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Pawel Zarebski[1], *Anna Zubkiewicz[2], Agnieszka Zubkiewicz-Kucharska[3]

Do adhesive molecules ICAM-1 and VCAM-1 affect the development and course of gastrointestinal tumors?

Czy molekuły adhezyjne ICAM-1 i VCAM-1 wpływają na rozwój i przebieg nowotworów przewodu pokarmowego?

[1]2nd Department and Clinic of General and Oncological Surgery, Wroclaw Medical University, Poland
[2]Department and Clinic of Gastroenterology and Hepatology, Wroclaw Medical University, Poland
[3]Department and Clinic of Endocrinology and Diabetology for Children and Adolescents, Wroclaw Medical University, Poland

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S u m m a r y

Solid tumors are composed of two compartments: cancerous cells constituting the essential mass of tumor and stromal tumor cells. Cell-cell and extracellular matrix-cell interactions are mediated by adhesive molecules (CAMs, cell adhesion molecules) and affect the growth, differentiation and migration of tumor cells. Abnormal ICAM expression may underlie in morphological disturbances, loss of cell-to-cell junctions, cytoskeleton disorganization, allowing cancer cells to detach from tumor mass and metastase.

The aim of this work is to present the current state of knowledge and results of new research on the expression of selected adhesion molecules: ICAM-1 and VCAM-1 in patients with esophageal, gastric and colorectal cancer.

Recently, the research of adhesion molecules in numerous cancers has been observed. It has been demonstrated that ICAM-1 participates in all stages of oncogenesis. The interaction of the host ICAM-1 with a ligand on a tumor cell and host cell during subsequent metastatic stages may become an attractive target for anticancer treatment. Studies have shown that VCAM-1 plays an important role in the process of tumor cell adhesion to endothelial cells and in the neovascularization process.

The concentration of soluble VCAM-1 in serum correlates with the expression of VCAM-1 in tumor tissue, and is significantly reduced after surgical removal of the tumor. In this aspect sVCAM-1 can be treated as a sensitive diagnostic and prognostic marker.

S t r e s z c z e n i e

Guzy lite zbudowane są z dwóch części: komórek zmienionych nowotworowo, stanowiących zasadniczą masę guza, i komórek podścieliska nowotworu. Interakcje komórka-komórka i komórka-macierz zewnątrzkomórkowa zachodzą przy udziale molekuł adhezyjnych (CAM) i wpływają na wzrost, różnicowanie i migrację komórek guza. Nieprawidłowa ekspresja CAM leży u podstaw zaburzeń morfologicznych, utraty połączeń międzykomórkowych, dezorganizacji cytoszkieletu, co pozwala komórkom nowotworowym na oderwanie się od masy guza i przerzutowanie.

Celem tej pracy jest przedstawienie aktualnego stanu wiedzy i wyników nowych badań dotyczących ekspresji wybranych molekuł adhezyjnych: ICAM-1 i VCAM-1 u chorych na raka przełyku, żołądka i jelita grubego.

W ostatnim czasie obserwuje się nasilenie badań molekuł adhezyjnych w licznych nowotworach. Dowiedziono, że ICAM-1 uczestniczy we wszystkich etapach ontogenezy, od bardzo wczesnych stadiów zapalnych poprzez etap adhezji komórek guza i leukocytów do komórek endotelium, do późnego etapu migracji komórek nowotworowych i zasiedlania kolejnych narządów. Interakcja ICAM-1 gospodarza z ligandem na komórce guza i komórce gospodarza w czasie kolejnych etapów przerzutowania może stać się atrakcyjnym celem leczenia przeciwnowotworowego. Badania wykazały, że VCAM-1 odgrywa istotną rolę w procesie adhezji komórek guza do komórek endotelium oraz w procesie neowaskularyzacji.

Stężenie rozpuszczalnego VCAM-1 w surowicy koreluje z ekspresją VCAM-1 w tkance guza i ulega istotnemu zmniejszeniu po operacyjnym usunięciu nowotworu. W tym aspekcie sVCAM-1 może być traktowany jako czuły marker diagnostyczny i prognostyczny.

Conflict of interest
Konflikt interesów
None
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Address:
*Anna Zubkiewicz
Department and Clinic of Gastroenterology and Hepatology
Wroclaw Medical University
ul. Borowska 213, 50-556 Wroclaw, Poland
tel.: +48 (71) 733-21-20
a.w.zubkiewicz@gmail.com

INTRODUCTION

Solid tumors are composed of two compartments: cancerous cells constituting the essential mass of tumor and stromal tumor cells. Tumor cells induce the formation of stroma, which is formed of connective tissue and blood vessels, and protects nutrition and gas exchange of tumor cells. Cell-cell and extracellular matrix-cell interactions are mediated by adhesive molecules (CAMs, cell adhesion molecules) and affect the growth, differentiation and migration of tumor cells (1). Abnormal ICAM expression may underlie in morphological disturbances, loss of cell-to-cell junctions, cytoskeleton disorganization, allowing cancer cells to detach from tumor mass and metastase. The adhesins allow tumor cells to stimulate angiogenesis and affect the formation of a metastase (2). The formation of new vessels is necessary to increase the tumor mass of both primary and metastatic lesions (3). The pre-cancerous state or the site of the secondary tumor focus may be inflammation, which is determined by the chemotactic action of pro-inflammatory cytokines as well as by the presence of adhesion molecules on the activated endothelium (2). Thus, tumor progression and its expansion into distant organs is strongly dependent on adhesion molecules, Numerous studies have shown that the clinical stage of the disease is a key prognostic parameter for the survival and recurrence of cancer (4). This means that the features characteristics for cancer cells such as the ability to survive, growth and forming metastatic leasions affect the overall survival of cancer patients, including esophageal, gastric and colorectal cancers.

The studies carried out in the last quarter of a century prove that adhesion molecules, on the one hand, participate in various stages of tumor angiogenesis, participate in its progression and metastasis, but on the other hand, adhesins, suppressor gene expression products have anticancer properties.

The aim of this work is to present the current state of knowledge and results of new research on the expression of selected adhesion molecules: ICAM-1 and VCAM-1 in patients with esophageal, gastric and colorectal cancer.

ICAM-1, VCAM-1: ADHESION MOLECULES FROM THE IMMUNOGLOBULIN SUPERFAMILY

Intracellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) belong to adhesion molecules from the immunoglobulin superfamily (IgCAM, immunoglobin cell adhesion molecule, IgSf, Immunoglobin Superfamily), to IgCAM system group (5).

ICAM-1 is glycoprotein with 80-114 kDa mass, the gene coding this protein is located on the short arm of chromosome 19 (19p13.2) (6). ICAM-1 occurs on the surface of endothelial cells, epithelial cells, e.g. thymus, fibroblasts, smooth muscle cells, and hematopoietic cells, e.g. on tissue macrophages, lymphoblasts, tonsil dendritic cells, lymph nodes and Peyer's patches. ICAM-1 plays an important role during a specific and unspecific immune response. ICAM-1 as major ligand for LFA-1 (lymphocyte function antigen 1) is an important factor in the process immunosurveillance (7). Strong ICAM-1 expression on lymphoma cells was demonstrated during transplant rejection and atherosclerotic lesions (8-10). ICAM-1 is a receptor for erythrocytes infected with *Plasmodium falciparum*, rhinoviruses, as well as some neurotrophic viruses, e.g. West Nile virus, Semliki Forest virus (SMV) and others (11, 12).

In the last decade, the relationship between the inflammatory process, insulin resistance, and disorders of carbohydrate metabolism and hypertension has been proven. The Salmenniemi study conducted on the obese adult group confirmed the relationship between ICAM-1 concentration and the occurrence of metabolic syndrome (13).

The vascular cell adhesion molecule 1 (VCAM-1) is a transmembrane glycoprotein of 110 kDa mass, made of 739 amino acids. The VCAM-1 coding gene is located on the short arm of chromosome 1 (1p21.2) (14). VCAM-1 expression induces proinflammatory reaction: IL-1, TNF-α or IFN-γ and lipopolysaccharides (LPS), mechanical factors – disturbed blood flow, and reactive oxygen species (ROS), lower antioxidants, ω-3 acids and nitric oxide. In 1990, VLA-4 (very late activation antigen-4) was identified, the first VCAM-1 ligand mediating B-cell adhesions in germinal centers (15). VCAM-1 was shown to be involved in the pathogenesis of autoimmune diseases, cardiovascular disease and infections (16). The main task of VCAM-1 is to control the movement of leukocytes, (with the exception of neutrofils on which VLA-4 is absent) across the endothelial barrier. Under the influence of proinflammatory cytokines, endothelial cells increase the expression of VCAM-1, which promotes adherence of monocytes to endothelial cells and is necessary in their migration. VCAM-1, which is absent at the resting endothelium cells, is detectable on dendritic cells of the lymph nodes, macrophages, bone marrow fibroblasts as well as on tumor cells, e.g. in acute lymphoblastic leukemia and acute myeloblastic leukemia, and in some central nervous system tumors (17).

ICAM-1 AS A MARKER OF NEOPLASTIC AND AUTOIMMUNE DISEASES

The involvement of adhesins in the pathogenesis of cancer and metastasis was the basis for their use in diagnostics and prognosis of cancers of lung, breast, genitourinary system, melanoma, pancreas and gastrointestinal tract. The combination of ICAM-1 on a tumor cell with LFA-1 on the surface of T lymphocytes results in an increase in their cytotoxic activity and sensitivity of tumor cells to lymphocyte-dependent cytotoxicity (18). It has been demonstrated that prostaglandin E2, produced by tumor stromal cells, inhibits the expression of ICAM-1 and thus reduces the cyto-

toxic effect of T lymphocytes (19). Such ICAM-1 activity could justify the results of research in breast, gastric and colorectal cancers, according to which an increase in ICAM-1 expression on cancer cells correlated with a better prognosis (20).

On the other hand, Schröder's and Rosette's observations showed a positive correlation between the expression of ICAM-1 and a more aggressive phenotype and greater metastatic potential in breast cancer (21, 22). Usami study in oral squamous cell carcinoma (SCC) have shown that ICAM-1 was expressed predominantly at the invasive front area of tongue SCC and correlated with invasion, lymph node metastasis and increased blood and lymphatic vessel density of the tongue SCC. Increased ICAM-1 expression in tongue SCC was correlated with increased macrophage infiltration within SCC nests. These findings indicate that ICAM-1 plays an important role in tongue SCC progression, which may result from the SCC-cell activity, angiogenic activity, lymphangiogenic activity and macrophage/SCC-cell adhesion (23).

The studies have shown that the contact between cancer cells and tumor stromal cells is directly influenced by tumor progression (24). Among tumor stromal cells, macrophages, referred to as Tumor Associated Macrophages (TAMs), support tumor progression by promoting tumor angiogenesis, tumor migration and intravention, and suppressing the immune response (25, 26). In some cancers, e.g. kidney cancer, ICAM 1 derived from cancer cells becomes a ligand between tumor cells and macrophages (27). It has been proved that this combination induces cell proliferation of kidney cancer, glioma cells, acts anti-apoptotic in malignant plasmocytes and prostate cancer cells resistant to hormonal therapy (28, 29). In 1991 a soluble form of ICAM-1 (sICAM1) was discovered and it was found that this isoform of ICAM-1 is also capable of binding to LFA-1 (30). The study showed that higher concentrations of sICAM-1 in serum of patients with cancer is associated with increased progression of the disease and poorer prognosis. Elevated concentrations of sICAM 1, which correlated with the progression of the tumor and distant metastases were found in melanoma, lung cancer, breast, liver and colon cancer (31, 32).

Thus, the biological significance of ICAM-1 and sICAM-1 expression in cancers remains controversial.

Increased sICAM-1 concentration was also demonstrated in the course of many autoimmune diseases, and its concentration correlated with the severity of the disease process. Some authors postulate the important role of sICAM-1 in the development of autoimmune inflammation process. However, other studies suggest that increasing the concentration of this adhesin in the course of the autoimmune or inflammatory process is a secondary effect associated with the anti-inflammatory reaction of the body and immunomodulatory properties of sICAM-1 (33).

VCAM-1-ITS ROLE IN TUMORIGENICITY AND METASTASIS

VCAM-1 is a multitasking adhesin that plays an important role in the adhesion of tumor cells to vascular endothelial cells, actively promoting tumor metastasis. Studies have also shown that it plays a key role in the angiogenesis process by allowing tumor growth. It has been proven that tumor microvessel density (MVD) correlates with tumor progression, hematopoietic metastasis and recurrences, e.g. in stomach cancer (34). The study showed that VCAM-1 can promote the migration of T cells, causing the accumulation of T cells in the tumor microenvironment (35). VCAM-1 expression was shown in breast, stomach, kidney, liver and melanoma cells (36). It is proven that in breast cancer, a strong expression of VCAM-1 in tumor tissue, significantly correlates with metastases to the lungs and bones and shorter survival (36-40). In the opinion of researchers VCAM-1 may be an independent prognostic factor in breast cancer, increased expression of this molecule correlates with a poorer prognosis (40).

The soluble form of VCAM-1 sVCAM-1 is the result of the exfoliation of VCAM-1 from endothelial cells, leukocytes and tumor cells. The high concentration of sVCAM-1, depending on the stage of the disease and its progression, was found in stomach cancer (41), large intestine (42), breast (43), prostate and bladder (44, 45).

EXPRESSION OF ADHESIVE MOLECULES IN GASTROINTESTINAL CANCERS

Esophageal cancer is pathologically classified into two major subtypes: esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC). The overall 5 yrs survival rate after surgical resection is 70-92% for patients without nodal involvement, but only 18-47% patients with lymph node metastasis (46).

Hosch's studies published in 1997 showed that the expression of HLA class 1 and ICAM-1 antigens on esophageal cancer cells was an important factor in reducing the risk of relapse, while the expression of ICAM 1 on HLA class I tumor cells was associated with a high risk of recurrence (47). According to Nair, the correlation between lymph node metastasis and the decrease in the expression of HLA class I antigens may indicate that tumor cell dissemination may be facilitated by the reduced ability of the immune system to recognize these cells (48).

In 2013, Liu proved that ICAM-1 can be a hepatocellular stem cell marker, and in 2015 Sheng Ta Tsai showed that ICAM-1 may be a potential marker for ESCC stem cells and thus serve as a therapeutic target in cytostatic therapy (49, 50). These studies have further demonstrated that ICAM 1 increases the metastatic potential of esophageal cancer cells, increases resistance to cytostatic drugs, e.g. cisplatin, and promotes tumorogenesis in mice with an inmunological defect. A negative correlation was also demonstrated

between ICAM-1 and p53 expression, suggesting that high expression of ICAM-1 may lead to cancer malignancy (50). Based on the meta-analysis of p53 expression on oesophageal cancer cells, it has been shown that this is a beneficial prognostic factor and correlates with overall survival (51).

Studies on the expression of ICAM-1 and sICAM-1 in stomach cancers are ambiguous. Fujihara et al. and Yashiro et al. showed a negative correlation between ICAM-1 expression on gastric cancer cells and tumor metastasis potential and noted that lower expression of this adhesin means better prognosis and decreased lymph node metastases. According to the authors this is the result of the immune response of the host (52, 53). According to other researchers, there is a positive correlation between sICAM-1 concentration, ICAM-1 expression on gastric cancer cells and tumor progression, metastatic potential, especially to the liver and poor prognosis (54-56). Maruo studies showed ICAM-1 overexpression in gastric cancer cells compared to normal cells. According to the authors, sICAM-1 exfoliated from the surface of cancer cells acts as an immunosuppressive substance that disturbs the function of the immune system in patients with stomach cancer (55). In tumors with a high grade there is a strong expression of ICAM-1 and severe peeling of sICAM-1 which causes the local immunosuppression and is one of the mechanisms of metastasis. The authors believe that the concentration of sICAM-1 can be used to monitor blood-borne metastases in patients with gastric cancer after surgery. In addition, the development of sICAM-1 absorption techniques can be used to reduce metastasis in these patients.

VCAM-1 expression was found on gastric cancer cells, the surrounding tissue, and its severity was determined by the extent of the cancer tumor (36). Japanese research group has shown that the expression of VCAM-1 in gastric cancer tissue was significantly higher compared to the expression in the tissues surrounding, gastric ulcer and in normal mucosa, which according to the authors suggest a crucial role of VCAM-1 in the development of gastric cancer (36). The authors also demonstrated that MVD, a reliable indicator of neoangiogenesis, in stomach cancer tissue with VCAM-1 expression was significantly higher compared to the tissue in which VCAM-1 was negative, which clearly indicates the involvement of VCAM-1 in tumor angiogenesis. It has been demonstrated that stomach cancer cells activate the vessel endothelial cells, which results in increased expression of VCAM-1 and tumor neovasculary, leads to tumor cell spread and infiltration of adjacent tissues (3). In Japanese group studies, VCAM-1 expression was observed in 26/28 patients with gastric cancer with lymph node involvement and in 5/13 patients without metastases ($P < 0.05$), what indicating that VCAM-1 expression may be associated with lymph node metastases (36).

Particularly noteworthy is the observation that the concentration of sVCAM-1 in the serum was high in patients with gastric cancer before treatment, in comparison to the control group, significantly decreased after the operative treatment compared to the pre-operative value ($p < 0.05$) (36). This observation may suggest that the concentration of sVCAM-1 has prognostic significance and indicates that the decrease in sVCAM-1 is associated with the reduction of tumor mass after surgery. Positive correlation between VCAM-1 tissue expression and serum sVCAM-1 concentration in patients with gastric cancer was also demonstrated (36).

In some reports, the expression of ICAM-1in colorectal cancer has been positively correlated with a less aggressive tumor phenotype and metastatic potential. Wimmenauer and Maeda studies have shown that the expression of ICAM-1 in colorectal cancer cells is a beneficial prognostic factor (57, 58). In addition, it was proven that transfection of ICAM-1 into the colon cancer cell line inhibited tumor growth and metastasis (20). According to Rein, the participation of ICAM-1 in the development and course of cancer is ambiguous and may depend on the simultaneous stimulation or inhibition of other membrane receptors on the surface of cancer cells (59). This further complicates the possibility of using ICAM-1 as a therapeutic target.

Maurer studies demonstrated that the expression of m-RNA VCAM-1 in colorectal cancers was 2-3 times higher compared to the m-RNA expression in normal tissues (60). SVCAM-1 test performed in a group of 150 patients undergoing surgery for colon cancer showed a decreased concentration of sVCAM-1 in tumor tissue. The concentration of sVCAM-1 correlated with: the stage of the disease according to the classification T, involvement of lymphatic and blood vessels, lymph node metastases, and the distance of metastases (61). The study also showed that distant metastases and decreased sVCAM-1 concentrations were independent risk factors for poor prognosis. It was immunohistochemically revealed intense expression of VCAM-1 in the tumor stroma with concurrent reduced sVCAM-1 concentration and poor prognosis. According to the authors, the decrease in sVCAM-1 concentration in patients with colorectal cancer significantly correlated with clinical-pathological parameters and prognosis, and suppression of VCAM-1 membrane exfoliation into its soluble form (sVCAM-1) in tumor stroma may affect tumor progression (61). While the membrane form of VCAM-1 participates in the process of tumor cell metastasis, the soluble form of VCAM-1 may inhibit tumor growth by competitive inhibition of VCAM-1 binding ligand and/or induction of T lymphocyte chemotaction.

CONCLUSIONS

Recently, the research of adhesion molecules in numerous cancers has been observed. It has been demonstrated that ICAM-1 participates in all stages of oncogenesis, from very early stages of inflammation through the step of adhesion of tumor cells and leukocytes to endothelial cells, to the late stage of tumor cell migration, and colonization

of subsequent organs. The interaction of the host ICAM-1 with a ligand on a tumor cell and host cell during subsequent metastatic stages may become an attractive target for anticancer treatment.

Studies have shown that VCAM-1 plays an important role in the process of tumor cell adhesion to endothelial cells and in the neovascularization process. VCAM-1 participates in the process of ontogenesis, tumor angiogenesis, and metastasis of cancer cells. Studies have shown that MVD in gastric cancer tissue is closely related to lymph node metastases and clinical stage, and VCAM-1 expression may be used as a marker for metastatic changes and for the purpose of anti-angiogenesis therapies. The concentration of soluble VCAM-1 in serum correlates with the expression of VCAM-1 in tumor tissue, and is significantly reduced after surgical removal of the tumor. In this aspect sVCAM-1 can be treated as a sensitive diagnostic and prognostic marker.

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