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THE ROLE OF ANDROGENS IN THE PATHOGENESIS OF ENDOMETRIAL CANCER

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Over the past decades, endometrial cancer has become the most common gynecological cancer worldwide. Its increasing incidence cannot be attributed only to the increasing age of women in socially secure countries. The leading risk factor for the endometrial cancer development is obesity, and its epidemic is gradually covering the female population of North Africa, Europe and Asia. Endometrial cancer is pathogenetically associated with hyperestrogenism, and this was the basis for the dualistic theory of clinical and pathological variants proposed by Ya.V. Bohman. The foundations of this theory about the hormonal dependence of endometrial cancer are now being actively supplemented by molecular genetic parameters of the TCGA classification. Recent studies show steroid dependence of endometrial cancer both on estrogens and, to a large extent, on androgens which are directly involved in the complex processes of transformation into estrogens. Published research data, rather contradictory and ambiguous, confirm the antiproliferative role of androgens in the pathogenesis of endometrial cancer. This review analyzes papers on the role of androgens in pathogenesis and their potential clinical antitumor application.

Keywords: endometrial cancer, androgens, androgen receptor, classification of endometrial cancer.

Endometrial cancer (EC) is a prevalent cancer globally [27]. It is the most frequent gynecologic cancer in developed nations, accounting for almost 5% of cancers in women. The overall incidence of uterine cancer has increased by 132% over the past 30 years, including a doubled number of patients under 40 years of age. The cumulative risk of EC in women under 74 years of age is 1.05% worldwide. However, this risk increases to 3% in countries with a higher sociodemographic index, particularly in North America and Europe [10, 44]. Leading gynecologic oncologists do not predict the incidence and mortality of EC to cease its growth, unlike other cancers [7]. The causes of this phenomenon are not limited to gerontological issues. Other risk factors include bradykinesia, obesity, insulin resistance, and a decrease in the number of prophylactic hysterectomies, as well as the use of hormone replacement therapy during menopause [6, 9]. Since the 1980s, EC has been generally subdivided into two types: type I, which is an estrogen-dependent endometrioid cancer of low malignancy, and type II, which generally includes hormone-independent non-endometrioid cancer of high malignancy [47]. The 2020 World Health Organization (WHO) classification of EC and the ESGO/ESTRO/ESP guidelines are also based on histological confirmation of uterine corpus cancer and surgical staging of the process. Features of EC morphogenesis such as lymphovascular invasion (LVSI) and the presence of tumor emboli in lymphatic and blood vessels are associated with an increased risk of metastasis, not only to lymph nodes but also to other tissues and organs. These features are included in the risk stratification model for adjuvant therapy. TCGA, a new molecular genetic classification system of EC, is intended to significantly change the degree of EC prognosis and optimize adjuvant treatment options [22, 38, 48]. However, clinical decision making is still largely dependent on the previous binary classification of EC into types I and II [9]. Type I EC typically expresses high levels of estrogen receptor α (*ER*). Type II EC is less likely to express *ER* and has a less favorable prognosis [36].

Genetic studies can identify the molecular 'fingerprints' of different EC histotypes. However, only *MSI* status is currently used as a pragmatic criterion for advanced EC, despite the fact that the majority of endometrial tumors contain at least one genomic alteration [1, 43]. Two of the five chemotherapeutic agents approved by the *FDA* for the treatment of EC effectively target programmed death ligand 1 (*PD-1*), which is overexpressed in hypermutated endometrial tumors with *MSI* compared to microsatellite stable tumors [28]. However, with the increased use of prospective clinical sequencing and the growing number of clinical trials, it is expected that EC treatment will move beyond routine variables such as tumor morphology and malignancy grade.

The endometrium is a morphologically and physiologically complex tissue that responds to changes in sex steroid concentrations, both systemic and local (intracrine) in nature. The tissue exhibits hormonal sensitivity in both normal and pathological states. Sex steroids are essential for maintaining the cyclic function or fertility of the endometrium. However, they may also contribute to the development of hormone-dependent endometrial diseases. Androgens and estrogens have similar structures. Additionally, estradiol, which is an aromatization derivative of testosterone, performs various functions in the female body through its specific receptors. These functions include the functioning of not only the reproductive organs but also the brain, bones, heart, vascular system, and liver. Sex hormones are key determinants of an individual's gender identity. Endogenous estrogens in men and androgens in women not only affect the health of each individual, but in certain conditions can also lead to pathologic processes

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with potentially life-threatening effects. It is important to note that androgens generally exceed estrogen levels, except during the preovulatory and follicular phases of the menstrual cycle. Most cases of EC occur during postmenopause. In pathogenetic variant I, EC is associated with excess estrogen and simultaneous suppression of progesterone production. After the onset of menopause, the levels of circulating estrogens sharply decrease while testosterone levels remain unchanged throughout the menopausal period. Menopausal women bodies use increased serum androgen levels to metabolically convert them to estrogens directly in adipose tissue, breast and endometrial cells. This provides an intracrine mechanism for aromatization of androgens into estrogens.

During the female reproductive age, androgen production is contributed to by both the adrenal reticular zone and theca cells of the gonads surrounding the ovarian follicles [13]. As age advances, the adrenal reticular zone undergoes involution and there is a sharp decrease in the number of ovarian follicles, which generally reduces androgen synthesis. However, both glands remain an important source of androgens during menopause. Dehydroepiandrosterone sulfate (DHEAS), dehydroepiandrosterone (DHEA), androstenedione (A4), testosterone and dihydrotestosterone (DHT) are the most common androgens found in women. According to Labrie et al, 2017, DHEA and testosterone are considered indicators of androgen secretion by the adrenal glands and ovaries, respectively. During menopause, estrogen production decreases markedly, but the ovaries continue to produce androgens, including DHEA, A4, and testosterone. In postmenopausal women, DHEA is the primary source of androgens and estrogens. About 20% of circulating DHEA is produced by the ovaries, while the remaining 80% is derived from the adrenal glands [19]. The enzyme steroid sulfotransferase type 2A1 (SULT2A1) converts DHEA to DHEAS, while the enzyme 3β-hydroxysteroid dehydrogenase type 2 (HSD3B2) converts it to A4. A4 is converted to testosterone by 17β-hydroxysteroid dehydrogenase type 5 (17β-HSD type 5), also known as aldo-keto reductase family 1 member 3 (AKR1C3) [25]. Testosterone is then converted to DHT by 5α-reductase. DHEAS, DHEA, A4 and testosterone enter the systemic bloodstream by interacting with sex steroid binding globulin (SHBG). In women, 80% of androgens bind to SHBG, 19% bind to serum albumin and only 1% of androgens are free. The active sex steroid is the 1% of free androgens, while the bound androgens enter the circulating resource, awaiting conversion to estrogens.

In addition to classical androgens, the adrenal glands also produce androgen metabolites that share a common oxygen atom at the C11 position, called 11-oxyandrogens. These 11-oxymetabolites are particularly interesting for the physiology of postmenopausal women because their levels, unlike classical androgens, do not decrease with age [2, 26]. Biologically active androgens, such as testosterone (T) and 5α-dihydrotestosterone (DHT), affect target tissues mainly through the androgen receptor (AR). Similarly, some 11-oxyandrogens, such as 11-keto-T (11-KT) and 11-keto-DHT (11-K-DHT), have a comparable affinity for AR binding as classical hormones [14, 35]. AR is a nuclear hormone receptor transcription factor [40] that is mainly localized in the endometrium, mesenchyme, and myometrium of the uterus. It is worth noting that epithelial cells in the functional layer of the endometrium increase AR expression when progestin levels drop during the normal menstrual cycle, resulting in decreased proliferative activity. However, AR expression in basal layer stromal cells remains unchanged during menstruation [12]. Several studies evaluated the expression of AR depending on the degree of malignancy of atypical endometrial hyperplasia and EC histotypes, and compared it with that in benign endometrial hyperplasia and in eutopic endometrium [46]. These studies showed that decreased AR was associated with a higher degree of EC malignancy; the lowest AR expression was found in tumors with non-endometrioid histology. While AR expression in primary endometrioid tumors appeared to correlate with lower malignancy and less aggressive disease, a high AR and estrogen receptor (ER) ratio in EC metastasis tissue correlated with poorer survival [46]. Overall, the data suggest that androgen receptor (AR) signaling in endometrial cells (ECs) is multifaceted and may vary throughout tumor evolution. Convincing evidence of the influence of androgens on EC risk was obtained in studies on patients with ovarian scleropolycystic fibrosis, in whom the risk of type I EC increased in the presence of hyperandrogenism. Tanaka et al. (2015) found that the level of DHT in patients with endometrial adenocarcinoma and ovarian scleropolycystosis was eight times higher than in healthy women [45]. In contrast, Hashmi et al. (2018) did not find such a correlation in their study of 89 patients with EC [15]. In a retrospective study, Shahin et al. (2021) analyzed 40 type I EC tumors and 12 type II EC tumors using AR immunohistochemical expression. Similarly, Mahdi et al. (2017) analyzed 209 cases of type I EC and 52 cases of type II EC. Both studies found a positive effect of AR expression on the prognosis of EC [21, 41]. Furthermore, Mahdi et al. (2017) discovered a significant correlation between AR expression and the absence of LVSI, resulting in a reduction in the number of metastatically altered regional lymph nodes. However, Shahin et al. (2021) did not find such a correlation [21, 41]. In their study of 86 EC samples, Tanaka et al. (2015) demonstrated that AR status did not have any independent prognostic value in patients with this tumor histotype [45]. It is evident that researchers hold polar opinions.

Endometrial tumor tissue contains the necessary enzymes to produce biologically active androgens from their precursors and 11-oxyandrogens. The expression of key enzymes involved in androgen metabolism, such as AKR1C and SRD5A enzymes, was studied in endometrial tumor tissue [16, 17]. Both endometrioid and non-endometrioid types of EC exhibit higher expression of several *SLCO* genes encoding transporters with broad substrate specificity compared to normal endometrial tissues. The upregulation of several transporters may account for the increased influx of steroid precursors, including DHEA-S, in endometrial tumors [30]. AKR1C3 is another important enzyme in androgen metabolism. Its overexpression is believed to contribute to the androgen pool in various pathologies [31]. Additionally, higher expression of AKR1C3 is associated with greater overall survival in EC [16]. It is worth noting that both endometrioid and non-endometrioid tumor tissues do not express CYP11B1, indicating that endometrial tumors are probably incapable of metabolizing classical androgens to 11-oxyandrogens. However, it is possible for 11-oxyandrogens to be produced locally from 11-oxyandrogen precursors, such as 11β-OH-A4, which are present in relatively high systemic concentrations. The presence of genes encoding HSD11B2 and SRD5A enzymes in endometrial tumors indicates this possibility. Furthermore, the expression of SRD5A1 and SRD5A3 isoforms in EC tissue suggests that DHT and 11-K-DHT may be formed locally [42].

Several studies reported an association between elevated serum androgen levels and the risk of developing EC. Postmenopausal EC patients were found to have elevated levels of DHEA,

DHEAS, A4 and testosterone compared to healthy populations. In recent years, two Mendelian randomization studies genetically analyzed hormone levels in over 12,000 EC patients over their lifetime and found that free testosterone was associated with an unfavorable disease course [24, 37]. Mullee et al. (2021) explain that high levels of androgens are actively converted by aromatase to estrogens in carcinoma tissue, promoting tumor cell proliferation [24]. The intracrine mechanism of aromatase expression is found not only in tumor cells but also in endometrial stem cells, which unites their proliferative potential and leads to an unfavorable outcome [4]. Qiu et al. (2014) demonstrated that AR enhances the proliferation of EC cells by binding to forkhead box A1 (FOXA1) and activating the Notch signaling pathway. Androgens and AR were also shown to stimulate the growth of EC stem cells and enhance cancer cell migration, promoting metastasis, by activating the epithelial-mesenchymal transition (EMT) [34]. Furthermore, Chen et al. (2014) found that androgens can stimulate the expression of immunocompetent CD133 cells. These cells are responsible for the formation of resistance of endometrial carcinoma to cisplatin chemotherapy [5].

A comparative study of 313 patients with EC and 354 age-matched healthy women showed that the highest serum concentrations of baseline androgens - DHEA, androstenedione and testosterone [23] are associated with an increased risk of developing EC. Clendenen et al (2016) reached an interesting and somewhat unexpected conclusion in their study. In their analysis of 161 cases of EC compared to data from 303 control patients, the authors found no evidence of androgens influencing the occurrence of EC in women under 55 years of age who were in peri- or early menopause. However, they did observe a significant increase in the incidence of EC in patients over 55 years of age with elevated serum levels of total and free testosterone [8]. The conclusion regarding the increase in systemic levels of total and free testosterone in menopausal patients requires clarification. This is because EC occurs in the vast majority of cases during this age period and is associated with hyperestrogenism due to androgen aromatization. It is believed that total testosterone levels gradually decline from the age of 65 years until the age of 80 years. During deep menopause, the levels of free testosterone and A4 increase, which is associated with an almost threefold risk of EC [8, 18].

The action of aromatase results in a decrease in androgen levels, which in turn suppresses estrogen expression in menopausal women. However, a low concentration of estrogen does not reduce the incidence of EC. Furthermore, there is a correlation between the androgen signaling pathway and the progestin signaling pathway. Aromatase catalyzes the conversion of androgens, such as androstenedione and testosterone, to estrogens, including estrone and estradiol. Drugs that inhibit aromatase are assumed to increase the concentration of androgens, which are its substrates, while simultaneously reducing estrogen synthesis. Tanaka et al. (2015) suggested that synchronized therapy with aromatase inhibitors and androgens may benefit patients with AR-positive EC. Androgens were shown to increase progesterone receptor expression in endometrial cells (ECs). This, in turn, suppresses the stimulatory effects of estrogens on tumor growth. Therefore, therapy with exogenous androgens may be a novel treatment for patients with type I EC who are insensitive to progestin treatment [29]. In mammalian cells expressing exogenous or endogenous AR, medroxyprogesterone acetate (MPA) exerts a marked agonist effect on androgens. After MPA treatment in vitro, a significant increase in AR transcriptional activity was observed in the COS-1 cell line [39].

Elucidating the role of androgens in the development of EC is difficult due to the complex hormonal interaction, cell specificity, androgen type and androgen exposure time, together with other yet undetermined factors [3].

Cancer patients typically experience alterations in their microbiome, which refers to the totality of the genomes of all microorganisms that make up the human body. Research demonstrated that various factors, such as menopausal status and body mass index, can impact the composition of the uterine microbiome in EC. This, in turn, can determine the specificity of premorbid chronic metroendometritis, which may contribute to the development of EC [47]. Pur et al (2020) conducted a study on untreated EC patients included in the TCGA study, examining whole genome and whole transcriptome data. The study found that most major cancer types, including EC, have a unique microbial signature that can distinguish cancer patients from healthy individuals [33].

Altered microbiota could be a possible source of androgens and 11-oxyandrogens in EC patients. The microbiota has a wide range of unique enzymes that can convert steroid molecules into potent androgens after deconjugating them from the glucuronic acid or sulfate group. For instance, a recent study investigated potential sources of androgens in patients with hormone-resistant prostate cancer. The study found that specific species of bacteria in the gut microbiome can convert steroids, such as pregnenolone and 17α-OH-pregnenolone, into classical androgens, such as DHEA and testosterone. In some patients, individual microorganisms were capable of inducing higher levels of testosterone [32]. Furthermore, the microbial community may use C21 glucocorticoids as an atypical source of androgens [11]. Some bacterial species of the gut and urinary tract microbiota were found to contain a bacterial enzyme that converts the glucocorticoid cortisol to 11β-OH-A4 [49].

In conclusion, it is widely debated whether androgens play a significant role in the pathogenesis of EC. While some researchers believe that the role of androgens remains incompletely understood, others consider it controversial. Androgens were shown to have an antiproliferative effect by directly confronting estrogens or activating progesterone receptor, which inhibits the effect of estrogens on the endometrium [29]. On the other hand, A4 and testosterone are precursors for both DHT production and estradiol synthesis as an aromatase substrate. The latter may serve as a negative regulator of DHT production in situ in endometrial carcinoma cells by limiting the availability of testosterone and/or A4 precursors. Aromatase expression in endometrial stromal cells in EC is directly associated with a poor prognosis. The enhancement of proliferative effect of androgens may be related to the activation of epidermal growth factor receptors in the stromal compartment [39].

The role of androgens in carcinogenesis, EC histotype formation, and treatment prognosis remains poorly understood. Fractions of androgens, their precursors, estrogen converters, and androgen receptors may be effective targets for updated endocrine treatment of progestin-resistant EC. The transformation of testosterone to DHT under the action of 5α-reductase is irreversible, leaving less testosterone available for conversion to estradiol. Furthermore, it is necessary to investigate the effect of DHT on endometrial tissue [20]. If aromatase inhibitors not only cause estrogen deprivation but also enhance the antiproliferative action of DHT, combination therapy with DHT and aromatase inhibitors may be a promising new endocrine intervention for the

treatment of endometrial carcinoma, particularly in postmenopausal patients.

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ACUTE CHOLECYSTITIS: PROBLEMS OF CLASSIFICATION AND WAYS OF SOLUTION

Acute cholecystitis undoubtedly remains an urgent problem of urgent abdominal surgery. The incidence of this nosology is 160 thousand cases per year. Postoperative mortality is in the range of 1,2-1,4%. Currently, the classification of acute cholecystitis, which is based on the Tokyo agreements, has received active distribution and use. However, this classification does not allow us to determine the degree of destructive process in the wall of the gallbladder. This often leads to a prolongation of the duration of conservative therapy and an increase in the percentage of intraoperative and postoperative complications. In this publication, we have tried to characterize the available classifications of acute cholecystitis, taking into account the advantages and disadvantages. And also, to propose a more rational classification from the point of view of a practical surgeon.

Keywords: cholelithiasis, acute cholecystitis, classification, destructive forms, gallstone disease, diagnosis.

Acute cholecystitis is one of the most common diseases in emergency abdominal surgery. According to A. Revishvili, the incidence of acute cholecystitis in the last 5 years is about 160 thousand cases per year. At the same time, operational activity in relation to this nosology increases, the frequency of which reaches 60-63%. At the same time, postoperative mortality is in the range of 1,2-1,4%, and in some regions 3-5% [13]. There is a problem of a high percentage of both intraoperative (10-15%) and postoperative complications (15-20%) [1,3,8,9]. Along with this, the frequency of purulent-septic postoperative complications reaches 7-15% [1].

It is known that currently there are a number of classifications of acute cholecystitis. The classification developed by V. Savelyev has found wide application in Russia. Savelyev divides acute cholecystitis into uncomplicated and complicated. The first variant includes the following forms: catarrhal, phlegmonous, gangrenous. Complicated, in turn, occurs in 10-15% of cases and includes complications such as mechanical jaundice, perivesical infiltration, perivesical abscess, gallbladder perforation, peritonitis, cholangitis, external and internal fistulas, empyema or dropsy of the gallbladder. Uncomplicated cholecystitis, according to V. Savelyev's classification, is primary due to thrombosis of the cystic artery, and secondary caused by an infectious agent [2]. It should be noted that, undoubtedly, this classification makes sense in operated patients. At the same time, at the time of admission of the patient to the hospital, we do not have the opportunity to establish a certain form of uncomplicated cholecystitis due to the large range of criteria. Along with the lack of clear criteria for the establishment of one form or another, there are no recommendations for the management of patients with a specific variant of this disease.

According to the pathogenesis, acute cholecystitis is divided into obturation, enzymatic and vascular. From the point of view of a practical surgeon, this division of acute cholecystitis has no value and is of particular interest only for theoretical medicine.

April 1, 2006 becomes a key date in the adoption of a new classification of acute cholecystitis, developed by a group of leading hepatologist surgeons in the Japanese capital. This classification is based on 3 groups of severity of acute cholecystitis [15,20]:

I st (mild stage) is characterized by the absence of multiple organ dysfunction and mild inflammatory changes in the gallbladder in patients with acute cholecystitis.

II st (moderate stage) was based on the following criteria: significant inflammatory changes in the gallbladder (emphysematous cholecystitis, gangrenous cholecystitis, peripusal abscess, biliary peritonitis), duration of the disease over 72 hours, leukocytosis over 18 x10^9/L.

III st (severe stage) is characterized by disorders in vital organs or systems: neurological disorders (decreased level of consciousness); renal insufficiency (oliguria, creatinine > 2 mg/dl (177 mmol/l); hepatic dysfunction (INR > 1.5); respiratory failure (PaO2/FiO2 ratio < 300); cardiovascular insufficiency (hypotension requiring correction with dopamine at a

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