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QUESTIONS ABOUT THE GENETIC AND EPIGENETIC MECHANISMS OF UTERINE SARCOMA DEVELOPMENT

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ABSTRACT

Uterine sarcomas are rare and highly aggressive malignant tumors of the female reproductive system characterized by significant histological diversity and poor prognosis. Their low incidence complicates the development of unified diagnostic and treatment approaches. The stage of the disease remains the most important prognostic factor, which led to the introduction of the specialized FIGO staging system. Modern molecular diagnostic methods, including NGS, CGH, FISH, and immunohistochemistry, make it possible to identify genetic alterations underlying tumor transformation. This expands the possibilities for early diagnosis, differential assessment, and personalized treatment of patients with uterine sarcomas.

KEYWORDS: uterine sarcomas, leiomyosarcoma, endometrial stromal sarcoma, FIGO, molecular diagnostics, immunohistochemistry, NGS.

Uterine sarcomas are rare but insidious neoplasms that make up about 1% of all malignant tumors of the female reproductive system and 3-7% of cases of uterine cancer.[1; 8] Their rarity and striking histological diversity have long served as an obstacle to the formation of a consensus on risk factors and optimal treatment strategies, which made it difficult to predict the outcome.[16]

Historically, histological classification has divided four main groups: carcinosarcomas (malignant mixed mesodermal tumors, 50% of cases), leiomyosarcomas (30%), endometrial stromal sarcomas (15%), and undifferentiated sarcomas (5%). Subsequently, the view on carcinosarcoma changed: it was considered mainly as a dedifferentiated or metaplastic form of endometrial cancer, given the nature of its metastasis. However, due to its exceptional aggressiveness, which exceeds the typical endometrial cancer, carcinosarcoma is still included in most retrospective sarcoma studies, as well as in the 2014 WHO classification, and it is assigned a special section among mixed epithelial and mesenchymal tumors.[3; 14]

The key prognostic factor remains the stage of the disease. For a long time, the 1988 system developed for endometrial cancer was used for staging sarcomas, but its prognostic value was insufficient. A breakthrough was the new FIGO staging system, introduced in 2009 specifically for SM.[24] It includes two sections: for leiomyosarcomas and endometrial stromal sarcomas (ESS), and separately for adenosarcomas. Currently, carcinosarcoma is evaluated according to the staging system adopted for endometrial cancer.[22]

The current understanding of the molecular pathogenesis of uterine leiomyosarcoma (LMS) is based on the use of a complex of high-tech molecular diagnostic methods that allow detecting genetic and epigenetic disorders underlying tumor transformation. The key ones are next-

generation sequencing (NGS), comparative genomic hybridization (CGH), fluorescent in situ hybridization (FISH), and immunohistochemical (IHC) studies.

Next-generation sequencing (NGS) is a high-performance analysis method that allows simultaneous detection of mutations in multiple genes, including *TP53*, *RB1*, *PIK3CA*, and others. This approach provides a detailed characterization of the mutational profile of the tumor and is used to detect both point mutations and small deletions/insertions.[21]

Genetic and epigenetic disorders in tumor transformation of uterine sarcoma. If we consider the current molecular pathogenesis of SM, in particular leiomyosarcoma, it should be noted that it is based on the accumulation of somatic mutations that affect key regulators of the cell cycle, apoptosis, and intracellular signaling pathways. As a result of these disorders, genomic instabilities are formed, which determine the aggressive biological behavior of the tumor.

A special place is given to inactivation of the TP53 gene encoding the p53 protein, which is a central regulator of the cellular response to DNA damage, one of the most frequent events. Loss of p53 function leads to disruption of apoptosis mechanisms, defects in DNA repair, and accumulation of mutations, which ultimately contributes to the development of genomic instability and clonal evolution of tumor cells. To date, it has been proven that TP53 mutations are associated with a high degree of malignancy, rapid progression, and an unfavorable prognosis.[10; 25]

Equally significant is the dysfunction of the RB1 gene, which controls the cell's transition from the G1 phase to the S-phase of the cell cycle. Its inactivation leads to disruption of the cell cycle, with the development of uncontrolled proliferation and cell division processes. In most LMS, combined TP53 and RB1 disorders are detected, which increases tumor aggressiveness, contributing to rapid tumor growth.[15; 17]

Mutations also occur in the PIK3CA gene, which leads to hyperactivation of the PI3K/AKT/mTOR signaling pathway, one of the key regulators of cell survival, proliferation, and metabolism. Activation of this pathway contributes to the inhibition of apoptosis, increased angiogenesis, and increased resistance of tumor cells to therapeutic effects. Interaction of PI3K/AKT signaling with other molecular disorders increases tumor progression and metastatic potential.[12]

Mutations in the SWI/SNF complex (ARID1A, SMARCA4), which is involved in chromatin remodeling and transcription regulation, play a special role in pathogenesis. Loss of function of the components of this complex leads to epigenetic dysregulation, impaired control of gene expression, and increased plasticity of tumor cells. In particular, ARID1A mutations are associated with impaired interaction of enhancers and activation of pro-inflammatory signaling pathways (IL-6/STAT3/NF-kB), which additionally stimulates tumor growth and cell survival.[3; 14; 23]

Thus, the combination of these genetic disorders forms the molecular basis of tumor transformation, providing.

- genomic instability.
- uncontrolled cell proliferation;
- suppression of apoptosis;
- activation of oncogenic signaling pathways;
- epigenetic deregulation.

These changes underlie the high aggressiveness, early metastasis, and resistance to therapy characteristic of uterine sarcomas, and represent potential targets for targeted therapy and personalized treatment.[2; 7]

Chromosomal rearrangements and fusion genes. Another mechanism that plays a key role in the pathogenesis of CM is chromosomal aberrations, which determine their morphological heterogeneity and clinical behavior. Unlike leiomyosarcomas, which are characterized primarily by a complex karyotype, endometrial stromal sarcomas (ESS) exhibit more specific and reproducible chromosomal translocations.

Low-grade endometrial stromal sarcoma is most characterized by translocation of t (7; 17) (p15; q21) with the formation of the JAZF1-SUZ12 fusion gene, which leads to a violation of the function of the Polycomb Repressive Complex 2 (PRC2), which is involved in epigenetic transcription suppression. As a result, the expression of genes that control cell differentiation and proliferation is deregulated. In highly malignant ESS variants, t(10;17)(q22;p13) translocation is detected with the formation of the YWHAE-NUTM2 fusion gene, which is associated with an aggressive clinical course and high mitotic activity of the tumor.[5]

Uterine leiomyosarcoma (LMS), on the other hand, is characterized by pronounced genomic instability and the absence of specific translocations. It is characterized by multiple chromosomal rearrangements, including amplifications of the 1q and 17p regions, as well as deletions of 13q (RB1 gene locus) and 10q (PTEN locus). These changes lead to a violation of the balance between oncogenic signals and the function of suppressor genes, increasing proliferation, invasiveness and resistance to therapy.

Fusion proteins formed as a result of chromosomal translocations function as abnormal transcription factors or epigenetic regulators. They can alter the structure of chromatin, activate oncogenic signaling pathways, and inhibit cell differentiation, thereby supporting the tumor phenotype and promoting its progression.

Chromosomal instability is a universal characteristic of malignant tumors, including SM. It is caused by

violations of the mechanisms of chromosome segregation in mitosis, defects in the formation and functioning of the mitotic spindle, as well as failures in the control points of the cell cycle. As a result, numerical and structural abnormalities of chromosomes occur, including aneuploidy, with the formation of intracancer heterogeneity, which, in turn, causes variability in the clinical course, the development of drug resistance, and a decrease in the effectiveness of therapy.[1]

II. Epigenetic disorders

Epigenetic changes, including DNA methylation, play an important role in the regulation of gene expression without changing the nucleotide sequence and are an essential component of the tumor process in SM.

One of the key mechanisms is global hypomethylation of DNA, which mainly affects repeated genome sequences such as satellite DNA and transposons. This phenomenon leads to reactivation of endogenous retroviral elements, an increase in the frequency of chromosomal breaks, and general genomic instability. In addition, hypomethylation promotes the activation of latent oncogenes and increases the transcriptional activity of tumor cells.

In parallel, local hypermethylation of the promoter regions of suppressor genes is observed, which leads to their transcriptional suppression. Among the most significant targets are: RASSF1A, a gene involved in the regulation of the cell cycle and apoptosis; its inactivation promotes uncontrolled cell proliferation; CDH1, encoding E-cadherin, a key protein of intercellular adhesion; its suppression leads to loss of cell cohesion, increased invasiveness and metastatic potential; MLH1, a component of the unpaired base repair system (MMRits epigenetic inactivation causes the development of microsatellite instability (MSI), which is accompanied by the accumulation of mutations and increased tumor heterogeneity.

Thus, the combination of global hypomethylation and local hypermethylation forms a characteristic epigenetic profile of the tumor, contributing to its progression, invasion, and resistance to treatment.[20]

Collectively, chromosomal and epigenetic disorders are interrelated processes that form the complex molecular architecture of CM and determine their biological properties, clinical course, and potential therapeutic targets.

Thus, if we summarize the main mechanisms of SM formation, we can conclude that they are a multi-stage process based on a combination of genetic and epigenetic disorders in the mesenchymal progenitor cell.

At the initiation stage, a primary "driver" event occurs: for ESS, chromosomal translocations with the formation of fusion genes (for example, JAZF1::SUZ12) are more typical, while for uterine LMS, complex genomic disorders occur, including TP53 inactivation, RB1, and other events associated with chromosomal instability. As a result, the control of the cell cycle, apoptosis and differentiation processes is disrupted, which creates conditions for clonal expansion of tumor cells.

An essential role is played by epimutations, that is, epigenetically determined switching off of genes without changing their nucleotide sequence. The most important mechanism is hypermethylation of promoters of DNA repair genes, including MLH1 and, more rarely, MSH2, which leads to a decrease in the efficiency of the mismatch repair system, accumulation of somatic mutations, and increased genomic instability. These mechanisms are described for endometrial tumors; for CM, these data are more limited, but they are considered biologically significant pathways that cause molecular destabilization in uterine body tumors.

A separate link in tumor transformation is disorders in chromatin-remodeling complexes, primarily SWI/SNF. Mutations or loss of function of ARID1A and SMARCA4 alter the availability of DNA for transcription factors, and normal differentiation programs are disrupted, which contributes to the cell's transition to a more aggressive, poorly differentiated phenotype. The example of SMARCA4-deficient undifferentiated ones, for which loss of function of the SWI/SNF complex is associated with high malignancy and an unfavorable course, is particularly indicative in SM.[13]

Fusion proteins, primarily JAZF1::SUZ12, are of crucial importance in ESS, which directly affect the work of Polycomb repressive complex 2 (PRC2), leading to changes in the distribution of the repressive histone label H3K27me3, disruption of normal gene silencing, and rearrangement of the transcriptional program of the cell. In other words, the fusion gene not only serves as a diagnostic marker, but also actively supports the tumor phenotype through epigenetic reprogramming.[9; 18]

As the tumor promotes and progresses, self-sustaining oncogenic loops are formed: abnormal transcription factors and fusion proteins recruit epigenetic modifiers, change the chromatin landscape, and thereby stabilize the expression of genes that ensure proliferation, survival, invasion, and drug resistance. Against this background, additional genetic and epigenetic events accumulate, intra-tumor heterogeneity occurs, and then the most aggressive subclones capable of invasion and metastasis are selected.[4; 6; 11; 19]

Thus, SM develops as a result of the interaction of three interrelated mechanisms: primary genetic drivers, epigenetic reprogramming, and clonal evolution. They result in loss of normal differentiation, increased proliferation, increased genomic instability, and the formation of an aggressive tumor phenotype.

CONCLUSION

Tumor transformation in SM is a multi-stage process where genetic and epigenetic disorders do not just co-exist, but actively interact and reinforce each other.

1. Genetic changes create fundamental" driving forces " of the tumor (oncogenic mutations, chromosomal rearrangements);
2. Epigenetic disorders provide plasticity and adaptation of the tumor, stabilizing the oncogenic program and promoting heterogeneity.

These interactions form a complex network of regulations in which disturbances at one level (a mutation in the chromatin remodeler gene) cause a cascade of changes at another (global changes in gene expression). Understanding these relationships is critical for developing combination therapies that simultaneously target the genetic drivers and epigenetic plasticity of the tumor.

Studies over the past 5 years show that molecular stratification of SM has shifted from histology to integrative analysis of genetic and epigenetic aberrations. The interaction of somatic mutations, chromosomal rearrangements, and epigenetic reprogramming forms an aggressive phenotype. These changes lay the foundation for a personalized approach, where therapy will target specific molecular drivers, and epigenetic changes can serve as both diagnostic markers and therapeutic targets. Further research should focus on the role of the tumor microenvironment and treatment resistance.

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