Advances in Medical Sciences 64 (2019) 423–429

Contents lists available at ScienceDirect

Advances in Medical Sciences

journal homepage: www.elsevier.com/locate/advms

Review article

Cell adhesion molecules in endometrial cancer – A systematic review

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ARTICLE INFO

Keywords:
Adhesion molecules
Cadherins
Catenins
Endometrial cancer
Immunoglobulin superfamily

ABSTRACT

Adhesive molecules are responsible for the cell-cell interaction and the surrounding intercellular environment creating normal tissue architecture. The role of adhesion proteins in cancer refers to angiogenesis, loss of tissue continuity, and deprivation of intercellular contact with the extracellular matrix, promoting the spread of cancer through the formation of metastases. The integrity of the epithelium is disturbed – with disturbances in the whole mechanism of cell connections, thanks to which cancer cells infiltrate surrounding tissues, and move to lymphatic and blood vessels. Adhesive molecules are divided into five main families: cadherin, catenins, integrins, the immunoglobulin superfamily and non-classical adhesion molecules. In the present review we describe the role of all five families of adhesive molecules in endometrial cancer.

1. Introduction

Endometrial cancer is the 15th most common malignancy in the world (according to 2018 statistics by the World Cancer Research Fund). Its incidence rates vary nearly 30-fold between countries worldwide. It is estimated that 2/3 of endometrial cancer cases occur in highly developed countries, mainly in northern and eastern Europe and North America. The risk of developing the disease is much higher in women in postmenopausal age and lower in women in premenopausal/perimenopausal age. It ranks 11th in the world among deaths from malignant tumors [1–3]. The 5-year survival rate for women with FIGO stage I and II is 74–91%, FIGO stage III 57–66% and FIGO stage IV 20–26% [4].

Over 80% of endometrial cancers is endometrioid adenocarcinoma associated with excessive estrogen secretion due to obesity, diabetes, hypertension, late menopause, nulliparity or hormone replacement therapy. However, obesity is a major factor in both pre- and postmenopausal age. In older women, androgens stored in fat tissue are aromatized and transformed into endogenous estrogen. Its excessive concentration stimulates chronically the endometrial tissue [3,5]. An increase in estrogen concentration may also contribute to the development of endometrial hyperplasia. Typical simple endometrial hyperplasia shows approximately 1% risk of endometrial cancer, whereas in typical complex hyperplasia the risk increases to around 3%. In contrast, atypical hyperplasia is associated with a high risk of developing cancer, even up to 30–40% [6]. The remaining endogenous risk factors include polycystic ovary syndrome, Lynch syndrome, estrogen secreting tumors, breast cancer or decreased immunity. The exogenous factors are exclusive estrogen therapy, tamoxifen therapy, dietary factors and previous radiotherapy [5].

Many genetic changes including microsatellite instability and mutations of oncogenes and suppressor genes have been described in the model of endometrial carcinogenesis. Therefore, two types of endometrial cancers have been distinguished. Type 1 includes estrogen-dependent endometrioid cancers characterized by good prognosis, high or moderate differentiation and location usually limited to the uterine body. This group mainly includes endometrioid adenocarcinoma and its variants: with squamous differentiation, viloglandular variant, secretory variant and ciliated cell variant. Carcinogenesis of this type is dominated by DNA replication errors, mainly satellite instability, and subsequent accumulation of mutations in genes such as: *PIK3CA*, *CTNNB1* (β-catenin), *PIK3R1*, *PTEN*, *ARID1A*, *MLH1* (*MSI*), *RASSF1A*. Type 2 (non-endometrioid) cancers characterize with mutations of the *TP53* and *PPP2R1A* genes, amplification of the *HER2/neu* gene, loss of heterozygosity of E-cadherin and at many other loci. This group includes others types of endometrial tumors, such as serous adenocarcinoma and clear cell adenocarcinoma. These types are not estrogen-dependent, have a poor prognosis due to rapid metastasizing and have a high risk of recurrence [5,7–11].

The most common method of treatment of endometrial cancer is surgery, depending on the advancement of the cancer: simple hysterectomy with adnexal removal in local disease, total abdominal hysterectomy in patients with apparent FIGO stage IIIB and in selected cases of FIGO stage IVA, sometimes also lymphadenectomy or omentectomy. Minimally invasive surgical treatment – laparoscopy, can be used in patients with apparent FIGO stage I endometrioid carcinomas with low

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https://doi.org/10.1016/j.advms.2019.08.003
Received 19 October 2018; Accepted 21 August 2019
Available online 17 September 2019
1896-1126/

to moderate risk of metastases to lymph nodes or in obese patients. In some patients, fertility-saving treatments may be included, but such criteria as endometrial intraepithelial neoplasia or well-differentiated endometrioid adenocarcinoma without muscular infiltration must be met. Such patients can undergo a 6-month hormone therapy. In adjuvant treatment, radiotherapy, chemotherapy, chemoradiotherapy and hormonal therapy are used. No approved targeted therapy is currently available for endometrial cancer. Clinical studies with mTOR inhibitors (PI3K/AKT pathway) showed a response below 10%. Also, tests with EGFR and HER-2, insulin/IGF1R or FGFR/VEGFR failed to bring the expected benefits [11]. However, attempts are being made to use trastuzumab in serous endometrial cancer, since in this histological type of estrogen-dependent cancer approximately 12–15% of cases show HER-2 gene amplification [11,12].

Considering the known involvement of genes such as *CTNNB1* (β-catenin) or *CDH1* (E-cadherin) in endometrial carcinogenesis, this review summarizes the role of adhesion protein expression in correlation with clinical-histopathological factors of endometrial cancer, and their diagnostic and therapeutic potentials.

2. Materials and methods

We carried out a literature review on July 10, 2018 using the MEDLINE/PubMed database (United States National Library of Medicine National Institutes of Health). The results were found by the keywords: (((((cadherin[Title/Abstract] OR e-cadherin[Title/Abstract] OR n-cadherin[Title/Abstract] OR p-cadherin[Title/Abstract] OR catenin[Title/Abstract]) OR integrin[Title/Abstract]) OR selectin[Title/Abstract]) OR igsf[Title/Abstract]) OR igcam[Title/Abstract]) OR icam[Title/Abstract]) OR vcam[Title/Abstract]) OR pecam[Title/Abstract]) OR ncam[Title/Abstract]) OR alcam[Title/Abstract]) OR l1cam[Title/Abstract]) OR cd44[Title/Abstract]) OR syndecan-1[Title/Abstract]) OR cd36[Title/Abstract]) AND ((endometrial cancer[Title/Abstract] OR endometrial lesions[Title/Abstract])).

In total, 282 articles were found (Fig. 1). We removed 2 articles since they were in duplicate and screened the remaining 280 articles of which we excluded 161 articles as we had no access to full texts, the articles were not published in English or the authors discussed other diseases. We then excluded 86 full-text articles since they presented too detailed analysis of pathways involving adhesion proteins, researches in the physiological states of endometrial tissues, endometriosis, cell line and animal studies or since they did not contain data useful for our analyses. Finally, 33 publications were analyzed in the present review. We also added to our analysis 27 publications which describe or review endometrial cancer and adhesion proteins: cadherins, catenins, integrins, immunoglobulin superfamily (IgSF) and non-classical adhesion molecules.

3. Review

Changes in adhesive properties are often associated with alterations in the expression and function of adhesion molecules that are commonly described in many cancers. These abnormalities give tumor cells an invasive and migrating phenotype. Deregulation of adhesion molecule expression is present at every stage of tumor invasion, including the detachment of tumor cells from the primary site, penetration into the interior of blood vessels, migration to distant organs and metastasis formation.

3.1. Cadherins and catenins

3.1.1. Cadherins

Cadherins are one of the most important adhesion molecules that mediate intercellular cell-cell adhesion. The cadherin family consists of classical cadherins that are calcium-dependent mediators of cell-cell adhesion and non-classical, including desmosomal cadherins and protocadherins. The most intensely studied are epithelial (E-), neural (N-) and placental (P-) cadherins. E-cadherins are expressed already in the embryonic development, in the blastula stage. They participate in the formation of endo- and ectodermal epithelium, and the loss of their

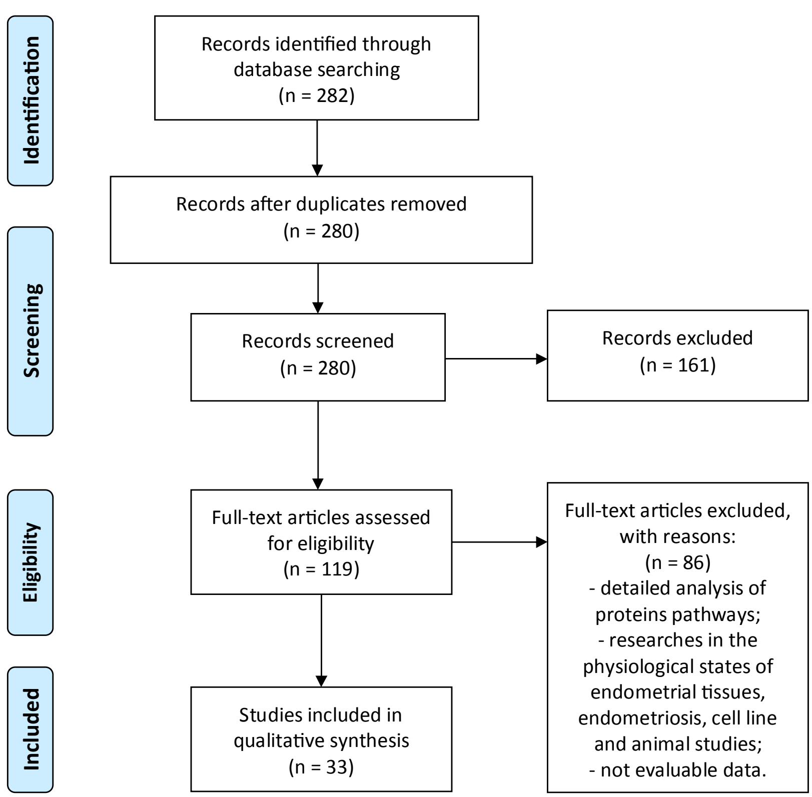

Fig. 1. PRISMA flowchart of study selection process. Adapted from Moher et al. [61].

expression in a certain group of cells leads to mesenchyme [13,14]. In mature organisms, they are expressed in epithelial cells and mediate the differentiation of the normal architecture of these tissues [13,15]. E-cadherins are membrane proteins. Their cytoplasmic domain interacts with a group of proteins called catenins, binding to β or γ catenin. Then the complex formed binds α-catenin, which directly affects the skeleton [16,17]. Frequently, tumors show a defect in the functioning of E-cadherin caused by the lack of a cytoplasmic domain (no interaction with catenins) or extracellular domain (no interaction with neighboring cells with simultaneous accumulation of catenins) and mutational changes. These disorders can lead to the detachment of tumor cells from the primary tumor mass, and thus increase their invasiveness [13,14].

In the normal endometrium, strong polarized expression of E-cadherin is observed. It is a membrane reaction, evenly distributed on the borders between cells. In simple endometrial hyperplasia, this expression is reduced but homogeneous. On the contrary, in the endometrium with atypical hyperplasia as well as in endometrial cancer cells, the expression is much weaker and located in the cytoplasm. In addition, various areas of tumor tissue show differentiated expression of E-cadherin, which reflects tumor heterogeneity of neoplastic epithelium [18–21].

Shaco-Levy et al. [22] also showed a significantly lower expression of E-cadherin in endometrial cancer compared to epithelial proliferation or endometriosis. Their study suggests that the loss of interactions of E-cadherins with the cadherin-catenin complex may become attenuated at an early stage of the hyperplastic process and is definitely involved in the progression of endometrial cancer. However, Ahmed et al. [23] showed higher expression of E-cadherin in endometrial cancer compared to atypical endometrial hyperplasia, but they did not differentiate between the membranous and cytoplasmic expressions.

The relationship between E-cadherin expression in tumor cells and the histological type of endometrial cancer has also been demonstrated. The loss of E-cadherin expression is more frequently observed in non-endometrioid cancers than in endometrial cancers [23,24]. In addition, the lower expression of E-cadherin also correlates with poorly-differentiated histological type (grade 3) according to FIGO [23,24]. Differences in the expression of cell adhesion molecules may therefore include changes in the types of histological differentiation of cancer.

Cancer stage may also be associated with abnormal E-cadherin expression. It has been demonstrated that the loss of E-cadherin expression is associated with deeper penetration of cancer cells into the myometrium, tumor proliferation in the uterus as well as metastasizing to the pelvic lymph nodes [25,26]. Ahmed et al. [23] also demonstrated a relationship of lower expression of E-cadherin with endometrial cancer cells infiltrating the lymph and blood vessels. Koyuncuoglu et al. [27] also observed a relationship of low expression of E-cadherin with III + IV infiltration rate as compared to I + II according to FIGO classification.

Moreover, the meta-analysis revealed a statistically significant relationship of E-cadherin expression reduction and overall post-operative survival in endometrial cancer [28]. These reports, however, are too few or not confirmed to indicate the prognostic potential of the expression of the adhesion protein E-cadherin. However, endometrial cancer patients with observed decreased E-cadherin expression may have poorer prognosis of the disease than patients with normal or higher E-cadherin expression.

P-cadherin, like other cadherins, regulates cellular homeostasis, by taking part in embryonic development, cell differentiation, maintaining the normal architecture of mature tissues, cell shape, polarity, growth and migration. It usually shows co-expression with E-cadherin, e.g. in breast and prostate epithelium. It is also involved in hereditary genetic disorders and in cancers [29]. Unlike E-cadherin, the expression of P-cadherin increases in tumor cells as compared to normal endometrium.

The increased expression of P-cadherin is also associated with a worse histological type of endometrial cancer, myometrium infiltration, dissemination in the uterus and metastases to local lymph nodes [25]. Stefansson et al. [30] also showed that higher expression of P-cadherin in endometrial cancer is associated with a shorter survival time for patients. In addition, the shift in the expression of E-cadherin to P-cadherin in tumor cells may be an important prognostic factor in endometrial cancer.

In contrast, N-cadherin is described as an adhesion protein of nerve cells. Interestingly, Singh et al. [31] showed high expression of N-cadherin more frequently in non-endometrioid tumors. However, they failed to find a correlation between N-cadherin expression and histological grade of the tumor. Further research may help to determine the contribution of N-cadherin to the histologic formation of endometrial cancer.

3.1.2. Catenins

Four types of catenins: alpha-, beta-, delta- and gamma- have been identified. α-Catenin binds cadherin-catenin complexes to cytoskeletal actin filaments by binding to vinculin and alpha-actin proteins. It has also been observed that α-catenin, not accompanied by other catenins in a complex, regulates the positioning of actin filaments. In this way, cadherin-catenin complexes stabilize epithelial architecture [32]. β-Catenin is also a component of cadherin-catenin complexes. It has armadillo repeat domain through which it participates in protein-protein connections. It also functions as a component of the Wnt signaling pathway, and can be an oncogene [33]. γ-Catenin (plakoglobin) is a constituent of desmosomes, although it may also bind to classical cadherins [17]. E-cadherin binds in a specific way to β-catenin or γ-catenin, while α-catenin combines with β-catenin or γ-catenin, but not with E-cadherin. Thus, there are two types of complexes: E-cadherin/α-catenin/β-catenin and E-cadherin/α-catenin/γ-catenin [17,33,34].

Similarly to E-cadherin, strong, uniform expression of α-catenin is observed in the normal epithelial endometrium (proliferative, secretive and atrophic endometrium). The hyperplastic epithelium exhibits weaker homogeneous reaction of α-catenin, whereas the atypical hyperplastic endometrium and endometrial cancer show weak and heterogeneous reactions [20]. This suggests that α-catenin downregulation may be associated with neoplastic transformation of endometrial tissues. Also, the expression of β-catenin decreases in the proliferating epithelium as compared to the normal endometrium. However, it has been demonstrated that the expression of β-catenin is much lower in endometriosis than in endometrial cancer [22]. However, Kim et al. [26] showed abnormal expression of α-catenin (loss of expression, heterogeneity, change in membranous location) in 27.3%, β-catenin in 18.2% and γ-catenin in 51.5% of endometrial cancer cases.

The impact of β- and γ-catenin expression location change from the membrane to the nuclear location has also been observed. Endometrial cancers with nuclear catenin expression were found to be poorly differentiated and more often associated with the presence of the second tumor [35]. Saegusa and Okayasu [36] described the relationship between β-catenin mutation and nuclear accumulation with squamous cell differentiation in G1 and G2 types of endometrial cancer. Schlosshauer et al. [37] observed nuclear expression of β-catenin in the subgroup of endometrioid adenocarcinomas, but not in serous cancer. The majority of endometrioid adenocarcinomas showed strong expression of β-catenin due to poor expression of E-cadherin. The researchers found that the expression patterns of E-cadherin and β-catenin are strongly associated with the histological subtype, which may help differentiate endometrioid adenocarcinoma and serous cancer as different entities and having separate genetic models. Mutational analysis of the *CTNNB1* gene revealed stabilizing β-catenin mutations in 10–20% of endometrioid endometrial cancers [38].

However, the status of the *CTNNB1* gene mutation in serous cancer is unknown. Abnormalities in the Wnt signaling pathway components may be involved in the pathogenesis of endometrioid tumors, and a common result is an increase in the level of β-catenin. The immunohistochemical staining pattern may also be useful for diagnostic purposes [35,32,38]. Singh et al. [31], however, did not show a correlation of the expressions of α-catenin, β-catenin and γ-catenin with the histological type and histologic malignancy grade of endometrial cancer. Scholten et al. [24] observed low expression of α- and β-catenin in poorly differentiated G3 cancers.

In correlation with the stage of endometrial cancer, only abnormal expression of γ-catenin was associated with the depth of tumor invasion in the myometrium. The expressions of α-catenin and β-catenin did not correlate with any clinical-pathological parameters [26]. Analyses of survival and catenin expression revealed only a relationship between low expression of β-catenin and shorter survival time of patients with endometrial cancer [30]. In addition, Kim et al. [26] found that the loss of expression of E-cadherin together with catenins predicts a much shorter survival than in the case of abnormalities in only one adhesion protein.

3.2. Integrins

Integrins are mainly engaged in the interactions between cells and the surrounding extracellular matrix (ECM), although some of them also interact with immunoglobulin type adhesion molecules present on the endothelial surface of blood and lymphatic vessels (ICAM, VCAM) [39]. Integrins are heterodimers built of α and β subunits that are non-covalently linked. So far, 18 different α and 8 β subunits are known, which through different combinations form 24 integrin complexes. Each cell can carry a variety of different integrins. They can bind multiple ligands, most of which bind to arginine-glycine-aspartate (RGD) amino acid sequences. This tripeptide is found not only in ECM macromolecules (collagen, laminin, fibronectin, vitronectin), but also in plasma (soluble fibronectin, fibrinogen, von Willebrand factor) and in cell surface proteins. In contrast, some integrins bind selectively to fibronectin or laminin. Due to their properties, integrins participate in complex processes such as blood clotting, inflammation, migration, tissue differentiation and cell division [40]. Very few studies have been conducted with the involvement of these proteins in endometrial cancer.

The beta 1C integrin is one of the adhesins investigated in this group. It is an alternative component of the variant of beta 1A integrin subunit, which contrary to beta 1A inhibits proliferation of epithelial cells. Normal endometrial epithelium exhibits high cytoplasmic expression of beta 1C. The expression of this protein was reduced in endometrial hyperplasia and was even much lower in endometrial cancer [41]. Moreover, the authors showed higher percentage of beta 1C integrins of immunoreactive cells in two well-differentiated cancers and lower percentage of it in two poorly differentiated endometrial cancers. However, the correlation between beta 1C integrin immunoreactivity and cancer differentiation, cancer stage or its histological type could not be statistically assessed due to a relatively small number of cases (N = 18) [41].

The expression alpha (v) beta (6) integrin (alphavbeta6) in endometrial cancer was also examined. Hecht et al. [42] showed that in the normal endometrium the expression of this integrin is weak, but it increases in endometrial cancer, especially in high-grade type. In addition, tumor cells in the lymph node metastases were strongly expressed, even when the alphavbeta6 expression was only focal in the primary tumor. However, no relationship was observed between the expression of this integrin and the histological type or the severity of the cancer.

3.3. Immunoglobulin superfamily (IgSF)

The IgSF family is the most numerous group of proteins, as well as the most diverse group (often called IgCAMs). Main members are intercellular adhesion molecules (ICAMs), vascular-cell adhesion molecules (VCAM-1), platelet-endothelial cell adhesion molecules (PECAM-1), and neural-cell adhesion molecules (NCAM). They are connected by extracellular domain, which contains 5–6 immunoglobulin repeats. Most of them are type I transmembrane proteins, built of the extracellular domain, single transmembrane domain and cytoplasmic tail. Due to Ig domains and/or the fibronectin type-3 domain, they create homophilic or heterophilic binds (interacting with integrins or carbohydrates) to form cell-cell or ECM cell-like connections. Intracellular domains interact with cytoskeleton proteins, so that they can participate in the signal transmission in the cell. Physiologically endothelial IgCAMs are involved in the immune response and inflammation. They play an important role in targeting leukocytes for selective storage in the inflamed area. In contrast, NCAM is implicated in neuronal patterning. The role of IgCAMs is also known in the development of cancers; L1 cell adhesion molecule (L1CAM), NCAM, melanoma cell adhesion molecule (MCAM), PECAM-1, activated-leukocyte cell adhesion molecule (ALCAM) and ICAM-1 are involved in proliferation, local invasion, dissemination, extravasation, colonization and also immunological escape of cancer cells [43].

The L1CAM, also known as CD171, is one of the most widely examined adhesion proteins among the IgSF. It is a membrane glycoprotein, which plays a key role in neurogenesis through the regulation of cell adhesion and migration. In endometrial cancer and in other malignancies, L1CAM expression in cancer cells promotes the disease progression by increasing cell motility and invasion, and promoting metastases [44,45]. An extensive study conducted by Bosse et al. [46] on a group of 865 patients with endometrial cancer showed that the expression of L1CAM is a strong independent prognostic factor for distant recurrences and overall survival in stage I endometrial cancer. Cancers with higher level of L1CAM expression (more than 50% of positive cells) exhibited a much higher risk of distant recurrence, especially to the lymph nodes of the pelvis.

In Cox's multivariate analysis with respect to risk factors, such as age, depth of invasion, histologic grade, invasion of the lymphatic spaces (LVSI) and mode of treatment, L1CAM expression remained an independent prognostic factor for distant recurrence and overall survival. Moreover, the role of L1CAM expression was assessed in 1021 cases of stage I endometrial cancer, where positive expression was noted in 17.7% of cases [46]. Patients with positive L1CAM expression were found to have worse disease-free survival and shorter overall survival. The prognostic importance of these parameters was strictly associated with positive but not with negative L1CAM expression. According to the authors, the expression of L1CAM in FIGO I type cancers indicates the need for adjuvant therapy. L1CAM may serve as the therapeutic target using fully humanized anti-L1CAM antibody, which is currently being prepared for the clinical use [47].

Another protein examined in the endometrial cancer is ALCAM. It participates in cell-cell adhesion through homotypic (ALCAM-ALCAM) or heterotypic (ALCAM-CD6) interactions between adjacent cells. ALCAM performs a function in the process of epithelial morphogenesis, hematopoiesis, inflammatory responses, neuronal outgrowth and also tumorigenesis of many cancers [48]. Immunohistochemical analysis shows a gradual increase in membrane expression of ALCAM from normal endometrium to atypical hyperplasia. Cytoplasmic expression has been reported in a few cases of simple and complex hyperplasia. In contrast, in endometrial cancer, mainly homogenously strong staining in all parts of the tumor is observed, rarely membranous or cytoplasmic strong staining or heterogeneous loss of membranous staining [49]. In extensive studies, Devis et al. [48,50] demonstrated a decreased expression of ALCAM in the tumor front along tumor stages and in tumors with myometrial invasion > 50%. In addition, ALCAM showed co-expression with epithelial markers (E-cadherin/β-catenin) at the superficial area, and with mesenchymal markers at the invasive front (COX-2, SNAIL, ETV5, and MMP-9). In patients with early-stage endometrial cancer, the relapse-free survival was worse in patients with ALCAM positive than in those with negative ALCAM. This difference was more significant in patients with early stage moderately–poorly differentiated tumors. In multivariate analysis, the positive reaction of ALCAM protein in cancer cells was an independent prognostic factor in the early stages of the disease. In addition, these studies have indicated ALCAM as an important molecule in the dissemination of endometrial cancer by regulating migration, invasion and cell metastasis [48,50].

3.4. Non-classical adhesion molecules

Apart from the described molecules mediating cell adhesion, there are also other molecules, e.g. CD44 or Syndecan-1 that do not fit in the separated groups of cadherins, catenins, selectins, integrins and immunoglobulin (IgCAM) superfamily. The neoplastic process is frequently associated with the expression of various CD44 isoforms, which in normal conditions can promote cancer cell migration to the lymphatic structures, and thus metastasis formation.

The first reports on the adhesion protein CD44 revealed that the expression of CD44 isoforms may play a role in the functional changes in normal endometrium. Tempfer et al. [51] showed that the expressions of CD44v3, CD44v5, CD44v6 and CD44v7-8 isoforms in normal endometrial tissue are higher in the secretory phase as compared to the proliferative phase of the menstrual cycle. In this study, the expressions of CD44v3, CD44v5 and CD44v7-8 isoforms in the group of patients with endometrial cancer had no prognostic effect. The monodimensional analysis demonstrated a correlation between CD44v6 expression with reduced survival time. However, the multivariate analysis correcting the unstable histologic malignancy grade revealed that CD44v6 is not a prognostic factor in endometrial cancer [51]. On the contrary, Leblanc et al. [52] found overexpression of CD44 (variants encoded by exons 3–10) and CD44v3 in endometrial adenocarcinomas as compared to normal endometrium. No such correlation was noted for CD44v6 isoform. A correlation was observed of CD44 overexpression with lymphatic space infiltration and myometrium invasion. Also, Wojciechowski et al. [53] noted that the expression of CD44 in endometrial cancer was much more intense than in normal endometrium. Moreover, the expression of CD44 was weaker in serous cancers than in endometrioid tumors. However, they found no statistically significant correlation between CD44 expression and clinicopathological features such as histologic grade, depth of invasion, infiltration of the uterine cervix, infiltration of the serous membrane and appendages, invasion of lymphatic spaces, lymph node involvement and distant metastases, i.e. FIGO stage.

The subsequent studies on the expression of CD44s (standard form, comprises exons 1–5 joined to exons 16–20) and CD44v6 isoform in normal endometrium, endometriosis and adenomyosis also showed lack of reactions of these proteins in the proliferative phase and a positive expression in the secretion phase. The expression of these proteins in endometrial hyperplasia was similar to that observed in normal proliferative endometrium, whereas endometrial adenocarcinomas demonstrated abnormal positive reactions to CD44s and CD44v6 [54]. Hoshimoto et al. [55] compared the expression of CD44s, CD44v3 and CD44v6 in endometrial hyperplasia with endometrial cancer. The expression of CD44s was similar in both lesions. The expressions of CD44v3 and CD44v6 were rare or missing in endometrial hyperplasia, whereas in endometrial cancer they were positive in 8% and 35% of cases, respectively. Moreover, positive expression of CD44v3 showed a statistically significant correlation with tumor grade (G13 – poorly differentiated) and lymph node involvement. However, no correlation was found between the expression of CD44v6 and clinicopathological factors [55].

On the contrary, Stokes et al. [56] showed that a deeply invasive endometrial cancer is associated with constant lack of CD44v6 expression. In their study, the lack of CD44v6 expression was found in cancers invading > 50% thickness of myometrial tissue. They suggest that the lack of CD44v6 expression in endometrial cancer can be correlated with a more aggressive course. Also, Ayhan et al. [57] revealed an inverse correlation of CD44v6 expression with tumor size, lower uterine segment invasion, nuclear and structural grade, infiltration of the myometrium and serous membrane, invasion of lymphatic spaces and metastases to the appendages. Moreover, they found that patients with negative expression of CD44v6 in cancer cells showed a higher percentage of recurrences and shorter disease-free survival time.

Another well-known cell adhesion molecule is Syndecan-1, belonging to heparan sulfate proteoglycan family. As a cell surface receptor it takes part in cell-cell interaction, cell-matrix adhesion, and growth factor signaling. Therefore, it regulates important cellular processes, such as: migration, development, neovascularization, microbial pathogenesis and tumorigenesis [58]. Kim et al. [59] showed that expression of Syndecan-1 is statistically significantly greater in patients with complex hyperplasia without atypia or atypical hyperplasia than in simple hyperplasia, and statistically significantly greater in atypical hyperplasia in comparison to complex hyperplasia without atypia. Also, Syndecan-1 expression is more frequently positive in hyperplastic and malignant endometrial tissue than in normal endometrium. This report indicates that Syndecan-1 expression appears to be useful as a predictive indicator in endometrial hyperplasia. Another study showed that Syndecan-1 expression in endometrial cancer can be observed in both epithelial and stromal cells [60]. Moreover, the authors showed that epithelial Syndecan-1 expression is statistically significantly lower in advanced stage, high grade, deep myometrial invasion, cervical involvement, lymph node metastasis, lymph vascular space involvement and positive peritoneal cytology. Whereas stromal Syndecan-1 expression was statistically significantly higher in high-grade tumors. Changes in epithelial and stromal Syndecan-1 expression may be associated with tumor progression. Furthermore, Hasengaowa et al. [60] indicate that stromal Syndecan-1 expression can serve as an indicator of poor prognosis in patients with endometrial cancer. Its high stromal expression was an independent prognostic factor for both disease-free and overall survival.

4. Conclusions

Numerous studies indicate the involvement of cell adhesion disorders in the development of endometrial cancer. Especially differences in the expression of cell adhesion molecules may be related to the histological differentiation of endometrial cancer. The changes in their expression and location also contribute to the invasiveness of cancer cells. Cell adhesion molecules may become the therapeutic target of endometrial cancer in the future.

Declaration of competing interest

The authors declare no conflict of interests.

Financial disclosure

The authors have no funding to disclose.

The author contribution

Study Design: Łukasz Lewczuk, Katarzyna Guzińska-Ustymowicz.
Data Collection: Łukasz Lewczuk, Anna Pryczynicz, Katarzyna Guzińska-Ustymowicz.
Statistical Analysis: Łukasz Lewczuk, Anna Pryczynicz.
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Literature Search: Łukasz Lewczuk, Anna Pryczynicz.
Funds Collection: Katarzyna Guzińska-Ustymowicz.

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