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Role of membrane components in the initiation and progression of tumour growth in endometrial cancer

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Abstract

This review discusses the role of membrane components in the initiation and progression of endometrial cancer. Cancer cells that are the substrate of the tumor growth are subject to multiple interactions both among themselves and with the tumor microenvironment.The cell membrane of tumor cells undergoes changes, resulting in simplified antigenic structure and the expression of molecules found in embryonic tissues, changes in the intercellular contacts that maintain epithelial homeostasis. Dense contacts form the basis for the preservation of normal endometrial histological organization. These changes also affect intercellular contacts, leading to the alteration of mechanical properties and invasive growth of tumor cells. In addition, components of dense contacts are participants of intracellular signal transduction pathways. The review highlights the potential role of claudin proteins, specifically in tight junctions and intracellular signaling, as promising targets for further study. Epithelial-mesenchymal transformation (EMT) represented in normal tissues in processes of reparation, plays a significant role in endometrial cancer progression, and the altered characterization of E-cadherin and β-catenin is important in understanding EMT's role in the disease. Researchers are focusing on the E-cadherin as a component of oncogene activation pathways. Hyperestrogenemia (high serum estrogen levels) is known to underlie Type I endometrial adenocarcinoma. Additionally, estrogen receptors and claudins are implicated in intracellular signaling activating cell proliferation both in the norm and in the course of disease. Recent research also involved other molecules serving as targets for estrogens, e.g. claudin proteins. Change of clausin expression profiles mediated by sex hormones manifest both in suppression and replacement of one protein with another. Further study of cell membrane-associated markers has the potential to provide insights into tumor biology and aid in the development of new therapeutic approaches for endometrial cancer.

Keywords: endometrial cancer, cell membrane structures, cancer initiation, cancer progression, cell junction, claudins, E-cadherin, β-catenin, intracellular signalling, hyperestrogenemia.
Conflict of Interest: nothing to disclose.

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Роль мембранных компонентов в инициации и прогрессии опухолевого роста при раке эндометрия

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Аннотация

В настоящем обзоре мы предприняли попытку систематизировать значение мембранных компонентов в инициации и прогрессии опухолевого роста при раке эндометрия. Клетки, составляющие субстрат опухолевого роста, подвержены множеству взаимодействий как между собой, так и с опухолевым микроокружением. Наблюдается упрощение антигенной структуры клеточной мембраны опухолевых клеток, экспрессия молекул, характерных в том числе для эмбриональных тканей, изменение свойств межклеточных контактов, поддерживающих эпителиальный гомеостаз. Плотные контакты составляют основу сохранения нормальной гистоархитектоники. Изменения их свойств, выраженные в замене одних компонентов другими, определяют механические свойства опухолевых клеток, для которых характерны инвазивный рост и метастазирование. Помимо этого, компоненты плотных контактов являются участниками внутриклеточных путей передачи сигнала. Перспективными, на наш взгляд, выглядят исследования роли белков-клаудинов, являющихся компонентами плотных соединений. В этом обзоре мы собрали имеющиеся сведения о клаудинах как о компонентах клеточных контактов и участниках внутриклеточной сигнализации. В патогенезе эндометриального рака немаловажной характеристикой является эпителиально-мезенхимальная трансформация (ЭМТ), широко представленная в

нормальных тканях в процессах, связанных с репарацией. Изменение характеристик Е-кадгерина и β-катенина не могло быть не рассмотрено в рамках обсуждения роли ЭМТ в прогрессии рака эндометрия. Кроме того, исследователи все больше обращают внимание на Е-кадгерин как компонент путей активации онкогенов. Известно, что в основе эндометриального рака I типа лежит гиперэстрогенемия (высокие сывороточные урови эстрогенов). Рецепторы эстрогена, бесспорно, включены во внутриклеточную сигнализацию, активирующую пролиферацию клеток в норме и патологии. Кроме того, недавние исследования указывают на другие таргетные для эстрогенов молекулы. Таковыми являются клаудины. Изменение профилей экспрессии клаудинов под влиянием половых гормонов выражаются как в снижении, так и в замещении одного белка другим. Несомненно, дальнейшее изучение маркеров, ассоциированных с клеточной мембраной, может уточнить биологические свойства опухоли и служить основой поиска таргетных молекул для разработки новых путей терапии рака эндометрия.

Ключевые слова: рак эндометрия; мембранные компоненты; инициация; прогрессия; клеточные контакты; клаудины; Е-кадгерин; β-катенин; пути внутриклеточной сигнализации; гиперэстрогенемия.

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Список сокращений
ЗНО – злокачественное новообразование; ЭК – эндометриальная карцинома; ЭМТ – эпителиально-мезенхимальная трансформация.

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BACKGROUND

In 2023, in the Russian Federation there were 29,233 registered cases of endometrial cancer. According to the evaluation of the P.A. Herzen Moscow Scientific and Research Oncological Institute, it amounts to 8.0% of the total malignant tumor rate in Russian women. Endometrial cancer accounts for 37.34 cases per 100,000 population, and the average annual increase rate is 1.89%. Mortality from uterine malignant neoplasms, excluding cervical cancer, increases with age, starting from the age group of 25-29 years and reaching its maximum in the age group of 65-69 years at 6.59% [1]. In recent years, there has been some decrease in the overall mortality rate from endometrial carcinoma (EC) [2].

Following the pathogenetic criteria, there are two types of EC. Type I EC develops against a background of hyperestrogenemia (approx. 80% cases). It is preceded by atypical glandular hyperplasia of the endometrium / endometriosis intra-epithelial neoplasia. Type II EC develops against a background of endometrial atrophy in the absence of hyperestrogenemia, includes serous-papillary and clear cell types, and is more aggressive and estrogen-independent. Surgery remains the main method of treatment of uterine malignant neoplasms. In addition to hysterectomy, neoadjuvant chemotherapy is used, and approaches to targeted therapy based on tumor heterogeneity are being developed. There is evidence, based on tumor genome analysis (The Cancer Genome Atlas, TCGA), indicating heterogeneity in the genetic characteristics of endometrial carcinoma. The analysis identified the following molecular and genetic subtypes of EC: Group 1, *POLE*-ultramutated EC, associated with a favorable prognosis; Group 2, EC with microsatellite instability (MSI), showing intermediate prognosis; Group 3, EC with low copy-number alterations, also associated with intermediate prognosis; Group 4, EC with high copy-number alterations and TP53 mutations, associated with poor prognosis [3].

Considering the foregoing, there is practical interest in looking for targets to develop targeted therapy of endometrial adenocarcinoma.

The tumor consists of several key components, including the tumor parenchyma itself, its microenvironment (the stroma, immune system cells, and tissues providing trophic support and drainage for the tumor substrate, blood and lymphatic vessels). Most targeted therapy drugs under development focus on direct and/or indirect effects on tumor-specific biomarkers.

The cells comprising the substrate of the tumor growth are subject to a multitude of interactions between one another and their microenvironment. Such interactions are often corrupt making the tissue differentiation go back to the early stages of ontogenesis. Along with a simplification of the antigen structure of the cell membrane of the tumor cells, molecules are expressed that are characteristic for embryonal tissue. Interactions of cells with one another are also of importance, since they support the epithelial homeostasis.

This review is an attempt at systematizing the existing data on the changes in the structure of intercellular interaction (junctions) and cell interaction with their environment matrix, and their role in the pathogenesis of the endometrial carcinoma.

STRUCTURE AND FUNCTION OF MEMBRANE COMPONENTS IN NORMAL ENDOMETRIUM AND DURING PHYSIOLOGICAL REGENERATION

Cell Junctions

The primary participants in cellular interactions within tissues are intercellular junctions. These consist of protein molecules with distinct characteristics, each performing a specific function. Intercellular junctions connect cells to one another to maintain cellular polarity, stability, and the integrity of glandular structures. By preserving the polarity of the cell layer, intercellular junctions play a crucial role in regulating their mobility relative to the basement membrane.

Tight junctions, hemidesmosoma

Tight junctions are located in the uppermost part of the lateral cell membrane of two adjacent cells, thereby

regulating intercellular transport between cells (gate function) and maintaining apicobasal polarity (fence function). Tricellular tight junctions (tTJs) are formed in the intercellular contacts of three neighboring cells near their apical surfaces and are seen in polarized epithelia [4]. Tight junctions consist of three main membrane proteins: occludins, claudins, and adherens junctions molecules. The claudins are likely crucial in the protective and barrier functions of the junctions, intercellular differentiation, and support of epithelial polarity.

The hemidemosoma connect the intracellular filaments with the basal plate. Tricellulin (TRIC) was the first identified molecular component of tricellular tight junctions, and the Angulin-1/LSR, the novel integral membrane protein localized at tricellular tight junctions (tTJs).

Claudin proteins

Claudins (claudin-1, -2, -3, -4, -5, -7) are synthesized in endometrial epithelial cells and serve as components of tight junctions. Their secretion normally increases during the secretory phase of the endometrium.

E-cadherin and β-catenin are synthesized on the lateral membrane of glandular epithelial cells during the proliferative and early secretory phases, with protein synthesis decreasing during the secretory phase. E-cadherin represents one of the key epithelial adhesion molecules that plays a critical role in maintaining both cellular polarity and suppression of epithelial-mesenchymal transition (EMT) processes.

Adherens junctions

Adherens junctions and desmosomes interconnect adjacent cells. While adherens junctions are associated with intracellular actin bundles, desmosomes are linked to intermediate filaments.

Gap junctions

Gap junctions are intercellular membrane channels that directly connect the cytoplasm of adjacent cells, enabling the exchange of ions, second messengers, and small metabolites. Each gap junction channel consists of two hemichannels (connexons), with each hemichannel composed of six protein subunits (connexins).

The proteins of gap junctions are connexins Cx26, Cx32, Cx43. The increase of connexin Cx26 synthesis is seen in the epithelial cells of the endometrium during the proliferative phase, but the synthesis stops in the secretory phase [5]. Unlike tight and adherens junctions, the gap junctions are present in the stromal cells of the endometrium. These channels consist of the Cx43 protein. Similar to other connexins of the endometrium, the level of the Cx43 in the stromal cells of the endometrium also decreases during the secretory phase [6].

Normal EMT

The epithelial-mesenchymal transition (EMT) process is an important property of a healthy endometrium securing its physiological function. The EMT processes are well studies in the embryonal development, at the same time, there appear numerous proof of importance of these processes for the phenotypical and functional flexibility of the endometrium vital for the successful decidualization, regeneration and reepithelization, and embryo implantation [7].

Contact inhibition

Epithelial homeostasis is maintained through cellular polarity and cell density. Disruptions of these processes lead to malignant transformation of normal epithelia. Epithelial cells exhibit contact inhibition, a mechanism that arrests cell division and motility. Here, “cell motility” refers to the ability of individual cells to lose apicobasal polarity, undergo genetic rearrangements that drive cytoskeletal reorganization, and acquire an invasive phenotype [8]. It ensures tissue reparation in the process of normal physiological processes and in the response to damage.

ENDOMETRIUM FUNCTION IN MALIGNANT TRANSFORMATIONS

Molecular mechanisms of malignant transformation of epithelia include the PAR3 (partitioning defective), TGF-β (tumor-growth factor) and Hippo-signal pathways. The mutations of the *KRAS* protooncogene are found in almost 25% of adenocarcinomas including the endometrial carcinoma and endometriosis (adenomyosis).

Alterations in tumor cell motility in endometrial carcinoma have been extensively studied using the Sawano cell line. This line was established from uterine endometrial adenocarcinoma and carries a heterozygous KRAS G13D mutation with wild-type *BRaf*. Sawano cells exhibit high horizontal motility at low cell density, while at high cell density, their growth and motility are temporarily arrested due to contact inhibition. Under high-density conditions, this cell line initiated multilayered growth. Furthermore, in the presence of MAPK (mitogen-activated protein kinase) inhibitors, the cells maintained a highly differentiated state [9].

It is worthwhile focusing on these factors and analyze the structure of tricellular junctions. We have identified claudin proteins, occluding and adherens junctions as the main contributors to tight junctions. The transmembrane protein Angulin-1, a component of tTJs, is to be focused on.

Tricellular tight junctions, macropinocytosis, Angulin-1/LSR

Current evidence indicates tumor progression in colorectal cancer, pancreatic cancer, and lung adenocarcinoma cell lines, mediated through EGF-dependent claudin-2 and TGF-β-dependent angulin-1/LSR pathways [10, 11].

In the tissues of the endometrioid endometrial carcinoma, as well as in the endometriosis tissues, the angulin-1/LSR is located not only in the subapical zone but on the lateral surface of the membrane as well. There is evidence as to simultaneous decrease of expression of this protein with the growth of malignancy potential of endometrial carcinoma. The decreased expression of the angulin-1/LSR is seen in phases G2 and G3 of the cellular cycle in the cells of the endometrioid endometrial carcinoma, and the TRiC (T-complex protein Ring Complex) decreases as early as in G1 phase.

The apoptosis-stimulating protein of p53-2 (ASPP2) is an inducer of apoptosis that functions through binding with p53 and the epithelial polarity factor PAR3. ASPP2 suppression

promotes cell migration and invasion, downregulates LSR expression, and upregulates phosphorylated YAP as well as claudin-1, -4, and -7 expression with comparable efficiency to LSR loss [12].

The *PARD3* gene belongs to the par-3 family acting as regulators of cell polarity. The adaptor protein plays a crucial role in regulating asymmetric cell division and polarization processes in epithelial cells. Evidence suggests it serves as a key component of epithelial tight junctions [13]. In a study utilizing small interfering RNAs (siRNAs), J. Peng et al. (2021) demonstrated that transfection of HEC-1A cells with si-Par3 resulted in tight junction shortening, which enhanced tumor cell migration and invasion.

Using the Sawano EEC cell line, the authors also demonstrated impaired epithelial barrier function along with increased tumor cell proliferation, migration, and invasion [14].

T. Kohno, T. Kojima (2022) performed studies demonstrating the LSR ligand role in the regulation of cellular motility through atypical macropinocytosys [9]. Macropinocytosis is an actin-driven process of nonspecific uptake of micrometer-sized (visible by light microscopy) extracellular droplets. This process has been described in mammalian cells, among others [16]. Macropinocytosis serves as an important mechanism for nonspecific internalization of extracellular components [17]. In the recent years, additional functions of macropinocytosys were identified, such as intracellular drug introduction pathway, bacterial and viral infection, and nutrient consumption pathway by tumor cells. The LSR ligand is a fragment of the C-terminal peptide of the β-subunit of the Clostridium perfringens ι-toxin. In the Sawano and HPAC cell lines, the LSR downregulates the expression on of the latter and causes the barrier function to decrease resulting in an increased malignant transformation of the cells. In a monolayer of Sawano cells with a preserved mechanism of contact inhibition in the conditions of high cell density, the introduction of the LSR ligand leads to a transient fast enhancement of the horizontal motility of the cells. This process requires micropinocytosis initiated by the emergence of a gap between neighboring cells. LSR-ligand-driven pinocytosis does not occur neither in the apical nor in the basal membranes. Besides, in the course of accumulation of the macropinosomas there was not observed a significant accumulation of actine filaments. In the presence of the quinolinic inhibitor Rac1 (NSC23766) or in the cells expressing the dominant-suppressed Rac1, LSR-ligand-driven macropinocytosis is suppressed. The activity of Rac is required to activate the JNK (c-Jun N-terminal kinase) and instrumental in the subsequent enhancement of cell motility. In the Sawano cells, stimulation with the LSR ligand enhances cell motility through JNK activation. The JNK inhibitors, or silencing of the JNK gene not only suppresses the cell motility but also inhibits macropinocytosis [15].

EMT, loss of E-cadhedrin

Transforming growth factor (TGF)-β is a pleiotropic cytokine regulating the growth, differentiation, apoptosis, migration, cell adhesion and immune response. TGF-β activates the Smad-signal pathway through two its receptors on the cell membrane (TβRII and ALK5/TβRI), resulting in the Smad-mediated transcription regulation [18]. The analysis of potential candidates of prognostic factors of clinical outcomes demonstrates a correlation between the expression of TGF-β and its receptor and survivability in endometrial cancer. It was shown that the high expression of TGF-β and its receptor TGFβ1 correlates with a low overall survival [19]. K. Horiguchi *et al*. (2009) showed that TGF-β induces transcription of Snail through KRas-signaling, which results in the epithelial-mesenchymal transformation in the pancreatic carcinoma cells Panc-1 and HeLa cells [20]. This indicates, in the first place, a correlation of the Ras-signal pathway, Hedhehog-pathway and EMT; in the second place, it sheds some light on the dual role of TGF-β in the carcinogenesis.

LEF-1 is a component of the TCF/LEF-1, the factor associated with some types of malignant neoplasms, specifically, colorectal cancer [21]. In the endometrium, the LEF-1 is expressed in the norm[1]. In mouse experiments, D.N. Shelton *et al*. (2012) demonstrated that the expression profiles of LEF-1 and Cyclin D1—a known proliferation marker and target of the Wnt/β-catenin/LEF-1 signaling pathway—coincided and peaked during proestrus (equivalent to the human endometrial proliferative phase and ovarian follicular phase), corresponding to conditions of elevated estradiol (E2) levels [22].

Epithelial cell adhesion molecule (EpCAM) is a membrane protein known to function as an mediator in the intercellular interaction and cell and intercellular matrix interaction. The current data as to the role of EpCAM hyperexpression are contradictory: on the one hand, EpCAM is supporting the normal histoarchitecture of epithelia, on the other hand, the adherens molecule might activate the intracellular pathways promoting cell invasion [23, 24]. Y.T. Hsu *et al*. (2016) report that the EpCAM integral protein is split into the extra- and intracellular domains (EpEX and EpICD, respectively) when induced by activated EGFR. The EpICD, subjected to nuclear translocation, together with the LEF-1 acts as activator of transcription of target genes responsible for epithelial-mesenchymal transformation [25].

G-protein-coupled receptor 64 (GPR64) is a member of the GPCR family. *GPR64* was identified as the target gene of the β-catenin/T-cell factor (TCF) in the ovarian endometrioid adenocarcinoma. It was shown that the downregulated expression of *GPR64* together with the deletion of the GPR64 gene increases the malignant potential of the tumor and upregulates the processes of cell proliferation, migration and invasion; GPR64 regulates expression of Cx43 and activity of AMP-activated protein kinase (AMPK) in the endometrium cancer cells [26].

The Hippo-signal pathway is an important contributor to the maintenance of cellular polarity and density of the cell layer; the inactivation of the pathway may result in the increase of cell proliferation and decrease of apoptosis this leading to the tumor genesis and progression [27].

[1] The Human Protein Atlas [Internet]. Tissue expression of LEF1. Staining in endometrium. 2000 [cited 2025 Feb 12]; [about 2 p.]. Available from https://www.proteinatlas.org/ENSG00000138795-LEF1/tissue/endometrium

The nuclear component of this signaling pathway is also regulated by multiple other pathways. Inactivation of the Hippo signaling pathway triggers activation of its primary effector oncogenes, YAP/TAZ, which in turn promote tumor invasion, migration, and proliferation in endometrial cancer [28]. YAP/TAZ are transcriptional coactivators that move between the cytoplasm and the nucleus, where they recognize the cis-regulatory elements and interact with other transcription factors, specifically, with members of the TEA domain family (TEAD). Emerging evidence clarifies the crosstalk between the Wnt-signaling pathway that governs β-catenin accumulation and activity (canonical pathway) and the transcriptional coactivator TAZ [29, 30].

Various signaling pathways, including Wnt/β-catenin- and Notch-pathways, induce the EMT and downregulate the expression of E-cadhedrin. The experiment on the HEC-1A, HEC-1B, KLE cell lines of the endometrial carcinoma showed that the knockdown of the fibulin-4 gene may bring about the activation of the Wnt-pathway and promote the EMT. Upregulation of the fibulin-4 expression may suppress the Wnt-pathway and prevent the EMT, but this question calls for further research [31, 32]. In the HeLa cervical cancer cells, the overexpression of EFEMP1 (EGF-containing fibulin-like extracellular matrix protein 1), also known as fibulin-3, results in the enhancement of angiogenesis and progression of tumor growth through the VEGF-pathway [33]. Besides, EMP undergoes regression under the influence of other inhibitors of the Wnt-signaling pathway.

The Hedhehog-signaling pathway ensures the proper cell differentiation in the embryo. Its disruptions in the embryogenesis account for the teratogenic effect. Its role in the adult organism however is completely opposite: the activation of the Hedhehog-pathway has proven relation with the development of malignant neoplasms of the brain, lungs, mammary glands, prostate, and skin. The activation of the Hedgehog-signaling pathway results in the upregulation of expression of the Snail protein and downregulation of E-cadhedrin and tight junctions [34].

Claudin proteins

The family of claudin proteins is an integral part of tight junctions. Claudins are considered to be instrumental in the processes of maintenance of cell polarity, cell monolayer and EMT regulation, since their loss promotes destruction of cell junctions. Abnormal expression of claudin proteins affects cancer progression in several ways: firstly, changes in claudin expression lead to disruption and leakage of tight junctions, which promotes tumor metastasis and invasion; secondly, loss of cell polarity increases the delivery of nutrients and growth factors to the tumor and enhances the invasive potential of tumor cells; thirdly, reduced intercellular adhesion increases the risk of metastasis and promotes tumor invasion [35].

In endometrial adenocarcinoma, overexpression of claudins-3 and -4 directly correlates with tumor grade. A significant increase in levels of claudins-1, -3, -4, and -7 compared to normal endometrial cells is observed in serous-papillary endometrial carcinoma, the most aggressive variant of type II estrogen-independent endometrial carcinoma. These tumor cells show decreased synthesis of claudins-2 and -5 [36].

The abnormal expression of the claudin-6 protein may result in disruption of integrity of tight junctions through various mechanisms; it is a factor in the tumor genesis and progression [37]. Available data indicate that claudin-6 is normally expressed in embryonic tissues of the stomach, lungs, and kidneys, but is not detected in healthy adult human tissues. [38, 39]. Other research, however, does not prove this thesis, and the mechanisms of claudin-6 expression regulation remain understudies and contradictory [40].

Claudin-6 is known to be expressed in various tumors and to play an important role in the tumor growth genesis and progression. Increased expression of claudin-6 has been demonstrated in endometrial carcinoma. Knockdown of the CLDN6 gene may suppress proliferation and migration of the HEC-1-B endometrial carcinoma cell line through the PI3K/Akt/mTOR signaling pathway [41].

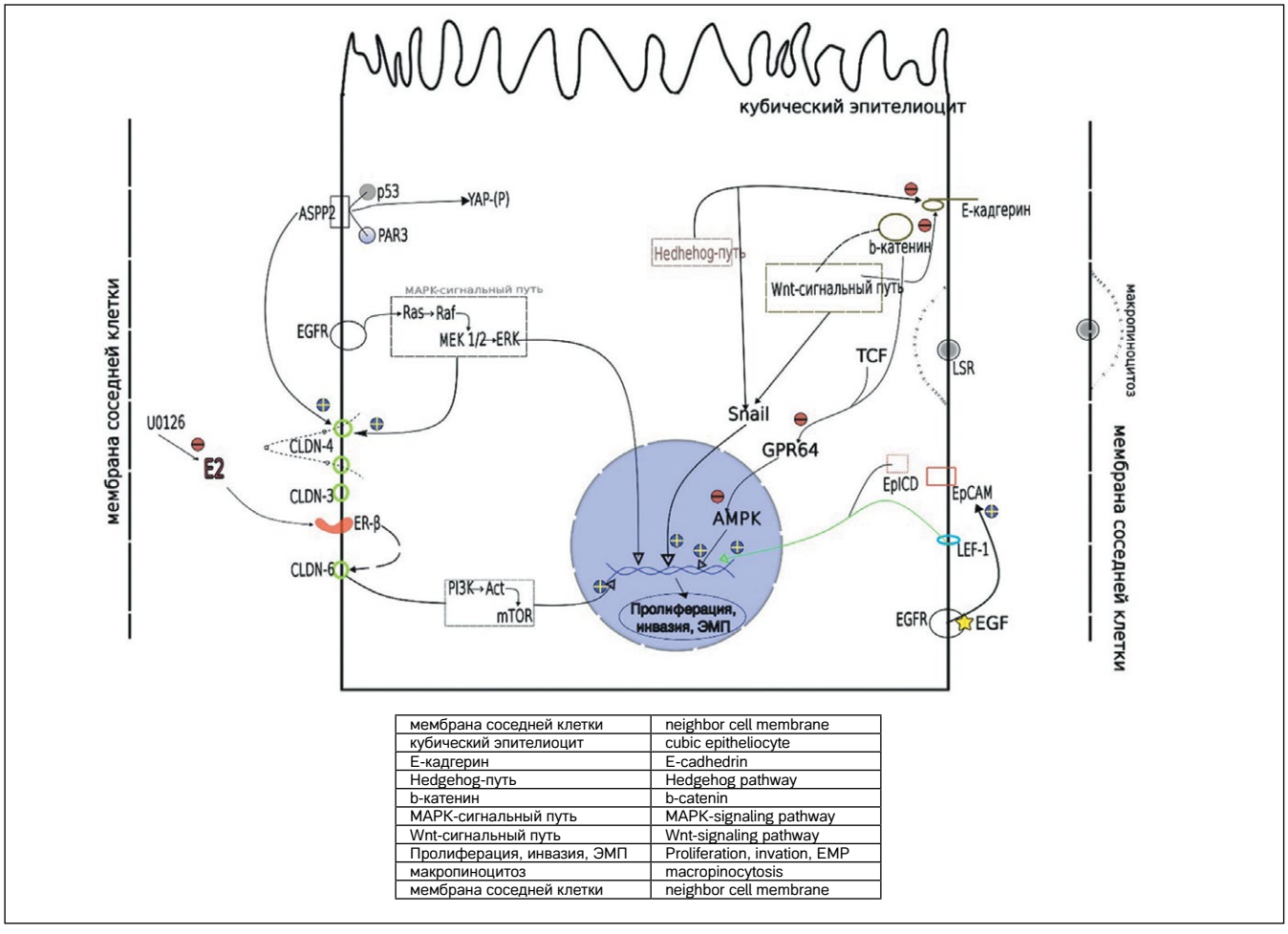
In epidemiological studies, C. Zhang *et al*. (2021) demonstrated that high claudin-6 expression serves as an independent prognostic factor for worse recurrence-free survival in endometrial cancer within the following clinical subgroups: age over 60 years; body weight over 80 kg; body mass index above 30; FIGO Grade IB or higher; postmenopausal status; large residual tumor after neoadjuvant chemoradiotherapy [42].

The influence of sex hormones on the expression of tight junction proteins, including claudins, is of interest. Thus, M. Someya *et al*. (2013) report that estradiol (E2) induces overexpression of claudin-3 and -4. Effects opposite to those described, i.e., a decrease in conditional 'pro-oncogenic' claudins, are mediated by progesterone (P4) stimulation. Barrier and fence functions in Sawano endometrial cancer cells were reduced under high-dose E2 exposure. These results indicate an increase in claudin-3 and -4 that do not fulfill tight junction functions under E2 influence in the pathogenesis of endometrial adenocarcinoma [41]. The question of biphasic effect of estradiol on claudin-4 expression remains debated [43, 44]. The biphasic effect of estradiol, within the scope of influence on the expression of tight junction proteins under consideration, is manifested in the increased expression of claudin-4 mediated by low doses of E2 and its suppression by high doses of estradiol.

It is necessary to explain the differences between the barrier and fence functions of tight junctions. The barrier function is defined by the ability of tight junctions to regulate the diffusion of soluble substances through intercellular spaces. Examples include hormones such as the aforementioned E2 and P4. The fence function of tight junctions consists in their ability to prevent mixing of molecules from the apical membrane domain with molecules of the lateral cell membrane surface.

The increased expression of claudin-3 induced by E2 is suppressed by the MAPK pathway inhibitor U0126. A decrease in claudin-4 expression is also observed under conditions of inhibited intracellular signaling through both the MAPK pathway and Hedgehog pathway (inhibitor: cyclopamine).

It has been established that estrogens regulate claudin-6 expression at the transcriptional level through estrogen receptor beta (ER-β). ER-β activation can trigger tumor cell autophagy via claudin-6 overexpression and inhibit migration



мембрана соседней клетки	neighbor cell membrane
кубический эпителиоцит	cubic epitheliocyte
E-кадгерин	E-cadhedrin
Hedgehog-путь	Hedgehog pathway
b-катенин	b-catenin
МАРК-сигнальный путь	MAPK-signaling pathway
Wnt-сигнальный путь	Wnt-signaling pathway
Пролиферация, инвазия, ЭМП	Proliferation, invation, EMP
макропиноцитоз	macropinocytosis
мембрана соседней клетки	neighbor cell membrane

Figure 1. *Relation of membrane structures to intracellular signaling pathways complicit in the malignant transformation of endometrial glands.*
Рисунок 1. *Связь мембранных структур с путями внутриклеточной сигнализации, опосредующими злокачественную трансформацию желез эндометрия.*

and invasion in breast cancer cells. There are other claudin family proteins whose expression is altered by sex hormones (**Fig. 1**).

Connexin proteins

Disruption of gap junction contacts, or aberrant connexin expression, represents one of the key mechanisms in carcinogenesis. In endometrial carcinoma cells with hyperplasia, the synthesis of Cx26 and Cx32 proteins, as well as Cx43 in endometrial stromal cells, is reduced, leading to impaired gap junction intercellular communication. Studies indicate that dysregulation of gap junction intercellular communication may occur at relatively early stages of endometrial carcinogenesis. The correlation between reduced connexin synthesis and cancer progression is supported by the fact that estrogen receptor-alpha activation, a major etiological factor in endometrial hyperplasia and adenocarcinoma development, disrupts gap junction communication and downregulates expression of connexins Cx26 and Cx32 in endometrial carcinoma cells [45].

CONCLUSION

The classical understanding of endometrial cancer pathogenesis describes it as a condition arising from abnormally high proliferative activity of glandular structures under the influence of external and internal factors. The primary contributing factors include sex hormones, directly affecting cellular metabolism in cells expressing nuclear estrogen and progesterone receptors. Another significant factor of excessive proliferation is local hypoxia. It occurs in various pathological processes, such as inflammation, local and systemic circulatory disorders, and impaired nutrient utilization, which force cells to switch to anaerobic glycolysis and beta-oxidation of lipids, which in turn become major sources of free radicals in cells.

In addition to the aforementioned factors, attention should be paid to the intrinsic properties of epithelial cells that contribute to maintaining normal histoarchitecture. We have attempted to compile data on the relationship between widely expressed molecular components supporting homeostasis, such as EGFR, and minor specialized components involved in maintaining cellular polarity and monolayer organization.

Identification of molecular disorders occurring in the tumor cells allows clarification of biological properties of the tumor, their role and place in the tumor growth pathogenesis and prognostic significance. While some molecules acts as potential malignancy markers, others may indicate degree of malignity, serve as outcome predictors or as direct targets for targeted treatment with drug.

For the diagnosis of endometrial cancer, the following markers are clinically significant in practice: tumor suppression markers (p53), differential diagnostic markers for determining histogenesis (p16), tumor receptor profile

markers, tumor proliferative potential markers, and specific antigen markers.

Intercellular contacts mediate interactions between tumor cells and their microenvironment. We have attempted to summarize available data on tumor cell interactions with the external environment and metabolic changes that enhance proliferation, invasion, and metastatic potential.

Development of classification of endometrial carcinoma based on the alteration of cellular junction protein alterations might be an interesting task in the study of this pathology. There exist epidemiological data, albeit unsystematized, that indicate differences in the survival of patients with endometrial cancer and various profiles of claudim cadhedrin proteins and other cellular adhesion molecule expression.

We believe that an association exists between altered E-cadherin expression patterns in tumor cells in EEC and increased cellular motility. In our opinion, such patterns are to include loss of E-cadhedrin expression near the apical membrane and its preservation only along the basolateral surface of the cells undergoing malignant transformation. Considering the important role of EMT in carcinogenesis in EEC it might be allowed that the combination of E-cadhedrin loss near the apical membrane and the aberrations in claudin expression (replacement of one claudin type with another, loss of claudins normal for the type of tissue) are to be considered molecular pattern of a risk of malignant transformation. It is suggested that data on alterations in the structure and function of intercellular junctions will have the highest clinical relevance when examining diagnostic specimens (scrapings). Further detailed investigation of the clinicopathological role of intercellular junction molecules will help clarify the biological properties of tumors and facilitate the development of drugs targeting this aspect of tumor growth.

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