive for ESS. We have previously found the JAZF1/JJAZ1 fusion in 80% of 18 classic ESS, and in none of the two UES [29]. This is in line with previous data from others, showing that UES were mostly negative for this translocation, whereas the percentage of positive ESS cases and non-malignant endometrial stromal nodules (ENS) was quite high [28,30,31]. Overall, data suggest that JAZF1/JJAZ1 gene fusion is present only in a subset of primary ESS tumors. One recent study showed that 32% of ESS ($n = 27$) and none of UES cases ($n = 17$) were positive for this gene fusion [7]. These variations in prevalence might be based on (i) methods used for tissue collection and/or preservation, (ii) detection methods, or (iii) differences between patient populations. They also indicate the heterogeneity of ESS/UES, an issue which can only be solved by analyzing larger number of samples.

Recently, new chromosomal translocation t(10;17) (q22;p13) was reported in a distinct group of ESS, fusing two genes: YWHAE, encoding a member of the 14-3-3 family, and either *FAM22A* or *FAM22B*, respectively [32,33]. Tumors with YWHE-FAM rearrangements are associated with high-grade morphology and aggressive clinical behavior which is important for prognostic and therapeutic purposes [34,35].

Although detection of these genetic alterations is undoubtedly an improvement in diagnostics for differentiation between ESS and UES, clinical utility and potential benefit for therapy needs to be established.

Wnt pathway deregulation in ESS/UES

The role of Wnt pathway in embryogenesis, in adult tissue homeostasis and in tumor development is quite well described. The canonical Wnt signaling pathway, involving ß-catenin, is deregulated in ESS/UES [36]. With a genome-wide cDNA library, more than 300 genes deregulated in ESS could be detected. Among the most strongly deregulated genes, there were secreted frizzled-related protein 4 (SFRP4) and SFRP1, putative modulators of the Wnt-signaling pathway [37,38]. SFRP4 was down-regulated in ESS and UES as compared with non-malignant proliferative endometrium, as shown by QRT-PCR and *in situ* hybridization (Fig. 1a and 1b). SFRP4 expression in UES was even lower than in ESS, but this finding was validated in a relatively low number of UES cases only and requires further proof. Interestingly, recent methylation studies have not shown hypermethylation of the SFRP4 promoter sequence which would have explained such down-regulation [39]. Thus, other mechanisms must be responsible for deregulation of SFRP4 in ESS and UES. Different SFRP-family members can bind to Wnt molecules and prevent their binding on frizzled receptors located in the cell membrane and subsequent activation of the Wnt pathway. This results in activation of disheveled protein and inhibition of glycogen synthase kinase-3ß, an enzyme responsible for ß-catenin phosphorylation. Subsequently, non-phosphorylated ß-catenin accumulates and is translocated into the cell nucleus forming complexes with T-cell factor/lymphoid enhancing factor (TCF/LEF). The latter is a transcription factor that stimulates TCF/LEF mediated gene expression and further activates the expression of numerous genes stimulating cell proliferation. Indeed, ß-catenin is increased in ESS and UES in comparison with non-malignant endometrium, indicating activation of the Wnt signaling pathway in tumor tissue (Fig. 1b). In addition, an increased translocation of ß-catenin from cytoplasm into the nucleus and a positive correlation with proliferation marker Ki-67, especially in more aggressive UES cases has been shown [36]. Overall, SFRP4 seems to act as a tumor suppressor gene regulating the cytosolic ß-catenin pool in the cell. Interestingly, Feng et al. found that proliferation markers, such as Ki-67, are also predictive for a high recurrence of ESS [40]. By using immunostaining, Ng et al. detected nuclear ß-catenin staining in 40% of ESS and suggested this method to be potentially useful for diagnosis, especially for distinguishing ESS from leiomyosarcoma, which are negative for nuclear ß-catenin [41]. Kildal et al. found strong nuclear ß-catenin staining in 61% of the 82 ESS cases [42]. However, they also found nuclear ß-catenin staining in 31% of normal endometrial stroma samples. Thus, the diagnostic and