The role of adhesive molecules in endometrial cancer: part I

Rola molekuł adhezyjnych w raku endometrium. Część I

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Abstract

The carcinogenesis is a result of both functional and structural disorders in the tissue. It initiates as a mutation in a gene encoding protein that is essential for cellular function. The subsequent cascade of events leads to accumulation of mutations and loss of cellular function. The cell loses its tissue-specific morphology, disconnects from other cells and extracellular matrix and migrates – the invasion begins. It is now clear that adhesive molecules are a key player in this cascade. These proteins of the cell membrane surface are responsible for attachment of the cells to each other and to the extracellular matrix. These interactions are crucial for both structural and functional tissue organization. Lack of this homeostasis destroys the tissue architecture, impairs its function and results in invasion. Abnormal expression of adhesive molecules was reported in all examined cancers, including endometrial cancer.

Endometrial cancer is the most common gynaecological cancer in developed countries. Although in many cases it is diagnosed and treated in early stages, and thus with good results, some patients cannot be cured. A complete knowledge of the pathogenesis of the disease will be helpful in identifying patients with negative prognostic factors, increased risk of recurrence and, perhaps, finding other therapeutic options. In the paper we are trying to sum up the up-to-date knowledge of the role of adhesive molecules in pathogenesis of endometrial cancer.

Key words: adhesion, adhesive molecules, carcinogenesis, invasion, metastasis.

Streszczenie

Nowotworzenie to wynik zaburzenia struktury i funkcji tkanki na wielu poziomach. Proces zaczyna się od mutacji w kluczowym dla komórki genie, kodującym istotne dla procesów komórkowych białka. Następuje kaskada wydarzeń prowadząca do kumulacji mutacji i zaburzająca funkcję komórki. Traci ona charakterystyczną dla tkanki morfologię, ścisły kontakt z otoczeniem i zaczyna migrować – rozpoczyna się inwazja. Jak się okazuje, istotną rolę w tej kaskadzie odgrywają molekuły adhezyjne – powierzchniowe białka błon komórkowych, odpowiadające za połączenia komórek między sobą oraz komórek z przestrzenią międzykomórkową. Pełnią one kluczową funkcję w strukturalnej i funkcjonalnej organizacji tkanek. Naruszenie wyznaczonego przez nie porządku prowadzi do zaburzenia struktury i funkcji tkanki oraz rozwoju fenotypu inwazyjnego. Wykazano nieprawidłową ekspresję wielu molekuł adhezyjnych we wszystkich badanych nowotworach, w tym w raku endometrium. Jest on obecnie najczęstszym nowotworem złośliwym narządów płciowych kobiet w krajach rozwiniętych, w tym w Polsce. Choć w większości przypadków jest rozpoznawany we wczesnym stadium, kiedy rokowanie jest dobre, części pacjentek nie udaje się wyleczyć. Poznanie biologii tego nowotworu może ułatwić identyfikację pacjentek z rakiem endometrium o gorszym rokowaniu oraz, być może, znaleźć nowe opcje terapeutyczne. Poniższa praca jest próbą przedstawienia obecnego stanu wiedzy na temat roli adhezyn w patogenezie tej choroby.

Słowa kluczowe: adhezja, molekuły adhezyjne, karcynogeneza, inwazja, przerzut.

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Introduction

Endometrial cancer is currently the most common malignant neoplasm of female genital organs in developed countries. In Poland the morbidity systematically increases and recently it reached a level comparable with high developed countries of 14.3 per 100,000 inhabitants in 2007 (standardized morbidity ratio), which gives it the fourth place among all female malignant neoplasms. Despite that, endometrial cancer mortality is low and amounts to 2.2 per 100,000 inhabitants (in 2007), which places this disease beyond the top ten female malignant neoplasms [1, 2]. This results from quite a high recognition rate in early stages of the disease, when prognosis is very good [3, 4]. However, some patients, especially those with unfavourable prognostic factors, cannot be cured. It concerns patients in advanced stages of the disease, with the presence of distant metastases and lymph node metastases, profound infiltration of uterus muscle, high grade carcinoma – often of a clear cell or papillary-serous type. A better knowledge of cancer biology is certainly a key to therapeutic success. Although spectacular successes have been achieved in this field so far, still many mechanisms crucial for carcinogenesis need to be explained. One of the mysteries to be solved seems to be the role of adhesive molecules in the development of endometrial cancer. For several years the adhesive molecules have been the subject of intensive research in the context of their role in pathogenesis of various neoplasms. Many mechanisms, in which adhesive molecules participate, are undoubtedly common for most neoplasms. However some of them are distinctive for particular tissues and histological types of tumours. To a smaller extent, endometrium has also been the subject of research with regard to the role of the adhesion phenomenon in the process of carcinogenesis.

Phenomenon of cellular adhesion. Adhesive molecules

Almost all cells require constant contact – junction with surrounding extracellular matrix (ECM) and other cells. Interactions resulting from adherence of cells to surroundings determine a proper structure of tissues and their functioning. Lack of adhesion between cells and cells & extracellular matrix leads to architectural tissue disintegration and impairs its function. Such a situation occurs in malignant neoplasms and the process of carcinogenesis at each stage proceeds with disorder of this tissue homeostasis [5, 6]. Three groups of macromolecules: adhesive molecules, extracellular matrix (ECM) proteins and proteins of the so-called "adhesive plate", binding adhesive molecules with cell cytoskeleton, form functional complexes that are responsible for adhesion [7].

Extracellular matrix

Extracellular matrix (ECM) is a "scaffolding" built from macromolecular proteins, glycosaminoglycans and proteoglycans, responsible for keeping a proper tissue structure. Cells adhere to this scaffolding through specialized adhesive molecules, mainly integrins and CD44. Such an interaction, apart from the structure, determines proper communication between cells and their function: a correct tissular identification of cells, cell differentiation, regulation of growth, proliferation, apoptosis or migration [6–8].

Loss of contact between the cell and ECM through proper integrins in a healthy tissue leads to apoptosis, the so-called anoikis. Cancer cells, despite the loss of contact with extracellular matrix, are not subject to apoptosis though. Hence a crucial antineoplastic role of anoikis in healthy tissues is suggested [6–8].

Among ECM components hyaluronic acid (HA) plays a particularly significant role in carcinogenesis. Due to its strong negative charge, hyaluronic acid binds a large amount of water causing tissue relaxation and making space for moving cells (migration & invasion). Its main cellular receptor is CD44 [9]. Dynamic changes of cellular receptors affinity (local increase and decrease), both of integrin-type as well as CD44, to matrix proteins and hydrated hyaluronic acid are responsible for cell migration e.g. in the process of neoplastic invasion.

Adhesive molecules

As it was mentioned, adhesive molecules are a few families of transmembrane particles responsible mainly for adherence of cells to extracellular matrix and cells between each other (both homo-, and heterophilic adherence). Thus, their presence determines a correct tissue structure and functioning, outside-in & inside-out cell signalling which control the most important cellular processes including gene expression, cell growth cycle, apoptosis and migration [6–10].

The role of adhesive molecules in carcinogenesis has been the subject of intensive research for several years. Yet in the 1940 it was proved that separation of cancer cells required much less force than disruption of junctions between cells of a healthy tissue [11].

Cadherins

Cadherins is a family of adhesive molecules responsible for adherence of homologous cells (of one kind). This process is crucial for tissue architecture and prevents "escape" of cells to surrounding tissues [7]. The main representatives of this family are the so-called classical (type-I): N-, P-, E- and R-, B-cadherin and about 10 other particles (so-called atypical cadherins of type-II) [6, 12]. Extracellular cadherin domains of two neighbouring

cells combine with each other via lateral dimerization (zipper mechanism), making homotypic junction dependent on Ca^{2+} ions [7, 12, 13]. Cytoplasmic cadherin domain combines with a cytoskeleton protein – actin, through catenins β, α & γ [7, 8, 12]. This complex is not only structural but, first of all, functional. Catenins determine correct functioning of cadherins and reduction of their expression or weakening of this compound's force leading to dysfunction of cadherins and cadherin-dependant adhesion [7, 8]. Cadherins play a crucial role in organization of tissue structure during ontogenesis and maintaining it in a mature organism [12, 13]. Loss of cadherin function or cadherin-catenin complex in a mature organism leads to relaxation of intercellular junctions and disruption of tissue structure allowing for progression towards an invasive phenotype.

The cadherin-catenin complex plays a significant signalling role in cell process control, taking part in Wnt signalling cascade, responsible for regulation of the cell growth cycle [7, 12, 13]. Moreover, the cadherin-mediated junction between cells stimulates itself an intracellular tyrosine phosphorylase and events dependent on it. The cadherin-catenin complex also participates in signalization via Ras pathway and signalling pathways controlled by integrins [7]. E-cadherin is a model cadherin, one of the most important epithelial adhesive molecules, which makes complexes, the so-called adherence junctions (or zonula adherens), between cells of the same type [7, 8, 12]. This epithelial cadherin, playing a particular role in neoplastic invasion, is encoded by the CDH1 gene, which – as the first ever – was called a suppressor gene. A lot of experimental research and studies determining expression of this adhesive molecule in healthy epitheliums and cancers have proved its important role in carcinogenesis [8, 13]. Antibodies against E-cadherin destroy intercellular junctions, changing tissue morphology and increasing cell invasiveness. Stable epithelial cells are subject to metamorphosis into mobile, invasive cells of fibroblast morphology [12]. Loss of E-cadherin or its reduced expression have been observed in the vast majority of examined cancers: in colon, breast, oesophagus, lungs, prostate, head and neck squamous cell carcinoma, cancer of pancreas, endometrium (including our own research, not published yet) or uterine cervix in almost all research. Loss of E-cadherin correlates with increased cancer invasiveness, predisposition to metastases, high FIGO classification, low grade and worse prognosis [12–15]. However transfection of cancer cells with cDNA encoding E-cadherin decreases its invasive potential [12]. An important role in the process of oncogenesis is also played by N-cadherin, encoded by the CDH2 gene and called an invasion promoter. An increase in expression of N-cadherin accompanied by a loss of E-cadherin is observed in cancers while gaining invasive potential (so-called cadherin switch) [8].

Because of the role of endometrium in reproduction, especially at the moment of implantation and cyclic, hormone-dependent changes of tissue morphology, adhesive molecules, including cadherins, play a particular role in endometrial cells. E- & P-cadherins were discovered in glandular epithelium – but not in stroma, in the course of the whole menstrual cycle but their location changes according to the hormonal phase [12, 16]. Before menstruation E-cadherin, α- & β-catenin concentrate near intercellular junctions. This order is destroyed during menstruation when cadherin-dependent intercellular junctions break and the tissue disrupts [12, 17]. Cadherins seem to play a crucial role in the process of blastocyst implantation. E-cadherin is present both in trophoblast cells and in endometrium. Progesterone (and also estradiol), whose role is to prepare endometrium for receiving blastocyst, stimulates the expression of E-cadherin [12, 17].

At the turn of the 20th and 21st century, after a series of work on the role of cadherins, especially E-cadherin, in other cancers, some research concerning their role in endometrial cancer was published. The results mostly proved the role of these adhesive molecules in oncogenesis, which is well-known from other cancers. It turned out that in endometrial cancer the expression of E-cadherin was getting weaker or the function of the so-called E-cadherin complex (catenins, proteins p120CAS, IQGAP1) was impaired [15, 16, 18, 19]. Reduced expression of E-cadherin in endometrial cancer correlates with clinical and pathologic parameters of the disease: grade [16, 19–22], with non-endometrioid types of endometrial cancer [14, 18–21], a high stage according to FIGO classification [18, 19], deep myometrial invasion [19, 22] and ability to invade beyond the uterus and to form remote metastases [16, 19–21], including lymph node involvement [14, 22]. Tumours with a low expression of E-cadherin reveal clear predisposition to invasion. In some research a disordered expression of E-cadherin turned out to be an independent unfavourable prognostic factor [14, 19, 21]. However, some reports on the role of E-cadherin in endometrial cancer have led to conclusions that are surprising from the theoretical point of view. Mell et al. [21] demonstrated a positive correlation of expression of E-cadherin and depth of myometrial invasion. The authors put forward a hypothesis that, perhaps, in advanced stages of cancer, with remote metastases, E-cadherin is re-expressed, like in breast and prostate cancer. Schlosshauer et al. [23] stated that the expression of E-cadherin was higher in serous cancer than in low-differentiated endometrial cancer. Also other cadherins, particularly P-cadherin, turned out to play a significant role in the progression of endometrial cancer. Its excessive expression, especially in combination with loss of E-cadherin (so-called cadherin switch) would have a significant unfavourable prognostic value [19]. Such a cadherin switch has

already been observed for E-cadherin & N-cadherin in prostate cancer and head & neck squamous-cell carcinomas [8].

Integrins

Integrins are a very large family of adhesive molecules, present in cells of all tissues, responsible above all for interaction of cells with extracellular matrix and also between cells [4, 8, 17]. These are heterodimers composed of common chain β, similar for all types, and chain α uncovalently connected with it and specific for each integrin, which is responsible for ligand properties. Currently at least 9 isoforms of chains β & 15 isoforms of chain α are known, each with different specific adhesive and signalling role [6, 24]. A large amount of various integrins are involved in an enormous number of interactions and thus play a very important signalling role.

Integrins, contrary to cadherins, are responsible for creating mainly heterotypic, heterophilic intercellular junctions. These junctions are responsible for adhesion of cells of various types and result from interaction of integrins with other adhesive molecules, mainly belonging to the immunoglobulin-like superfamily, e.g. ICAM-1, ICAM-2, VCAM-1 [8]. They play a crucial role in a metastatic cascade at several stages and they can both act as invasion promoters and inhibitors [8, 10]. Binding of integrins with their ligands in extracellular matrix, mainly with laminin, collagen, fibronectin, thrombospondin, vitronectin, von Willebrand's factor and complement component C3b1 is decisive for the cell contact with its surroundings. These interactions are crucial for tissue organization during ontogenesis, cell migration and differentiation. In a mature organism integrins are responsible for maintenance of tissue structure, they participate in wound healing, inflammatory reaction, clot formation and platelet aggregation [4, 6].

Integrins, bound to their ligands and activated, become a transmitter of outside-in & inside-out cell signalling. Those signals are responsible for regulation of vital cellular processes like tissue identification, regulation of proliferation, apoptosis, differentiation and expression of genes [4, 24].

Dysfunction of this interaction leads to incorrect functioning of tissue cells, including oncogenesis and cancer invasion. Conversely, in a healthy tissue loss of junction between integrins and ECM induces a programmed death of epithelial cells (already mentioned anoikis). It can be prevented by stimulation of expression of specific integrins [4].

In most cases, in humans, cancer cells express the same integrins as the cells of healthy tissues. However, appearance of new integrins, disturbance or even loss of expression were also described [25]. Disorganization of integrin expression appears as early as at initial stages of oncogenesis. Administration of monoclonal antibodies against β1-integrins in breast cancer caused a change of tissue morphology into non-malignant: cell divisions were inhibited, junctions between cells were reconstructed as well as cytoskeleton and cell polarization [4]. It was shown that some integrins can activate metalloproteinases which are responsible for destroying extracellular matrix in the process of invasion [6]. Integrins are responsible for local, dynamic changes of adhesion forces towards extracellular matrix and migration of cancer cells. Weakening of adhesion in primary tumour allows for escape of cells whereas local intensification makes their migration along ECM proteins possible. This migration and further adhesion to basement membranes are dependent on integrins [4, 6]. Cancer cells circulating in vessels form conglomerates with thrombocytes, for which integrins are responsible as well. VLA-4, an integrin present on cancer cells membranes, can be responsible, by analogy to leucocytes in the inflammatory reaction, for binding these cells via VCAM-1, to the endothelium and arresting them by the vessel wall. This allows for extravasation of cancer cells to the target tissue [6]. An increased activity of integrins in a newly formed vessel endothelium during intensive angiogenesis is observed and administration of monoclonal antibodies against these integrins inhibits the development of metastatic tumours in animals [4].

In healthy endometrial epithelium, the expression of α2, α3, α6 and β4 of integrins was shown, and the expression of α1, α4 and αvβ3 proved clearly dependent on the menstrual cycle: all of them appear in the secretory phase and the first one in the periovulatory period. To a smaller degree they are present in postmenopausal endometrium and endometrial cancer. In endometrial cancer the spectrum of adhesive molecules is similar to that observed in healthy tissue. In most cases a gradually decreasing expression is being observed along with a grade increase, whereas this tendency is most evident in the case of α6β4 integrin. Loss of α6β4 is particularly distinct on cells tearing off the basement membrane. On the other hand, a loss of α2β1 would be connected with an increased risk of lymph node metastases, regardless of depth of myometrial invasion or grade [25]. In endometrial cancer, like in breast, colon, gastric or ovarian cancer, there was revealed an increased expression of αvβ6 integrin, a significant mediator of TGFβ activation, especially in low-differentiated and metastatic tumours. However, the expression in primary tumour did not reveal any correlation with depth of myometrial invasion or presence of metastases themselves [26]. A disproportion in expression of subunits αv (85%) & β3 (26%) was also observed [25]. In endometrial cancer a significant inhibition of β1c integrin chain expression is observed – a variant which, contrary to β1a, inhibits proliferation of epithelial cells and is a crucial regulator of this process [27].

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