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ORIGINAL ARTICLE

The content of steroid hormones in the mitochondria of unchanged and tumor tissue of the uterine body

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ABSTRACT

Mitochondria regulate a wide range of processes, including stress responses, metabolism, immunity, differentiation, redox homeostasis, and steroidogenesis, and also serve as the principal intracellular source of reactive oxygen species (ROS). Mitochondrial dysfunction has been linked to the development of various pathological conditions, including the growth of both benign and malignant tumors.

Purpose of the study. Determination of the level of steroid hormones in the mitochondria of various tissues of the uterine body.

Materials and methods. The study included 65 patients with benign and malignant diseases of the uterus: 25 patients with endometrioid adenocarcinoma of the uterus (EAC) of low differentiation (G3) stage II–III; 15 patients with leiomyosarcoma of the uterus stage I–III; and 25 patients with uterine myoma. Mitochondria from native samples of uterine tumors were isolated by differential centrifugation in a high-speed refrigerated centrifuge Avanti J-E, Becman Coulter. For the comparison group, mitochondria were isolated from intact uterine tissue. The levels of estradiol (E2), testosterone (T), progesterone (P4), and cortisol were determined using standard ELISA kits (Monobind, USA) in mitochondria isolated from the indicated tissues. A statistical analysis of the results was conducted using the Statistica 10.0 software package.

Results. Irrespective of the nature of the tumor process (benign or malignant), a decrease in the P4 level by 2.7 to 9.1 times, but an increase in the content of cortisol by 1.3 to 3.7 times and T by 2.1 to 3.7 times were detected in the mitochondria of uterine tumors. Conversely, the concentration of E2 in the mitochondria of uterine fibroids exhibited an increase of 2.2 times compared to the indicators in the mitochondria of the intact uterus. No significant differences were observed in the mitochondria of EAC, while a decrease of 1.4 times was noted in the mitochondria of uterine sarcoma.

Conclusion. There is a change in the content of steroid hormones in In the mitochondria of uterine tumors, consisting in an increase in the concentrations of cortisol and testosterone and progesterone deficiency regardless of the type of pathology, but a relative or absolute deficiency of estrogens only in the mitochondria of malignant tumors. Changes in the steroid background of tumor mitochondria, compared with the mitochondria of the intact uterus, probably have a significant effect on both the energy balance of cells and the production of ROS, as well as on proliferative processes.

Keywords: mitochondria, estradiol, progesterone, testosterone, cortisol, uterine adenocarcinoma, uterine myoma, uterine leiomyosarcoma

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ОРИГИНАЛЬНАЯ СТАТЬЯ

Содержание стероидных гормонов в митохондриях неизмененной и опухолевой ткани тела матки

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РЕЗЮМЕ

Митохондрии регулируют множество процессов, включая стресс, метаболизм, иммунитет, дифференцировку, окислительно-восстановительный баланс и синтез стероидов, а также являются основным внутриклеточным источником активных форм кислорода (АФК). Нарушение митохондриальной функции связано с развитием различных патологических состояний, включая рост доброкачественных и злокачественных опухолей.

Цель исследования. Определение уровня стероидных гормонов в митохондриях различных тканей тела матки.

Материалы и методы. В исследование включены 65 больных с доброкачественными и злокачественными заболеваниями матки: 25 больных с эндометриоидной аденокарциномой матки (ЭАК) низкой степени дифференцировки (G3) II–III стадии; 15 больных с лейомиосаркомой матки I–III стадии и 25 больных с миомой матки. Митохондрии из нативных образцов опухолей матки выделяли методом дифференциального центрифугирования на высокоскоростной рефрижераторной центрифуге Avanti J-E, Becman Cjulter. Для группы сравнения митохондрии выделяли из интакной ткани матки. В митохондриях, выделенных из указанных тканей, с использованием стандартных ИФА наборов Monobind (США) определяли уровни эстрадиола (Е2), тестостерона (Т), прогестерона (Р4) и кортизола. Статистический анализ результатов проводили с помощью пакета программ Statistica 10.0.

Результаты. Независимо от характера опухолевого процесса (доброкачественного или злокачественного), в митохондриях опухолей матки выявлено снижение уровня Р4 в 2,7–9,1 раза, но повышение содержания кортизола в 1,3–3,7 раза и Т в 2,1–3,7 раза. Концентрация Е2 в митохондриях миомы матки была повышена в 2,2 раза по сравнению с показателями в митохондриях интактной матки, не имела значимых отличий в митохондриях ЭАК, и снижалась в 1,4 раза в митохондриях саркомы матки.

Заключение. В митохондриях опухолей матки происходит изменение содержания стероидных гормонов, заключающееся в повышении концентраций кортизола и тестостерона и прогестероновом дефиците вне зависимости от типа патологии, но относительном или абсолютном дефиците эстрогенов только в митохондриях злокачественных опухолей. Изменение стероидного фона митохондрий опухолей, по сравнению с митохондриями интактной матки, вероятно оказывает существенное влияние как на энергетический баланс клеток и выработку активных форм кислорода (АФК), так и на пролиферативные процессы.

Ключевые слова: митохондрии, эстрадиол, прогестерон, тестостерон, кортизол, аденокарцинома матки, миома матки, лейомиосаркома матки

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Соблюдение этических стандартов: в работе соблюдались этические принципы, предъявляемые Хельсинкской декларацией Всемирной медицинской ассоциации (World Medical Association Declaration of Helsinki, 1964, ред. 2013). От всех пациентов получено подписанное информированное согласие на взятие и передачу биологического материала для проведения научных исследований, государственных заданий в общественно и социально-полезных целях. Протокол этического комитета ФГБУ «НМИЦ онкологии» Минздрава России № 22 утвержден 05.09.2023.

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BACKGROUND

Mitochondrial intracellular and extracellular communication networks regulate a vast array of processes, including stress response, metabolism, immunity, differentiation, redox balance, and steroid biosynthesis, and are responsible for the generation of reactive oxygen species (ROS) [1]. In addition, mitochondria play a key role in maintaining chromatin integrity and in the execution of acrosomal reactions [2]. Mitochondria contain their own circular DNA (mtDNA), which, due to the absence of DNA-binding proteins such as histones, is approximately 100 times more susceptible to ROS-induced damage and mutations than nuclear DNA (nDNA), which is protected by histones. Moreover, mtDNA repair processes are less efficient than those of nDNA, and the mutation rate of mtDNA is 10–17 times higher [3]. Disruption of mitochondrial activity is closely associated with a number of pathological conditions, including neurological and metabolic disorders, as well as tumor development [1].

Uterine tumors are among the most common pathologies of the female reproductive system. In malignant transformation, one of the earliest metabolic alterations is the reprogramming of cellular energy metabolism [4]. Mitochondria play a direct role in this metabolic reprogramming, supporting tumor cell survival and proliferation. Mitochondrial dysfunction manifests through disturbances in Ca^{2+} homeostasis, elevated ROS levels, and alterations in the steroid balance that contribute to genetic instability [5].

Mitochondria in uterine tissues contain all the essential enzymes involved in steroid hormone biosynthesis. Within mitochondria, the cytochrome P450 side-chain cleavage enzyme plays a key role in the degradation of the aliphatic tail of the cholesterol molecule, initiating the steroidogenic pathway that produces pregnenolone [1].

Steroid hormones such as estrogens, progesterone, androgens, and glucocorticoids influence mitochondrial function through their receptors localized within mitochondria. These hormones regulate the expression of genes involved in energy metabolism, apoptosis, and redox homeostasis [6, 7].

Benign and malignant uterine tumors exhibit distinct metabolic characteristics that affect their progression and response to therapy. Steroid hormones modulate mitochondrial activity, including ATP production and intracellular ROS generation, which regulate cell maintenance, viability, and overall physiological integrity [8]. It has been shown that tissues of affected endometrium display increased oxidative damage and mtDNA deletions, which correlate with altered levels of sex hormones and their receptors [9].

There is evidence that mitochondria in uterine fibroids exhibit enhanced activity, as indicated by increased mitochondrial mass and membrane potential, associated with high sensitivity to progesterone. Through the mitochondrial receptor RP4-M, progesterone enhances oxidative phosphorylation [10]. In contrast, malignant tumors often shift toward glycolysis (the Warburg effect), resulting in reduced mitochondrial activity and altered steroid hormone regulation [11, 12].

Purpose of the study: to determine the levels of steroid hormones in mitochondria isolated from uterine tissue unaffected by tumor processes (intact mitochondria) and in various uterine tumor formations.

MATERIALS AND METHODS

The study included 65 patients with benign and malignant uterine diseases who underwent surgery at the Gynecology Department of the National Medical Research Center for Oncology in 2023–2024: 25 patients with low-grade (G3) endometrioid adenocarcinoma of the uterus (EAC) stage II–III; 15 patients with uterine leiomyosarcoma stage I–III; and 25 patients with uterine myoma. All patients had morphologically verified diagnoses confirmed by postoperative histological examination. The age of the patients in all groups ranged from 52 to 84 years.

The study was conducted on native intact and pathological tissues obtained during hysterectomy from 65 patients. For EAC and uterine leiomyosarcoma, tumor tissues were used, while for uterine myoma, samples were taken from the myomatous node and a fragment of visually and morphologically unchanged uterine tissue (intact uterine tissue).

Mitochondria were isolated from all tissues obtained during surgery using differential centrifugation

on a high-speed refrigerated centrifuge Avanti J-E, Beckman Coulter, USA, according to the methods of M. V. Egorova, S. A. Afanasyev (2011) [13] and A. P. Gureeva et al. (2015) [14]. To disrupt intercellular connections, cell walls, and plasma membranes, tissues were mechanically processed by mincing with scissors and homogenizing in a glass homogenizer with a Teflon pestle (Potter–Elvehjem homogenizer). For each gram of tissue, 10 ml of isolation medium was added (0.22 M mannitol, 0.3 M sucrose, 1 mM EDTA, 2 mM TRIS-HCl, 10 mM HEPES, pH 7.4).

The tissues were homogenized and centrifuged for the first time for 10 min at 3000 g, at a temperature of 0–2 °C. The second and third centrifugations were performed at 20,000 g for 20 min at 0–2 °C. Between centrifugations, the mitochondrial pellet was resuspended in the isolation medium. Mitochondria were further purified from lysosomes, peroxisomes, melanosomes, etc., by centrifugation in a 23 % Percoll gradient. The suspension of subcellular structures was layered on the Percoll gradient and centrifuged for 15 min at 21,000 g, resulting in separation into three phases; the lower mitochondrial layer was collected and resuspended in the isolation medium. The subsequent washing of mitochondria was performed by centrifugation for 10 min at 15,000 g at 0–2 °C.

Mitochondrial samples (protein concentration 4–6 g/L) were stored at –80 °C in the isolation medium until analysis. Before ELISA analysis, mitochondrial samples were subjected to freeze–thaw cycles to disrupt mitochondrial membranes and release intramitochondrial contents. The purity of mitochondrial fractions isolated by the described method was confirmed by electron microscopy, which revealed no nuclear or cytoplasmic components, and by flow cytometry analysis.

In mitochondria isolated from the above tissues, the levels of estradiol (E2), testosterone (T), progesterone (P4), and cortisol were determined using standard ELISA kits (Monobind, USA) and an immunoassay analyzer Infinite F50 (Austria).

Statistical Analysis

Statistical analysis of the results was performed using the Statistica 10.0 software package. The data were tested for normality using the Shapiro–Wilk test (for small samples). Comparison of quantitative data between groups was carried out using Student's t-test and the Mann–Whitney test. Data in the tables are presented as $M \pm m$, where M is the arithmetic mean and m is the standard error of the mean. A value of $p < 0.05$ was considered statistically significant. The results were processed in accordance with general recommendations for medical research.

STUDY RESULTS

The content of steroid hormones in mitochondria of intact uterine tissue and in various tumor processes is presented in Table 1. It was found that the level of E2 in mitochondria of uterine myoma was 2.2 times higher, while in mitochondria of uterine leiomyosarcoma it was 1.4 times lower ($p < 0.05$) compared with the indicators in mitochondria of intact uterine tissue. No significant differences were found in E2 content in mitochondria of EAC (G3).

The content of P4 was found to be reduced to varying degrees in mitochondria of uterine tumors compared with mitochondria of intact uterine tissue: in myoma by 4.9-fold, in low-grade EAC by 9.1-fold, and in sarcoma by 2.7-fold. At the same time, mitochondria of uterine tumors were oversaturated with T. Its level was higher than in mitochondria of intact uterus: in myoma by 2.1-fold, in EAC by 3.7-fold, and in sarcoma by 2.1-fold. The cortisol content in mitochondria of uterine myoma, EAC, and sarcoma was higher than in mitochondria of intact uterine tissue by 2.6-, 3.7-, and 1.3-fold ($p < 0.05$), respectively.

When comparing the levels of steroid hormones in mitochondrial samples from malignant and benign uterine tumors, significant differences were found in E2 levels – they were lower in EAC and leiomyosarcoma compared with uterine myoma by 2-fold and 3.1-fold, respectively. The concentration of P4 in mitochondria of uterine myoma was 1.8-fold lower than in mitochondria of leiomyosarcoma, but 1.8-fold higher than in mitochondria of EAC. The content of T in mitochondria of uterine myoma was 1.7-fold lower than in EAC and showed no significant differences compared with leiomyosarcoma. The level of cortisol in mitochondria of uterine myoma was 1.5-fold

lower compared with EAC mitochondria but 2-fold higher compared with leiomyosarcoma mitochondrial samples.

Considering the metabolic precursors and products involved in the synthesis of steroid hormones, the ratios P4/T, P4/cortisol, E2/T, and E2/P4 were calculated (Table 2).

A significant decrease in the P4/cortisol ratio was found in mitochondria of uterine myoma by 12-fold, in EAC (G3) by 32.7-fold, and in sarcoma by 3.5-fold, indicating a predominance of glucocorticoid synthesis. The P4/T ratio also showed a marked decrease compared with that in mitochondria of intact uterus: in mitochondria of uterine myoma by 10.6-fold, in EAC (G3) by 33-fold, and in sarcoma by 5.5-fold.

The E2/T ratio in mitochondria of uterine myoma did not differ significantly from that in mitochondria of intact uterus, whereas in EAC (G3) and sarcoma it decreased by 3.3-fold and 2.9-fold, respectively, indicating a shift in sex steroid balance toward hyperandrogenism. In contrast, the E2/P4 ratio was increased in all mitochondrial samples: by 10.8-foldin myoma, 10.1-fold in EAC (G3), and 2-fold in sarcoma.

Compared with mitochondria of uterine myoma, in EAC mitochondria the following ratios were decreased: P4/T by 3.2-fold, E2/T by 3.4-fold, and P4/ cortisol by 2.7-fold. In mitochondria of leiomyosarcoma, compared with uterine myoma, the ratios P4/T and P4/cortisol were increased 1.9-fold and 3.5-fold, respectively, while E2/P4 and E2/T ratios were decreased 5.8-fold and 3.1-fold, respectively.

DISCUSSION

Mitochondria are multifunctional centers regulating the synthetic and energetic components of ho-

Table 1. Levels of steroid hormones in mitochondria of uterine body tissue

Mitochondrial samples	E2, nmol/g protein	P4, nmol/g protein	T, nmol/g protein	Cortisol, nmol/g protein
Intact uterine tissue (*n* = 25)	0,10 ± 0,007	0,59 ± 0,05	0,18 ± 0,01	3,2 ± 0,23
Uterine myoma (*n* = 25)	0,22 ± 0,02 p^1 = 0,0000	0,12 ± 0,009 p^1 = 0,0000	0,38 ± 0,03 p^1 = 0,0000	8,2 ± 0,71 p^1 = 0,0000
EAC (G3) (*n* = 25)	0,11 ± 0,007 p^2 = 0,0000	0,065 ± 0,005 p^1 = 0,0000 p^2 = 0,0000	0,66 ± 0,04 p^1 = 0,0000 p^2 = 0,0000	11,9 ± 0,91 p^1 = 0,0000 p^2 = 0,0023
Uterine leiomyosarcoma (*n* = 15)	0,07 ± 0,007 p^1 = 0,0000 p^2 = 0,0000	0,22 ± 0,02 p^1 = 0,0000 p^2 = 0,0000	0,37 ± 0,037 p^1 = 0,0000	4,16 ± 0,35 p^1 = 0,0230 p^2 = 0,0001

Note: p^1 – statistically significant compared with the value in intact tissue; p^2 – statistically significant compared with the value in myoma.

Table 2. Ratios of steroid hormone levels in mitochondria of uterine body tissues (arbitrary units)

Tissue samples	E2, nmol/g protein	P4, nmol/g protein	T, nmol/g protein	Cortisol, nmol/g protein
Intact tissue (*n* = 25)	3,3 ± 0,09	0,17 ± 0,005	0,56 ± 0,005	0,18 ± 0,003
Uterine myoma (n = 25)	0,32 ± 0,008 p^1 = 0,0000	1,84 ± 0,05 p^1 = 0,0000	0,58 ± 0,006	0,015 ± 0,0004 p^1 = 0,0000
EAC (G3) (*n* = 25)	0,10 ± 0,003 p^1 = 0,0000 p^2 = 0,0000	1,72 ± 0,03 p^1 = 0,0000	0,17 ± 0,004 p^1 = 0,0000 p^2 = 0,0000	0,0055 ± 0,00007 p^1 = 0,0000 p^2 = 0,0000
Uterine leiomyosarcoma (*n* = 15)	0,6 ± 0,008 p^1 = 0,0000 p^2 = 0,0000	0,32 ± 0,005 p^1 = 0,0000 p^2 = 0,0000	0,19 ± 0,005 p^1 = 0,0000 p^2 = 0,0000	0,052 ± 0,002 p^1 = 0,0000 p^2 = 0,0000

Note: p^1 – statistically significant compared with the value in intact tissue; p^2 – statistically significant compared with the value in myoma.

meostasis, as in addition to energy production they serve as sites for the synthesis of various hormones, neurotransmitters, and biogenic amines [1, 15]. It is known that mitochondria can dynamically and reversibly adapt to energetic, environmental, and other endogenous or exogenous stress factors. The basis of this adaptation lies in temporary molecular and functional changes rather than necessarily dysfunctional processes. Mitochondria act as systemic signaling hubs, transmitting information both within and between cells [16]. Alterations in mitochondrial function are believed to be involved in the pathogenesis of many diseases, such as cancer, cardiovascular, and neurodegenerative disorders, and understanding mitochondrial mechanisms and implementing adaptive strategies may offer an integrated approach to treating chronic diseases and restoring health [17]. Since the enzyme P450scc, responsible for the initiation of steroid hormone synthesis, is localized on the matrix side of the inner mitochondrial membrane, mitochondria occupy a central role in steroidogenesis [18].

This study examined changes in the content of steroid hormones in endometrial mitochondria depending on the underlying uterine pathology – whether it was benign tumor growth (uterine myoma) or malignant (low-differentiated endometrioid adenocarcinoma, EAC G3, or uterine leiomyosarcoma). It was found that mitochondria of all uterine tumors demonstrated unidirectional changes in the levels of progesterone, testosterone, and cortisol compared with mitochondria from intact uterus, while E2 levels varied depending on the tumor type. These alterations in mitochondrial steroid profiles may be related to the diverse functions of the studied hormones. Regardless of benign or malignant nature, all tumor mitochondria showed decreased progesterone levels but elevated testosterone and cortisol levels, differing only in magnitude. The most pronounced changes were observed in mitochondria from EAC (G3), showing minimal progesterone concentrations and maximal testosterone and cortisol levels compared with mitochondria from intact uterus.

It is known that mitochondrial steroid hormones, including glucocorticoids, androgens, and estrogens, exert both physiological and pathological effects, contributing to aging and the development of various diseases [19].

Glucocorticoid hormones penetrate mitochondria and directly interact with mtDNA, which may enhance oxidative stress and release of cytosolic mtDNA [20]. Elevated cortisol concentrations in mitochondria of uterine tumors may promote the accumulation of reactive oxygen species (ROS). Mitochondria are both the main target of ROS-induced epithelial cell damage and the primary ROS producer during oxidative phosphorylation [21]. Studies have shown that significantly higher levels of MDA and 8-OHdG (a modified nucleoside reflecting DNA damage) are found in endometrioid lesions compared with normal endometrium. mtDNA mutations are associated with elevated MDA and 8-OHdG levels, whereas E2 or an ERβ-selective agonist stimulates increased activity and expression of MnSOD [22].

P4 is believed to protect epithelial cells from oxidative damage and mitochondrial dysfunction through the c-MYC/SIRT1/PGC-1α signaling pathway [23]. It has been reported that P4, the second major endogenous female steroid hormone after estradiol, inhibits chronic inflammation and oxidative stress in mouse models [24]. Moreover, P4 possesses well-documented anti-inflammatory and antioxidant properties across various conditions [25] and has been shown to protect different cell types from oxidative damage [26].

The progesterone deficiency identified in this study in mitochondria of uterine tumors may therefore indicate reduced cellular protection against oxidative injury in all investigated formations.

Testosterone affects mitochondrial function in multiple ways, including altering the structure of these organelles. Androgens stimulate mitochondrial biogenesis via the AR/PGC-1α/TFAM pathway, increasing mitochondrial content through induction, transcription, and replication of mtDNA, which encodes 13 essential components of the respiratory chain [27]. However, mtDNA mutations or copy number alterations are known risk factors for mitochondrial dysfunction, leading to excessive ROS production and ATP deficiency, frequently observed in hereditary metabolic diseases [28]. Evidence also

suggests the presence of androgen receptors in mitochondria, whose overexpression, particularly in prostate cancer cell lines, reduces the activity of respiratory chain complexes I, II, and III [29]. However, sex-specific differences exist in testosterone's impact on mitochondria: in men, testosterone promotes energy expenditure and prevents metabolic disorders such as obesity and type 2 diabetes, whereas in women, elevated androgen levels increase the risk of type 2 diabetes and are commonly observed in patients with polycystic ovary syndrome [30].

It can be assumed that on one hand, mitochondrial hyperandrogenization in uterine tumors contributes to mitochondrial biogenesis and maintenance of cellular energy balance, while on the other hand, it may promote excessive ROS production and mitochondrial dysfunction.

The study revealed diverse changes in estradiol levels in tumor mitochondria depending on the pathological process. E2 concentration in mitochondria of uterine myoma was increased compared with intact uterine mitochondria, showed no significant difference in EAC (G3), and was decreased in sarcoma mitochondria. Normally, estrogens protect mitochondria from oxidative stress, enhance their biogenesis, and improve energy metabolism, whereas a decline in E2 levels – for example, during menopause – leads to mitochondrial dysfunction, which may contribute to various pathological conditions, including neurodegenerative disorders and tumor growth [31, 32].

Each mitochondrion contains about 1,200 different protein types, of which 13 are encoded by mitochondrial DNA and the rest by nuclear DNA [33]. Cross-talk between nuclear and mitochondrial genomes is essential for mitochondrial biogenesis and is regulated by a network of transcription factors that include estrogen-related receptors [34].

Estrogen and androgen receptors share localization and activity within both mitochondria and the nucleus, suggesting a synergistic relationship between estrogens and androgens in regulating mitochondrial function [35].

The calculated E2/T ratio showed a significant decrease compared with intact uterus only in malignant processes, whereas mitochondria of uterine myoma exhibited no significant differences.

There is evidence of altered levels of mitochondrial estrogen receptors in endometrial mitochondria under various gynecological pathologies, including adenomyosis. It is suggested that mitochondrial estrogen receptor β (MtERβ) continues the estrogen-induced signaling pathway within mitochondria, influencing mtDNA transcription, interacting with mitochondrial respiratory complex V, and enhancing activity of complex IV, thereby promoting ATP generation [10]. Moreover, estrogen deficiency has been shown to reduce the expression of genes involved in mitochondrial respiratory chain, oxidative phosphorylation, and glucose and lipid metabolism in ovariectomized rats [36].

CONCLUSION

The conducted study revealed significant alterations in the content of steroid hormones in mitochondria of uterine tumors. The obtained data demonstrate a general trend across all examined neoplasms – a decrease in progesterone levels accompanied by increased concentrations of testosterone and cortisol compared with intact tissue. The key difference between benign and malignant growth appears to be associated with the balance between estradiol and testosterone. It can be assumed that the identified hormone concentration profiles create distinct metabolic environments within mitochondria. The preservation of estradiol–testosterone balance in myoma may favor oxidative phosphorylation, whereas the pronounced shift toward androgens in malignant tumors potentially promotes oxidative stress and may be associated with a metabolic switch to glycolysis

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