

INTEGRIN RECEPTORS IN PRIMARY LUNG CANCER

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In the present review recent data regarding the role of integrins – an important category of adhesion molecules mediating interactions among cells and components of the extracellular matrix – in lung cancer development is discussed. Investigations have shown that down-regulation of $\alpha 3$ integrin subunit may contribute to enhanced tumorigenicity of c-myc-overexpressing small cell lung carcinoma, while the loss of αv integrin expression is correlated with recurrence in node-negative lung carcinoma. Increased expression of $\alpha 1\beta 1$ and $\alpha 2\beta 1$ integrins have been shown to be positively correlated with increased metastatic ability in squamous cell carcinoma. $\alpha 3\beta 1$ integrin is a most critical integrin for pulmonary development and epithelium integrity and its reduced expression in small cell lung cancer is probably related to the increased aggressiveness of this type. Pulmonary cancer cells generally express fewer integrin receptors than the normal epithelium. Additionally, since the ability of malignant cells to interact with extracellular matrix components is thought to be important, integrin dependent migration of lung cancer cells is a crucial process. **Key Words:** lung cancer, integrins, adhesion molecules.

In multicellular organisms the development of adhesion bonds either among cells or among cells and components of the extracellular matrix, is a crucial process. That is why it plays a main role both at early stage of tissue consistence and later on. This happens because the adhesive process is directly related to the differentiation, architecture and normal tissue development. The extracellular matrix consists of different proteins and various polysaccharide molecules. The interactions either among cells or among cells and substratum are mediated by some molecules, which are named adhesion molecules [1–3]. These molecules are very important because they determine if one cell remains somewhere and where or if it migrates and where as well as when it stops. Adhesion molecules participate in the processes of embryogenesis and normal growth, leukocytes migration and extravasation, wound healing, blood coagulation and inflammation, as well as in tumor invasion and metastasis [4].

Since 1889 Paget had expressed the question: “What is this that determines which organs will suffer in case of a generalized cancer?” [5]. Today more than a hundred years later, the question is still unanswered. However, new data is accumulated. The theory of adhesion bonds between cells that at first was reported by Coman in 1944, a little after the 2nd World War, is nowadays, at least in part, explained by cell adhesion [6]. Cell adhesion is a key process. It has been postulated that changes in cell–cell and cell–matrix interactions account for the ability of cancer cells to transgress normal tissue boundaries and disperse to distant sites. Complex and coordinated reductions and increases in adhesion have been proposed to be necessary for tumor invasion and metastasis. It is now obvious that the basic characteristics of the malignancy as the out of control proliferation, the disorganisa-

tion of cellular and morphological differentiation, the tumor cell invasion and migration to distant organs can be explained by the observed changes in adhesion molecules, in the primary site and the metastatic organ–target too [4, 5].

Adhesion molecules belong to five known families: integrins, cadherins, immunoglobulin supergene family (IgSF), selectins and CD44. These molecules are different genetically and biochemically, but in some cases they play roles that correlate with each other.

Integrins are transmembrane glycoproteins that form heterodimers consisting of an alpha (α) and a beta (β) subunit. There are 15 different β subunits and 9 α subunits. The particular combination of α and β subunits determines the specificity for ligand binding (Table). Integrins are secreted by epithelial cells and by any type of cell that derives from the three primary spermatic zones. Most of them are SAM (substrate adhesion molecules) mediating interactions among cells and components of the extracellular matrix. Some of them may be CAM (cell–cell adhesion molecules) participating in cell–cell interactions too, i.e.g. the $\alpha 4\beta 1$ and the LFA–1 (lymphocyte function associated–1). Integrins that are expressed by lymphocytes mediate heterotypic adhesion cell to cell, binding with some members of the IgSF. Changes in secretion and/or in functional activity of integrins, appear to merely regulate the development and the progression of malignant tumors. While their presence is important for the cell installation and differentiation, their change leads to more aggressive behaviour. *In vivo*, changes of integrins have been observed in epithelial malignancies like lung can-

Table. Functional classification of integrin receptors based on their binding specificity

Integrin receptors	Binding specificity
Collagen receptors	$\beta 1-\alpha 1, \alpha 2, \alpha 3, \alpha v$
Fibronectin receptors	$\beta 1-\alpha 3, \alpha 4, \alpha 5, \beta 3-\alpha v, \alpha 11b, \beta 6, \alpha v, \beta 7-\alpha 4$
Laminin receptors	$\beta 1-\alpha 1, \alpha 2, \alpha 3, \alpha 6, \alpha 7, \beta 3-\alpha v, \beta 4-\alpha 6$
Vitronectin receptors	$\beta 1-\alpha v, \beta 3-\alpha v, \alpha 11b, \beta 5-\alpha v$
Others	$\beta 1-\alpha 8, \alpha 9, \beta 8-\alpha v$

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cer [7], breast cancer [8], colorectal cancer [9], prostate cancer [10], gastric cancer [11], pancreatic cancer [12], hepatocellular carcinoma [13], renal cell carcinoma [14], skin cancer [15], ovary cancer [16] and endometrial cancer [17].

Beta integrins appear to play a central role in migration of different human tumor cell lines including fibrosarcoma, bladder carcinoma and colon carcinoma [18]. In the present review article we are dealing with integrins adhesion receptors in primary lung cancer. The role of integrins in the migration of lung cancer cells has not been extensively investigated, offering a brilliant field of research. $\beta 1$ and $\beta 3$ integrins have been better investigated. Integrins are very important for the normal development of the lung, the host defence towards pulmonary infection and in pathogenesis of adult respiratory distress syndrome (ARDS) [19]. By using monoclonal antibodies there has been identified the participation of some integrin subunits in normal lung and particularly in bronchial epithelium, endothelium and smooth muscles of the lung.

Increased expression of $\alpha 1\beta 1$ and $\alpha 2\beta 1$ integrins have been shown to be positively correlated with increased metastatic ability in squamous cell carcinoma [20]. In addition, $\beta 1$ integrins show characteristic distribution patterns in solid tumors and they are potentially useful in tumors identification. $\alpha 3\beta 1$ integrin is a most critical integrin for pulmonary development and epithelium integrity and its reduced expression in small cell lung cancer is probably related to the increased aggressiveness of this type. $\alpha 3\beta 1$ is the main laminin binding integrin anchoring alveolar and bronchial epithelial cells to the basement membrane at all stages of human fetal lung development, as well as in adults [21]. Additionally, mice homozygous for $\alpha 3$ integrin gene deletion die shortly after birth appearing lungs that have markedly reduced branching from the mainstem bronchi and terminal bronchial epithelium being cuboidal rather than flattened as in normal lung is observed [22]. $\alpha 3\beta 1$ integrin was detected in bronchial epithelium and basement membrane of the airways. An apparent stepwise decrease in the expression of integrins including $\alpha 3\beta 1$ has been observed, in order, from normal bronchial epithelium to non small cell lung carcinoma and then to small cell lung carcinoma. Pulmonary cancers generally express fewer integrin receptors, than the normal epithelium [23, 24] and for non small cell lung carcinoma, the decrease in $\alpha 3\beta 1$ is significantly more common in poorly differentiated tumors [23].

On the other hand, Bartolazzi et al [25] reported that integrins are expressed in 82% of the patients with non small cell lung carcinoma (NSCLC) with no any association with the type and the degree of differentiation. On the contrary, only 13% of small cell lung carcinoma express $\alpha 3\beta 1$ integrin and its ligands which are located near the basement membrane of the cell.

Barr et al [26] correlated the decreased expression of $\alpha 3\beta 1$ integrin with the highly invasive and metastatic behaviour of small cell lung carcinoma (SCLC). In their study they used the most virulent SCLC cell line, the

one that overexpress the *c-myc* oncogene. The expression of *c-myc* is associated with reduced homotypic cell adhesion, small cell doubling time and enhanced soft agar cloning ability. In addition, *c-myc* expression leads to reduction of $\alpha 3\beta 1$ integrin, while the transfection of a full length gene encoding the $\alpha 3$ integrin reverses some of the effects of *c-myc*, by increasing SCLC cell aggregation and depressing soft agar cloning, but it does not affect the doubling time. The inverse relationship between *c-myc* and $\alpha 3\beta 1$ integrin has been demonstrated in other tumors too, as in neuroblastoma, where the increased expression of *N-myc* resulted in the reduced expression of $\alpha 2$, $\alpha 3$ and $\beta 1$ integrin subunits [27, 28], increase of tumor cell invasiveness and worsened tumor prognosis [28]. Finally, they observed that engaging the $\alpha 3\beta 1$ with specific antibody P1B5 enhances the soft agar cloning ability of the transfected cells, but it does not affect cell aggregation. These findings suggest that $\alpha 3\beta 1$ integrin may mediate the homotypic adhesion of SCLC cells and that unengaged $\alpha 3\beta 1$ integrin suppresses the growth of desaggregated SCLC cells. Thus, the down-regulation of the $\alpha 3$ integrin subunit may contribute to the enhanced tumorigenicity of *c-myc* overexpressing SCLCs by allowing the growth of tumor cells that have reduced contact with ligand-expressing substratum or cells, a condition that occurs during the growth of the primary tumor, tumor invasion and metastasis.

The $\beta 3$ class of integrins includes: the platelet glycoprotein $\alpha IIb\beta 3$ and $\alpha v\beta 3$ which binds fibronectin, fibrinogen, vitronectin, thrombospondin and von Willebrand's factor.

Given that cancer prognosis depends on the ability of cancer cells to detach from the primary site and to attach to the metastatic one, Bredin et al [24] support that $\beta 1$ and $\beta 2$ integrins play an important role in the tumor progression, on the whole, since these integrins connect with molecules that have anti-adhesion role, e.g. thrombospondin. Thus, they examined five cell lines representing the major types of lung cancer (adenocarcinoma, squamous cell carcinoma, small cell lung cancer, large cell lung cancer) by performing cytometric analysis to characterize their integrin expression. The main finding was that lung cancer cell migration towards extracellular matrix is integrin dependent. The basement membrane is normally impermeable to large proteins and cells. However, during tumor cell invasion, tumor cells attach to components of the extracellular matrix and the basement membrane, degrade it and migrate through the matrix [29]. Integrins appear to play a central role in this adhesion process. The same conclusions have been made in fibrosarcoma, bladder carcinoma and colon carcinoma [18]. The role of integrins for the migration of lung cancer cells has not been extensively investigated. In addition to mediation to cell adhesion and motility, the $\beta 1$ integrin family also participates in signal transduction [30, 31], tumorigenicity [32, 33] and growth regulation [33, 34]. Changes in expression or modification of the integrins have been noted during malignant transformation in various cells

but only a few studies have reported a clear correlation between the degree of transformation or malignancy and the pattern of the integrin expression. For example, high levels of expression of the $\alpha 1\beta 1$ and $\alpha 2\beta 1$ integrin have been related to increased metastatic ability in squamous cell carcinoma cells. In particular, Bredin et al demonstrated that all histological types express $\beta 1$ integrins, except large cell lung cancer. In squamous cell carcinoma and large cell carcinoma a $\beta 3$ integrin expression was found. All cell lines showed haptotactic and chemotactic migration towards fibronectin, laminin and type IV collagen, except the large cell line that did not show haptotactic or chemotaxis towards laminin and the squamous cell line, which did not show chemotaxis towards none of the three above mentioned elements. Using monoclonal antibodies, it was demonstrated that $\beta 1$ integrin was necessary for this chemotactic cell migration, while $\beta 3$ subunit was not. In large cell lung cancer, which does not express $\beta 1$ integrin, CD44 seems to have a mediating role.

Alterations in extracellular matrix, cell–cell and cell–matrix adhesion are thought to be important in tumor progression and metastasis. Keeping that in mind, Clarke et al [35] studied adenocarcinomas of the lung for immunohistochemical expression of integrins $\alpha 2$, $\alpha 3$, αv type IV collagen and type IV collagenase. Type IV collagen represents a major structural component of the basement membrane, essential for anchorage and growth of normal epithelial cells and benign epithelial proliferations [29]. Type IV collagenase is a neutral metalloproteinase that plays a major role in its metabolism. Loss of basement membrane permits lung cancer cells enter the blood and lymphatic vessels creating a systematic spread. Their results showed that integrins $\alpha 2$ and $\alpha 3$ and type IV collagenase expression differ in tumors that have and have not spread to regional lymph nodes, and that this finding might be prognostically and therapeutically important. In particular, it was found that with decreasing tumor differentiation, there is a progressive loss of type IV basement membrane collagen and decreased integrin $\alpha 2$ expression. Integrin αv was increased in tumors with nodal metastasis compared with those without metastasis. The importance of an integrin expression has been observed in melanoma too, where cells selected for low expression of $\alpha v\beta 3$ grew more slowly when injected into immunodeficient mice compared with cells expressing normal levels of $\alpha v\beta 3$ integrin. This inhibition is reversible with transfection of complementary DNA. In human melanoma, the vitronectin receptor is expressed in metastatic melanocytes, but not in benign melanocytes [36]. Loss of $\alpha 2$ and $\alpha 3$ integrin was associated with increased expression. Type IV collagenase expression was associated with lymph node metastasis and appears to be an independent predictor of shortened survival. So, measurable alterations in integrins and extracellular matrix may be of prognostic importance in resectable adenocarcinomas of the lung.

Contrarywise, Smythe et al supported that loss of an integrin expression is related with recurrence in pa-

tients with node negative lung carcinoma who underwent “curative” resection [23]. Neither histologic type nor tumor differentiation status correlated with recurrence during follow up. However, 75% of patients with negative nodes who exhibited recurrence lost an expression, compared with only 10% of patients with negative nodes who did not exhibit recurrence. So, loss of an expression may serve as a marker for patients with node negative non small cell lung carcinoma who are at high risk for recurrence, potentially directing additional therapies.

Interactions between carcinomatous cells and laminin, a major component of basement membranes, play a pivotal role during several steps of the invasion–metastasis cascade [37]. Integrin laminin receptors include $\alpha 1$, $\alpha 2$, $\alpha 3$, $\alpha 6$ and $\alpha 7$ in various combinations with $\beta 1$ and $\beta 4$. The differential expression of laminin receptors has been shown to modulate the invasive capability of malignant cells. The role of $\alpha 1$ in the invasive and metastasizing phenotype of epithelial neoplasms appears limited except for hepatocellular carcinomas [38], small cell neuroendocrine, and, notably, bronchioloalveolar lung carcinomas [39]. Downregulation of $\alpha 2$ has been reported in many different tumors [40], whereas data about $\alpha 7$ are fragmentary [41]. In contrast, $\alpha 3$ and $\alpha 6$ containing integrin laminin receptors have been consistently reported to be strongly expressed in numerous epithelia and their perineoplastic carcinomas [17, 40, 42–45].

As for squamous carcinoma and adenocarcinoma of the lung, Patriarca et al [46] showed that $\alpha 3$ integrin is strongly expressed and that it predominates over $\alpha 6$. In addition, it was found predominance of $\alpha 6A$ subunit expression over the one of $\alpha 6B$ subunit. It is remarkable that in normal bronchial epithelium, $\alpha 6$ colocalized with $\beta 4$, whereas in the tumor, $\alpha 6A$ frequently overlapped with $\beta 1$ in a circumferential pattern. It appears that $\alpha v\alpha 3/\alpha 6$ balance could play a role in the variable metastatic behaviour of neoplastic cells of different primary sites. Particularly $\alpha 3$ predominates over $\alpha 6$ in tumors with more precocious and often widespread metastatic properties, such as lung, kidney and ovary [42, 45–47]. Conversely, in tumors with somewhat more restricted or selective (lymphatic), and often sluggish metastatic proclivities $\alpha 6$ is often predominant over $\alpha 3$, i. eg colon [42, 44, 45], and endometrium carcinomas [17]. Similarly, in less aggressive carcinomas, predominance of $\alpha 6B$ was reported. Interestingly, in experiments *in vitro*, $\alpha 6A/\beta 1$ was shown to induce a migration capacity twice stronger than that induced by $\alpha 6B/\beta 1$ [48]. Interestingly in many cases, it was found a total switch from the hemidesmosome-associated laminin receptor ($\alpha 6/\beta 4$) of normal bronchial structures to the less structurally and spatially organized laminin receptor ($\alpha 6/\beta 1$). Finally, it was found an inverse correlation between $\beta 1C$ splice variant of $\beta 1$ and proliferation-related molecule ki-67.

This suggests that integrins might become future parameters of prognostic relevance. Notably a similarly inverse correlation was recently reported in some

breast carcinomas [49]. All these concern squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. Small cell carcinoma differ significantly in integrin expression profile [35, 47]. Integrins also differed significantly in pulmonary alveolar cell carcinomas in which $\alpha 1\beta 1$ and $\alpha 3\beta 1$ are consistently found, whereas $\alpha 6$ was consistently absent [47].

Interaction between cancer cells, extracellular matrix and endothelial cells is a crucial factor for metastatic cascade in lung cancer. The integrins that mediate this interaction are mainly $\beta 1$ integrins. It is interesting that it has been observed that integrin-like proteins that contain the amino acid sequence RGD (arginine–glycine–aspartic acid) can be used for preventing metastasis of the lung when they are given with antibodies which have this epitope. It is reminded that integrins are connected with substance by RGD sequence.

Bone marrow metastasis is a result of a multistep process that includes osteoclasts motivation and interaction between the adhesion molecules of the cancer cells and the ones of the bones. Several studies have shown the mediating role of $\beta 3$ integrins in motivation of osteoclasts and the expression of parathyroid hormone.

In conclusion, the role of integrins is multiplex, but there are a lot to be illustrated until they take their place in cancer diagnosis and therapy. Many studies are in process and it is very possible that soon some integrins will prove useful biomarkers.

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РОЛЬ МОЛЕКУЛ ИНТЕГРИНОВ ПРИ ПЕРВИЧНОМ РАКЕ ЛЕГКОГО

Обзор посвящен анализу последних данных о роли интегрин — молекул адгезии, опосредующих взаимодействия между клетками и внеклеточным матриксом, в развитии рака легкого. Результаты исследования свидетельствуют о том, что угнетение экспрессии субъединицы $\alpha 3$ интегрин может вносить вклад усиление туморогенности клеток мелкоклеточной карциномы легких, гиперэкспрессирующих α -туб, в то время как утрата экспрессии интегрин $\alpha 6$ коррелирует с рецидивом карциномы легких, не имеющей метастазов в лимфатических узлах. Установлено, что гиперэкспрессия интегрин $\alpha 1 \beta 1$ и $\alpha 2 \beta 1$ положительно коррелирует с повышенной метастатической способностью плоскоклеточной карциномы. Интегрин $\alpha 3 \beta 1$ важен для ткани легкого и целостности эпителия, и его пониженная экспрессия при мелкоклеточном раке легкого, возможно, определяет агрессивность этого типа рака. Вообще, опухолевые клетки экспрессируют меньше рецепторов интегрин по сравнению с нормальными эпителиальными клетками, что влияет на интегринзависимую миграцию опухолевых клеток.

Ключевые слова: рак легкого, интегрин, молекулы адгезии.