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Z. V. Chumak https://orcid.org/0000-0002-7487-1410
M. V. Shapoval https://orcid.org/0000-0002-1087-2609

POSSIBLE MECHANISMS OF HYPERPROLIFERATIVE PROCESSES DEVELOPMENT IN THE ENDOMETRIUM

Odesa National Medical University, Odesa, Ukraine

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Odesa National Medical University, Odesa, Ukraine

In the process of examining certain mechanisms of the onset of hyperproliferative processes and their localization and transition to a state of carcinogenesis in the endometrium, specific issues are considered in detail in the literature.

The aim of the work is to study the features and characteristics of the endometrial cell response at the current level of research.

Materials and methods. A search for original review articles was conducted in online resources and journals to analyze and substantiate certain features presented in Scopus, PubMed, Medline, Web of Science and Google Scholar. This analysis covers the period from 2018 to 2023.

Research results. As a result of the analysis, numerous disorders occurring in affected women were identified. In the literature sources, disorders are extensively described both within living cells and in relation to their development across all organs and systems. These changes in organism contribute to the growth and development of carcinogenesis.

Key words: endometrial hyperplasia, apoptosis, hyperproliferation, adenocarcinoma.

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З. В. Чумак, М. В. Шаповал
МОЖЛИВІ МЕХАНІЗМИ РОЗВИТКУ ГІПЕРПРОЛІФЕРАТИВНИХ ПРОЦЕСІВ В ЕНДОМЕТРІЇ
Одеський національний медичний університет, Одеса, Україна

У процесі розгляду певних механізмів виникнення гіперпроліферативних процесів і локалізації та переходу їх у стан канцерогенезу досить детально на сьогодні розглядаються певні питання з урахуванням того моменту, що рак та гіперпроліферація ендометрія посідають лідируючі місця в жіночому здоров'ї. У медичній літературі дуже багато даних щодо порушень у гіпоталамо-гіпофізарній ділянці, порушень у гормональному профілі, генах, процесах апоптозу та проліферації, структурах загального організму, починаючи від клітини до органів та систем, та багатьох інших змін. Тому натепер є перспективним розгляд людського організму загалом, починаючи від клітини й закінчуючи цілими системами, можливих механізмів розвитку гіперпроліферативних процесів в ендометрії, і, можливо, за рахунок таких даних будуть вирішуватися поставлені проблеми патогенезу, діагностики та лікування цієї патології.

Ключові слова: гіперплазія ендометрія, апоптоз, гіперпроліферація, аденокарцинома.

Introduction. The main place, the origin of human life on Earth is the uterus [1; 10; 11], which exists, gives life, and sometimes, perhaps, dominates the overall health. The existing data, as a result of research, confirm that all the changes that occur in the organ are quite confidently following the unchanging evolution of humanity's existence. To date, it has not been established at all what significant factors influence, exist and make it possible to prolong human life [12; 29].

Endometrial hyperplastic processes (EHP) are a common pathological form of the uterine mucosa [13; 17; 28]. According to various literature data, the frequency of their occurrence ranges from 15% to 50% among gynecological pathology. Changes in the incidence and classification of hyperplasia may reflect our understanding of the occurrence of endometrial carcinoma, which is currently growing and occupies a leading position among gynecological oncological pathologies [13; 18]. The development of endometrial cancer is a fairly common problem, especially in countries with advanced economies [17; 22; 25].

In medicine there is a constant scientific search, with the discovery of new factors in the direction of the classification of hyperproliferative processes in the endometrium [25; 26]. The exact criteria for diagnosing and predicting the likelihood and development of malignancy have not yet been identified. For clinical doctors, the morphological report is crucial in making a diagnosis. However, morphologists also have their own specific criteria for assessing and diagnosing endometrial conditions [19; 32; 37].

There is a great number of modern studies of foreign and domestic scientists, practitioners, pathologists and other specialists, but the mechanism of EHP development remains a mystery. The scientists face the problem of endometrial intraepithelial neoplasia, which was proposed by G.L. Mutter (2000) [38; 41]. This variant is a fundamental shift from the theory that estrogen stimulation on tissue cells leads to the occurrence of constantly growing hyperplasia with possible accumulation of cytological atypia, which can provoke development of oncological processes in the endometrium in the future [31; 32; 35].

According to a well-known point of view, the development of endometrial hyperproliferative processes is stimulated predominantly by the unregulated system of hyperestrogenism [9; 15; 36]. A set of studies confirming these changes was aimed at establishing and identifying this pathological form. However, these changes are not typical for 30–40% of patients and their treatment management is quite different.

A possible approach is to combine the existing pathological, immunohistochemical, molecular genetic and other methods based on the use of various modern biochemical methods, laser microdissection and other techniques that study proteins regulating apoptosis and mitotic activity, tumour suppressor genes and promoters, growth factors, interleukins, cytokines and other regulatory systems that can be informative in the approach to diagnosing the occurrence of endometrial pathology [8; 16; 38; 39].

The aim of the work is to study the peculiarities and characteristics of the response of endometrial cells to the intensity of hyperproliferation processes at the current level of research and possible options for their study.

Materials and methods. A search for original peer-reviewed scientific articles was conducted in Internet resources and journals using the keywords: endometrial hyperplasia, apoptosis, hyperproliferation, adenocarcinoma. We analysed and substantiated the features presented in Scopus, PubMed, Medline, Web of Science and Google Scholar. This analysis was performed for the period 2018–2023.

Research results and discussion. According to the International Agency for Research on Cancer, 19.3 million new cases of neoplastic diseases and 10 million deaths occurred in 2020 [2; 13; 14]. Companies are working around the world to produce new drugs for malignancy, but the processes are growing [4; 11; 23].

The processes of genetic disorders are quite significant. Genes determine the development of all proteins involved in this process. In the scientific medical world, there are many structures that can be studied: PTEN, MSI, KRAS, PT53, CDH1, PIK3CA, KRAS, EIG121, CDH1 and other genes [29]. However, F.S. Saghir et al. found that in the study of more than 28.869 genes, changes in 600 genes were detected, showing that these disorders occur in more women and are directed at several genes, and it is not possible to establish their priority [5; 21; 27; 28].

Much attention is paid to the development and formation of stem cells, comprehensive research is being conducted and much attention is paid to their reprogramming and the emergence of benign tumours, as a result of their dysregulation, with a high risk of genome damage [5; 7; 33]. This is probably why the development of cancer occurs in most countries with the most advanced economies. It should be noted that the risk of malignancy in a woman's organism is not fully understood.

Scientists consider EHP as an unphysiological excessive proliferation of the endometrial tissue due to glandular and stromal components. Studies have revealed the active influence of melatonin, serotonin, norepinephrine, histamine, bradykinin, insulin, parathyroid hormone and other biologically active peptides synthesised by APUD cells in the endometrium and organism on the development of EHP; this system is also promising for researchers [12; 14; 25; 36].

Damage to the cerebral cortex and hypothalamus can lead to disorders in the centres for the synthesis of gonadotropic hormones in the pituitary gland [24; 26], which, in accordance with extero- and interoceptive impulses, regulate and change the course of processes in the endocrine function of the ovaries [5; 27; 31]. These changes are quite common and are observed in the survival of the female population in Ukraine during martial law, but a certain theme exists in many countries around the world. The third year of the war is underway, and the consequences for women will be felt for a long time, as well as the hormonal disorders that arise and affect the reproductive system.

Many studies have established that there are many factors in the pathogenesis of pathological processes in the endometrial tissue that predispose to the occurrence of hormonal disorders. Changes in the endometrial tissue are caused by nervous and endocrine factors that exist in a rather complex interaction [8; 18; 25]. The central mechanisms of control of this system are united by the hypothalamus, its neurosecretory cells are capable of producing and secreting neurohormones [9; 14; 20], as well as perceiving and transmitting nerve impulses [13; 26]. Two types of these secretions in the hypothalamus have been identified: stimulating impulses to pituitary hormones (releasing factors); and those that inhibit secretion of the corresponding hormones (inhibitory factors) [14; 23; 31; 32].

Numerous studies proved that the hypothalamus-pituitary system works as a single mechanism that directs its function to the peripheral endocrine glands. The pituitary gland synthesises and secretes prolactin, follicle-stimulating hormone (FSH), luteinising hormone (LH), adrenocorticotropic hormone (ACTH), somatotropic hormone (STH) thyrotropin stimulating hormone (TSH) and melanostimulating hormone, oxytocin, vasopressin, antidiuretic – all of them are distributed in its specific functioning structures [3; 17; 39; 40].

During puberty, hypothalamic secretions cause a consistent increase in the production of gonadotropic hormones that affect ovarian function. It has been established that there are mechanisms for the formation of both long-term (between the ovaries, hypothalamus and pituitary gland) and short-term (between FSH, LH, and releasing factors) changes. Hyperplastic processes in the endometrial tissue can occur as a result of these neuroendocrine disorders [24; 38; 39].

Studying the state of the pluripotent endocrine gland – the ovary, which, in addition to the production of sex hormones (androgens, estrogens and progesterone), synthesises germ cells and more than 30 protein and paracrine regulators, which receives less attention [12; 23; 35]. The anlage of eggs in a girl's organism occurs as early as the 8th to 12th week of her intrauterine development, and therefore a mother may have many factors that characterise her ability to influence the formation of the "ovarian reserve potential". Changes in this system can provoke the development and formation of pathological conditions in the future [13; 28].

The endometrial tissue is a complex multicomponent system of mesenchymal origin. It undergoes its changes starting from childhood, adolescence, reproductive, premenopausal, perimenopausal, postmenopausal and senile ages [14; 21; 26; 39]. Many specialists in various fields study the expression of sex hormone receptors and their distribution in body tissues, paying attention to excessive estrogen stimulation of the endometrium, with insufficient progesterone exposure, which is called "unopposed". However, most researchers who focus on hyperestrogenic states argue that this ratio exists only up to a certain threshold, after which other relationship structures are activated [19; 27; 35; 40].

Changes that occur in the ovaries, disruption of their hormonal function occur due to changes in the peripheral organs, and in the system of estrogen and progesterone, as well as their joint interaction. It has long been established that an excess of 17β-estradiol (E_2) is not compensated by the sufficient availability of progesterone, which leads to hyperplastic changes in the endometrial tissue [13; 19; 41].

Hormones affect endometrial cells by binding to specific receptors on the cell surface and cytoplasm through the interaction of the hormone receptor complex with nuclear receptors [2; 11]. In the target tissues, the concentration of receptors is controlled by the content of the corresponding hormone in the blood. Finding out the state of the receptor apparatus is quite important for researchers, since the unique endometrium contains not only sex hormone receptors but also other receptor factors [5; 18; 27].

In the modern medical literature, both clinical and diagnostic, there is always a focus on studying the state of proliferation and apoptosis in this category of women with EHP. The occurrence and existence of endometrial carcinoma is a fairly common form of the disease, it is growing and increasing to occur at a young age, especially in countries with high economic status [14; 25; 26].

The states of pro- and anti-apoptotic markers (Ki-67, p53, p21, dcl-2, cycl-D1, bcl-2, BAX) [5; 11; 16], blood oxygen saturation (Hif-1α, Hif-1β, Hif-2α, Hif-3α) [8; 10; 22], angiogenesis factors (VEGF, bFGF), insulin-like growth factor (IGF-1, IGF-2) transforming growth factor (TGF-1α, TGF-1β) [6; 12; 30; 34], study of inflammatory processes (CD56, CD138), as well as many other factors that exist and contribute to the development of EHP, tumour growth and metastasis [35; 40].

Telomere length and telomerase activity in endometrial tissue are studied in detail. When studying and establishing critically short telomeres in a cell, which is accompanied by prolongation to a state of crisis, however, when telomerase is functioning, an obstacle to such telomere shortening or protection of the structure may occur. All these processes are quite manifest in the body and work to prolong or shorten the life of the cell [20; 34].

Historically, endometrial cancer was considered a postmenopausal disease, but with current trends, the problem is becoming younger and manifesting itself in pre- and perimenopausal age [25; 28; 37]. These health changes pose difficulties both in terms of diagnosis and treatment of this category of patients.

The existing electron microscopy data, immunomorphological and molecular genetic studies show heterogeneity of results. The meaning of genetic and phenotypic heterogeneity of the population of cells that make up the components of the endometrial tissue is to ensure tissue homeostasis [2; 11; 12].

For diagnostic and treatment purposes, it is necessary to remove the uterine mucosa, which is a strong enough irritant to affect the function of the gonads. After the histological diagnosis is made, a significant assistance in further treatment management is provided if the patient's treatment data is filled in correctly and rationally [3; 13; 35; 39]. In modern scientific and medical approaches, there is no system for a universal clinical and morphological classification that would help a pathologist, researcher or practitioner in providing information, most of which is often not sufficiently verified [5; 12; 18].

For a medical professional, there are many approaches to detect the presence of a cell clone capable of further autonomy and immortalisation. In many scientific fields, work is underway to identify mechanisms aimed at detecting tumour growth. In oncological research, a great number of processes during malignancy have been identified, but most remain unresolved [11; 41].

In general, such processes lead to the understanding that the human body is a balanced system with a total number of different factors affecting certain structures. For scientific researchers, in general, the identification or understanding of the processes of EHP oncogenesis seems to be quite problematic [12; 20; 26]. With an established approach and the development of general principles in treatment management, it is clear that such data require a multidisciplinary approach to solving the problem. In retrospect, the literature and research data have revealed major changes in the emergence of neoplastic processes, especially as for their mechanisms, but it is still difficult to definitively identify and determine the causes of malignant tumours [3; 18].

In understanding the development of a living organism, a lot of attention is paid to the existence of the most important engine in the environment and a single living cell [11; 28]. When analysing the occurrence of a condition that occurs throughout life and a pathological process that occurs in the body, scientists always ask themselves the question: what is the root cause of the changes, are they in the general body, genetic information, where the onset of the disorder lies, or does it occur in several organs simultaneously [10; 18; 26]. To understand and realise the existing realities and prospects of the population, the mechanisms of the evolutionary impulse, if from the organism to the target cell, at what real stage of the study the researcher stops and where the disorder is located. Specialists in different fields focus on the mechanisms of pathology, but all the processes that occur in a living cell, which ensures the existence of the whole organism, remain unchanged [4; 12; 25; 33].

Conclusions. This work would like to draw attention to a rather problematic and active process in the female body – endometrial hyperplastic processes, which develop and progress from the perimenopausal to the postmenopausal period, and also occur alongside malignancy. Taking into

account the problem of rejuvenation and the presence of malignancy, the issue of preserving the fertility of this category of women remains always problematic, which is reinforced and directed by therapy.

Understanding the mechanisms of the evolutionary origin of cancer cells in the body and the correction of their development may become one of the ways to prevent the development of malignancy in the body.

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Електронна адреса для листування chumakdoc@gmail.com