

ADHESION MOLECULES IN LUNG CANCER

K. Charalabopoulos, V. Papalimneou, A. Charalabopoulos*
Ioannina University Medical School, Ioannina 451 10, Greece

РОЛЬ МОЛЕКУЛ АДГЕЗИИ ПРИ РАКЕ ЛЕГКОГО

К. Чаралабопулос, В. Папалимно, А. Чаралабопулос*
Медицинская школа университета Янины, Янина, Греция

Adhesion molecules play an important role in normal and disease processes and are implicated in cancer invasion and metastasis. In the last decade, the role of some adhesion molecules in lung cancer as possible biomarkers has been enthusiastically investigated. In this review article we discuss the role of some integrins, E-cadherin, ICAM-1, VCAM, NCAM, CEA, selectins and CD-44 as novel tumor tools in the pathology of the lung cancer.

Key Words: adhesion molecules, lung cancer, cadherins, integrins, selectins, IgSF, CD44.

Молекулы адгезии принимают участие в ряде взаимодействий между клетками и субстратом как в норме, так и при патологии, а также играют важную роль в инвазии и метастазировании опухоли. В последние 10 лет исследована роль некоторых молекул адгезии как потенциальных биомаркеров рака легкого. В обзоре обсуждается роль ряда интегринов, Е-кадгерина, ICAM-1, VCAM, NCAM, CEA, селектинов и CD-44 при раке легкого.

Ключевые слова: молекулы адгезии, рак легкого, кадгерин, интегрины, селектины, IgSF, CD44.

The development of adhesion bonds among cells is a fundamental process, which plays a crucial role. Adhesion molecules act both in the initial phase of embryogenesis for tissue formation, as well as in normal architectural maintenance and physiological growth in adults. The development and physiological operation of all tissues of multicellular organisms are controlled through regulating reactions that occur among cells or between cells and their extracellular matrix components. In the last decade with the bulk of studies in the fields of physiology, biochemistry and genetics it has been revealed that many of these cell-cell or cell-matrix interactions are mediated by elements that are named adhesion molecules [1–3]. In normal, adhesion molecules participate in tissue growth and maintenance, white blood cells extravasation, blood coagulation, wound healing and inflammation. In cancer, they are involved in invasion and metastasis [4, 5].

In 1889, Paget posed the question, “What is it that decides which organs will suffer in the case of a disseminated cancer?” [6]. This question for more than a hundred years remains basically unsolved. However, many new studies and investigations have identified that the nature of cancer invasion and metastasis is based on a molecular level. The role of adhesion mole-

cules has been further elucidated in recent years and is regarded to be of utmost importance.

The theory of adhesion forces was at first developed in 1944 by Comman [7] who said, “Adhesive bonds are those that hold the cancer cells together and the loosening of these adhesive restraints between cancer cells allows them to detach and spread to distant sites in the body”. Fifty years onward from this hypothesis, results from research continue to urge more supporting experimentation to contribute to Comman’s theory. The adhesion molecules have been studied using monoclonal antibodies, which specifically bind to these telltale molecules. Furthermore, nowadays various genetic methods are available. Information about the initial site of the malignant cells as well as for their metastatic potential to invade in specific organs is crucial in recognizing the uncontrolled growth, disorganization of cells, morphological differentiation, invasion and metastasis to distant organs. All these processes can be explained, at least in part, by changes in the molecular specificity of the adhesion molecules in tumor cells both in primary site and in metastatic site [8].

Clinically, adhesion molecules may be proved good markers in some types of malignant tumors providing, furthermore, useful information in diagnosis and prognosis. Additionally, by the use of monoclonal antibodies conjugated with radiolabelled materials or drugs, adhesion molecules may be implicated in the treatment field as well. Until now, more than 100 adhesion molecules have been identified. They belong to five large families: integrins, cadherins, immunoglobulin gene superfamily (IgSF), selectins and CD44. Adhesion molecules have genetic and biochemical differences but always they interact and cooperate.

Histological types of the lung cancer. Lung cancer is the most common cause of death among all types of cancer. It is calculated that the number of deaths from lung cancer exceeds 600,000 persons per year,

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*Correspondence: Fax : +3 2651 0 97850;
E-mail: kcharala@cc.uoi.gr

Abbreviations used: CEA — carcinoembryonic antigen; CSF-1R — colony stimulating factor receptor; DCC — product of the deleted in colon cancer gene; ICAM-1, ICAM-2 — intercellular cell adhesion molecules; IgSF — immunoglobulin gene superfamily; LCNEC — large cell neuroendocrine carcinomas; LFA-1 — lymphocyte function associated antigen; NCAM — neural cell adhesion molecule; NSCLC — non small cell lung cancer; r-PDGF — receptor of the platelet derived growth factor; PECAM-1 — platelet endothelial cell adhesion molecule-1; SCLC — small cell lung cancer; VCAM — vascular cell adhesion molecule; VLA-3 — very late antigen-3.

worldwide. Adenocarcinoma is the most common type among all the histological types of lung cancer. Metastatic spread is the main mechanism of death in patients suffering from lung cancer. According to the histological characterizations of WHO (WHO, histological typing of lung cancer, 1982), lung cancer is classified into two large categories: small cell lung cancer (SCLC), which represents 20–25% of all lung cancer, and non small cell lung cancer (NSCLC) representing the rest of the cases. Adenocarcinoma, squamous cell carcinoma, adenosquamous cell carcinoma, and anaplastic large cell carcinoma are types of NSCLC. Adenocarcinoma is subdivided in bronchioalveolar, alveolar, lobular and mixed type. Bronchioalveolar carcinoma is a well-differentiated variety of adenocarcinoma; histologically it could be placed between adenocarcinoma and squamous cell carcinoma. However, its biological behavior differs significantly from the classical adenocarcinoma since it is characterized by multiple pulmonary locations resulting from its scattering by air dispersion. This characteristic peculiarity is observed only in this lung cancer histological type. Furthermore, bronchioalveolar carcinoma is less aggressive with a better prognosis comparing with the other histological types of the lung cancer.

Integrins. Integrins are transmembrane glycoproteins consisting of α and β subunits. There are at least 15 different α chains and 9 different β chains allowing thus by their combinations the presence of a large number of integrin molecules. They are mainly secreted by epithelial cells, but other cell types may also secrete integrins. The majority of integrins participates in cell-substratum interactions acting thus as receptors of extracellular matrix components e.g. collagen, laminin, fibronectin, and vitronectin [3, 9, 10]. Some members of the integrins family, such as $\alpha_4\beta_1$ and its closely related LFA-1 (lymphocyte function associated-1) can furthermore function as cell-cell adhesion molecules. Integrins found on lymphocytes intermediate in heterotypic reactions among cells, bound with some members of the immunoglobulin gene superfamily (IgSF). β integrins play an important role in metastatic cell migration in sarcoma Rous, bladder cancer, and colorectal cancer [10–12]. β integrins also participate in signal transduction, as well as in oncogenesis, and cell growth processes. Their critical role in lung cancer is still disputed and little data is available, offering thus a rich field of scientific research. Among integrins, β_1 and β_3 are the most studied. $\alpha_1\beta_1$ and $\alpha_2\beta_1$ integrins are virtually implicated in the metastatic process in squamous cell lung cancer. $\alpha_5\beta_1$ integrin is implicated in the carcinogenetic process in experimental animals suffering from ovarian cancer. This integrin has not at all been studied in humans suffering from lung cancer. Of all β_3 integrins, the $\alpha_{IIb}\beta_3$ which is restricted to platelets, and the $\alpha_v\beta_3$ integrin, it is nowadays well known that they represent receptors for fibronectin, fibrinogen, vitronectin, thrombospondin, and von Willebrand factor. It is of special interest that some peptide analogues containing the RGD (arginine-glycine-aspartic acid) sequence may

be useful in the prevention of lung cancer metastases to other organs, since when they were intravenously administered to mice, no lung cancer metastases in other organs were observed [13, 14]. It is notable, that this RGD sequence represents the integrins epitope.

Since cancer prognosis is dependent on the ability of cancer cells to detach from the primary site and to reattach to a secondary metastatic site, Bredin et al [15] supported the important interactive role of β_1 and β_3 integrins which bind to anti-adhesive molecules of the extracellular matrix e.g. thrombospondin. Furthermore, the same investigators studied the integrins expression in each of the main four histological types of lung cancer (adenocarcinoma, squamous cell carcinoma, small cell carcinoma and large cell carcinoma). They found that β_3 integrins were expressed in small cell and squamous cell types of lung cancer. In all histological types of lung cancer, with an exception of large cell and squamous cell carcinoma, hapto- and chemo-tactic mobility to fibronectin, laminin and type IV collagen was observed. It is well documented that carcinogenic transformation is clearly associated with alterations in the integrins expression. The VLA-3 integrin (very late antigen-3) as well as its ligands (laminin, fibronectin, type IV collagen, niteine, and endactin/hintogen) were studied immunohistochemically in the different types of lung cancer by Bartlazzi et al [16]. The $\alpha_3\beta_1$ integrin was expressed in bronchial epithelium as well as in the basement membranes of the airway tract. In NSCLC the same integrin was expressed in 82% of cases, not depending on the histological type and grade of the tumor [15]. Conversely, only 13% of the SCLC expressed the $\alpha_3\beta_1$ integrin and its ligands. Integrins play an important role in cancer prognosis. They can be used as biomarkers for disease progression. Patients with SCLC and lymph node involvement were studied. Loss of the α_v integrin expression was associated with a faster disease progression comparing with the group of patients without lymph node involvement [17].

Clark et al [18] studied the alteration in extracellular matrix components observed in patients with adenocarcinoma of the lungs. They investigated the α_2 , α_3 , α_v integrins, as well as the type IV collagen and type IV collagenase expression levels in those patients. They found that the progressive loss of the type IV collagen from the basement membrane as well as the reduced expression of the α_2 integrins were clearly associated with a lower grade in cancer differentiation [18]. Type IV collagenase expression was associated with lymph node involvement. When lymph nodes were involved, then the α_v integrin expression was significantly increased [18]. Other investigators have also shown that the cancer cell interactions with extracellular matrix components are mainly intermediated by β_1 integrins [19].

Furthermore, it was detected that bone metastasis in lung cancer cases is the result of a complicated mechanism which is largely influenced by the osteoclasts activation and the subsequent interactions between adhesion molecules and cancer cells. The mediating role of β_3 integrins in the osteoclasts activity as

well as in the parathyroid hormone secretion is very significant [20].

Cadherins. Cadherins are transmembrane proteins that represent the chief mediators of cell–cell adhesion via calcium dependent, homotypic interactions i.e. a molecule on one cell binds to cadherin molecules of the same type on another cell [21]. In the absence of calcium ions the cadherins are degraded rapidly by a specific protease. Cadherins form a family with dozens of members sharing some characteristics regarding their structure and function. Cadherins are the most important of adhesion molecules since when they are secreted, then the inhibition of activity of other adhesion molecules that participate in cell–cell adhesion has less or no meaning. Different types of cadherins exist. Most important are: 1) epithelial cadherin (E–cadherin) also known as LCAM, uvomorulin, Arc–1, and cell–CAM 120/80; 2) neural cadherin, (N–cadherin) which is expressed by nerve and muscle tissue; 3) placental cadherin, (P–cadherin); 4) retinal cadherin, (R–cadherin); and 5) vascular endothelial cadherin (VE–cadherin) which is expressed by vascular epithelia. Cadherins function is regulated directly by their binding to a series of intracellular proteins, named catenins, (α , β , and γ); they interact with the actin filaments of the cytoskeleton [22]. The group of catenins consists of α –catenin, β –catenin, γ –catenin, as well as the p120 molecule, which is regarded to be a new catenin. Loss of function and/or expression of anyone of the E–cadherin/catenin complex elements makes the cell unable to act adhesively. Reestablishment of the E–cadherin/catenin complex makes it once more capable for adhesion interactions. E–cadherin downregulation has been associated with a number of cancers including gastric cancer, pancreatic cancer, head and neck cancer, bladder cancer, prostate cancer, colorectal cancer, breast cancer and primary liver cancer [23–30]. Recent studies have shown a decreased expression of E–cadherin in lung cancer cases [31, 32]. In a recent study, it was shown that E–cadherin could be a useful prognostic indicator in the course of patients with lung cancer since levels of E–cadherin showed diagnostic sensitivity in 66.6, 47.6 and 43.7% of the patients with squamous cell carcinoma, SCLC, and adenocarcinoma, respectively [32]. The expression of E–cadherin/catenin complex was also studied in NSCLC cases. A decreased expression of E–cadherin, α –catenin, and γ –catenin was detected while β –catenin was not expressed at all [32]. Additionally, an association between E–cadherin/ α –catenin complex with the histological type of adenocarcinomas was found. A decrease in the expression of this complex was also found in poorly and moderately differentiated lung carcinomas. In the well differentiated carcinomas alterations like the above mentioned were not observed [32]. Alterations in E–cadherin/catenin complex were also found in NSCLC. It is well documented that this complex plays a fundamental role in the establishment of a malignant, aggressive phenotype.

Mesothelioma is a very aggressive carcinoma usually involving individuals exposed to asbestos. The differential diagnosis of mesothelioma from lung adenocarcinoma is often very difficult. It has been clearly shown that E– and N–cadherin can be used as diagnostic/differentiating markers in the above mentioned cancer types [33]. In particular, it was shown that N–cadherin is expressed in the pleural cells of mesotheliomas, whilst E–cadherin is not expressed in those cells. E–cadherin is expressed, though, in other epithelial cells of the lungs [30]. The reliability of these two cadherins as diagnostic and differentiating markers is confirmed by the use of the monoclonal antibodies and immunohistochemistry [31].

The expression of E–cadherin/catenin complex is also applied in the differential diagnosis between bronchoalveolar carcinoma and adenocarcinoma. This expression is much higher in bronchoalveolar carcinomas [34].

In SCLC, an expression of various cadherin types is observed. Particularly, downregulation of E–cadherin is found being directly associated with a less invasive ability in the primary site, but with a high metastatic potential [35, 36].

Immunoglobulin gene superfamily (IgSF). Members of IgSF are surface cell molecules sharing a segmental structural region consisting of 70–110 amino acids in the immunoglobulin chain. In this family belong molecules that are involved in cell recognition like the major histocompatibility antigens (MHC), lymphocyte function associated antigen (LFA–1), receptor of the platelet derived growth factor (r–PDGF), platelet endothelial cell adhesion molecule–1 (PECAM–1), colony stimulating factor receptor (CSF–1R). Furthermore, this superfamily includes molecules that participate in neural cell adhesion such as neural cell adhesion molecule (NCAM), vascular cell adhesion molecule (VCAM), intercellular cell adhesion molecules, (ICAM–1, ICAM–2), product of the deleted in colon cancer gene (DCC), and the since 1965 recognized carcinoembryonic antigen (CEA) [37–39]. IgSF members mediate the cell–to–cell adhesion interactions in homotypic (e.g., an ICAM on one cell binds to an ICAM of the same type on another cell) or heterotypic manner.

ICAM–1, VCAM–1 and LFA–1 play an important role in the inflammation processes of the air exchange route as well as in oncogenesis. ICAM–1 is expressed in NSCLC and LFA–1, which is a ligand for ICAM–1 participating in T–lymphocytes response, is moreover expressed in lung adenocarcinomas in contrast to the VCAM–1 expression [40]. ICAM–1 participates significantly in carcinogenesis and metastasis. Serum levels of ICAM–1 were apparently high in patients with lung cancer comparing to healthy individuals. Additionally, serum levels are directly associated with disease stages. Though, after therapeutic intervention serum ICAM levels seems not to be altered [41]. In patients with relapsing lung cancer who received blood transfusions, a negative correlation between ICAM–1 expression levels and metastasis was observed [42].

High NCAM serum titer is a dynamic biomarker for SCLC cases. Recently, it has already been exploited in clinical practice [43]. By using monoclonal antibodies against NCAM it is easy to identify the neurosecretory cancer cells which normally are absent in the respiratory epithelium. Thus, NCAM is a very good specific biomarker in neuroendocrine tumors of the lungs. NCAM is constantly expressed in SCLC and carcinoids. Possibly, this is valid for NSCLC cases, but a larger number of studies are still needed. Nevertheless, presence of neuroendocrine biomarkers in NSCLC may not be significantly associated with prognosis, though it is obviously implicated in the management field since NSCLC tumors with increased neuroendocrine differentiation seems to be highly chemosensitive. NCAM is not expressed in adenocarcinomas and squamous cell carcinomas of the lung. NCAM is a very sensitive indicator in tumors of neuroendocrine origin with 80, 93 and 58% expression in large cell neuroendocrine carcinomas (LCNEC), SCLC and carcinoids, respectively [43].

CEA is an oncofetal glycoprotein of the IgSF inter-mediating in cell adhesion requiring simultaneously the presence and function of some other adhesion molecules. It is well established that CEA and E-cadherin both participate in lung epithelial junctions as well as in the cytoskeleton formation. In SCLC decreased CEA expression was associated with high grade metastatic tumor ability [36].

It is well known that angiogenesis plays an important role in tumor growth and metastasis. A prevascular and a vascular phase are recognized in this phenomenon. Endothelial cells play a crucial role in both phases. Thus, antibodies against factor VIII and PECAM play an important role. PECAM is more sensitive in studying immunohistochemically the angiogenesis phenomenon. It has been clearly shown in NSCLC cases [44].

Selectins. Selectins are transmembrane glycoproteins with a domain rich in lectin that bind to carbohydrates and mediate in heterotypic reactions between blood cells and endothelial cells during the lymphocyte homing and leukocyte adhesion. The well known members of this group are P-selectin (also known as GMP-140 or PADGEM), E-selectin (also known as ELAM-1) and L-selectin. These molecules are found on the surface of activated endothelial cells, which have the suitable receptor. L-, P-, and E-selectin participate in calcium-dependent cell-cell adhesion, mediating the initial attachment of flowing leukocytes to the blood vessel wall during the capture and rolling step of the inflammatory adhesion mechanism [45]. Accumulation of leukocytes in inflammation in response to mediators is essential for effective host defense to infection and injury. E-selectin acts on stimulated by cytokines endothelial cells, so that these endothelial cells interact with cancer cells, leading to further progression of the metastatic process. The relation between serum levels of E-selectin and prognosis in NSCLC cases were studied by measuring serum levels of two carbohydrate antigens, the sialyl Lewis x (SLX) and the sialyl Lewis α (CA19-9) [46]. It was found that high

serum E-selectin levels in patients were associated with a worse prognosis comparing with patients who had normal serum E-selectin levels [46]. In more detail, when high serum levels of E-selectin were associated with high levels of carbohydrate antigens (SLX and CA19-9), then the prognosis was extremely poor [46]. Studies have also shown that carbohydrate antigens (SLX and CA19-9) play a role of ligands for selectins and are responsible for the cancer cell adhesion to the endothelium. The E- and P-selectins intermediate in these reactions. The carbohydrate antigens are found in different types of cancer. Mostly, they have been detected in lung cancer, gastric cancer, pancreatic adenocarcinoma and colorectal cancer, being detected either in cancer cell surface or in blood serum of patients. Thus, they have been proposed as important indicators in the diagnosis of cancer. Until now, research has shown that selectins and their ligands play an important role in cancer invasion and metastasis [47]. Another endothelial cell adhesion molecule, the Lu-ECAM-1, produced in lung blood vessels, is strongly associated with the metastatic implantation of melanoma cancer cells to the lungs.

CD44. CD44 is a cell surface glycoprotein that plays an important role in lymphocyte cell homing, activation of T-cells and adhesion of hyaluronate and other extracellular matrix proteins to cells, participating thus in the metastatic cascade [48]. Recent studies have shown that CD44 mediates cell-cell and/or cell-matrix interactions.

Many research data support the role of CD44 in the early cancer diagnosis. With the use of polymerase chain reaction (PCR), Matsumura et al [49] showed that the neoplastic tissues overexpress many CD44 splice variants. This phenomenon does not appear in normal tissues. The expression of a specific gene seems to be associated with the presence of metastasis. Of course, more research data is needed to support the above mentioned observations [49]. Various CD44 splice variants are dependent on different exon locations in the CD44 molecule. Until now at least nine splice variants of CD44 have been identified. The CD44v6 isoform is regarded to be a good prognostic indicator in the first stage of NSCLC patients. This fact is not valid for the CD44s variant [50].

In general, CD44 expression is associated with tumor development in colorectal cancer, breast cancer, bladder cancer, prostate cancer as well as in melanomas. Its expression is neither related to SCLC nor to NSCLC (brochioalveolar carcinoma of the lung is an exception). The normal bronchial epithelium strongly expresses CD44 at the basal part and not at the apical ones. In adenocarcinoma a decreased/absent expression of CD44 has been observed [51]. Further research is needed to elucidate and reevaluate the entire role of CD44 in lung cancer cases.

Conclusions. In recent years, a bulk of information on the role of adhesion molecules in normal and disease processes has been published. The interest is heating up among adhesion molecules that could be

possible biomarkers in diagnosis and prognosis of various malignancies. The role of different adhesion molecules in lung cancer has not sufficiently been clarified. Integrins play a crucial role in lung cancer, but only little data is available. $\alpha_1\beta_1$ and $\alpha_2\beta_1$ integrins are implicated in squamous cell carcinoma of the lungs. The role of $\alpha_5\beta_1$ integrin which is very well documented in experimental animals, has not at all been studied in human lung cancer cases. Peptide analogues with RDG sequence prevent lung cancer metastases to other organs in mice. β_3 integrins are expressed in SCLC and squamous cell types of lung cancer. $\alpha_3\beta_1$ integrin is expressed in the majority of NSCLC and in only 13% in SCLC. E-cadherin is downregulated in lung cancer, being furthermore a useful prognostic indicator with a significant diagnostic sensitivity in SCLC, squamous cell carcinoma of the lungs, and adenocarcinoma. Downregulation of E-cadherin, α -catenin, and γ -catenin (but not of β -catenin) is observed in NSCLC cases. In adenocarcinoma of the lung, a direct association between E-cadherin/catenin complex and tumor grade is observed. In mesotheliomas, N-cadherin (but not E-cadherin) is expressed. Thus, N-cadherin comes in very handy as a differentiating diagnostic tool mainly for lung adenocarcinoma. Bronchioalveolar carcinomas highly express E-cadherin. Various types of cadherins may be expressed in SCLC. ICAM-1 is expressed in NSCLC, while VCAM is not expressed. NCAM is a very good diagnostic marker in SCLC with exploitation in clinical use. Neurosecretory tumors constantly express NCAM, which is a very sensitive indicator in tumor cases of neuroendocrine origin. CEA expression is downregulated in SCLC in association with high tumor metastatic ability. PECAM is the most sensitive indicator of angiogenesis. High serum E-selectin levels are observed in patients suffering from lung cancer and are directly associated with the prognosis. CD44 is not expressed in SCLC or adenocarcinoma (except for alveolar cell carcinoma). However, for more reliable results, the role of CD44 needs to be reevaluated.

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