Invited Review

Adhesion molecules as targets for cancer therapy

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Summary. Adhesion molecules mediate cell-cell and cell-matrix interactions and are essential for numerous physiological and pathological processes. Recent evidence from many laboratories suggests that adhesion molecules play an important role in tumor progression and may promote tumor growth and organ-specific metastasis. Certain adhesion molecules may also function as tumor suppressors. In this review, we describe current concepts concerning the role of the adhesion molecules in the pathogenesis of cancer and the development of therapeutic approaches which make use of this information. Hence, by preventing tumor cells from interacting with each other or with their micro-environment, tumor growth and metastasis can be suppressed. The feasibility of using anti-adhesion strategies to treat cancer has been demonstrated in many animal models. Thus, monoclonal antibodies (MAbs) against adhesion molecules, synthetic peptidic and nonpeptidic analogues of the recognition sequences on their receptors, soluble adhesion molecules and antisense oligonucleotides can inhibit tumor growth and gene therapy can restore the functions of altered tumor-suppressive adhesion molecules.

Key words: Adhesion molecule, Cancer therapy, Tumor metastasis, Monoclonal antibody

Introduction

Adhesion molecules are widely expressed on the cell surface, basement membrane and extracellular matrix (ECM). They mediate cell-cell and cell-matrix interactions which are critical for a variety of physiological and pathological processes such as cell growth, differentiation and trafficking, embryogenesis, immune responses, inflammation, blood coagulation, wound repair and tumor development (Springer, 1990; Buck, 1995; Dedhar, 1995). Adhesion molecules include several distinct families such as integrins, cadherins, members of the immunoglobulin (Ig) superfamily, selectins, and some cell surface proteoglycans (Table 1). In addition to their role in adhesion, recent studies have demonstrated that these molecules may also function as signal transducers to regulate various cellular functions through G-proteins, phospholipids and protein kinases (Parsons, 1996; Ruoslahti, 1995). Alterations in the adhesive properties of tumor cells or the tumor microenvironment have been implicated in tumorigenesis and in the biological behavior of many malignancies (Albelda, 1993; Buck, 1995; Glukhovo et al., 1995). In this review, we will emphasize recent advances in our understanding of the role of adhesion molecules in tumor pathogenesis and in the development of antiadhesion approaches for improving cancer therapy.

The role of adhesion molecules in tumor growth and metastasis

Numerous studies have indicated that adhesion molecules are involved in the growth, invasion, and metastatic properties of many types of tumors (Albelda, 1993; Juliano and Varner, 1993; Buck, 1995). An increase or decrease in the adhesion of tumor cells to neighboring tumor or host cells, ECM and endothelial cells (ECs) may occur at different stages of tumor development and progression. Different adhesion molecules may also be involved in different types of tumors. In this review, we focus only on those adhesion molecules known to be associated with tumor growth and metastasis (Table 1).

Integrins are the largest family of cell adhesion molecules that mediate cell-matrix and cell-cell adhesion. They are transmembrane heterodimers composed of an α-chain and a β-chain. At least 15 α and 98 subunits have been described. An α-subunit can associate with more than one β-subunit to form different integrin molecules, and vice versa. Integrins on the cell surface serve as receptors for many proteins such as the Ig superfamily and cell-matrix proteins including fibronectin (FN), vitronectin (VN), laminin (LM) and collagen. Most integrins have multiple ligand specificities, and more than one integrin can often bind to the same ligand (Buck, 1995). A short amino acid...
### Table 1. Classification of cell adhesion molecules.

<table>
<thead>
<tr>
<th>FAMILY</th>
<th>NAME</th>
<th>CLUSTER OF DIFFERENTIATION (CD)</th>
<th>LIGAND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Integrins</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>I 81 (very late activation antigens)</td>
<td>α1β1 (VLA-1)</td>
<td>CD49a/CD29</td>
<td>Coll, LM</td>
</tr>
<tr>
<td></td>
<td>α2β1 (VLA-2)</td>
<td>CD49b/CD29</td>
<td>Coll, LM, FN</td>
</tr>
<tr>
<td></td>
<td>α3β1 (VLA-3)</td>
<td>CD49c/CD29</td>
<td>LM, Coll, FN</td>
</tr>
<tr>
<td></td>
<td>α4β1 (VLA-4)</td>
<td>CD49d/CD29</td>
<td>FN, VCAM-1, ICAM-2</td>
</tr>
<tr>
<td></td>
<td>α5β1 (VLA-5)</td>
<td>CD49e/CD29</td>
<td>FN, INV</td>
</tr>
<tr>
<td></td>
<td>α6β1 (VLA-6)</td>
<td>CD49f/CD29</td>
<td>LM, INV</td>
</tr>
<tr>
<td></td>
<td>αvβ3</td>
<td>CD51/CD29</td>
<td>FN</td>
</tr>
<tr>
<td>II 82 (LeuCAM)</td>
<td>αLβ2 (LFA-1)</td>
<td>CD11a/CD18</td>
<td>ICAM-1, -2, -3, E-selectin</td>
</tr>
<tr>
<td></td>
<td>αMβ2 (Mac-1, CR3)</td>
<td>CD11b/CD18</td>
<td>Factor X, endotxin</td>
</tr>
<tr>
<td></td>
<td>αXβ2 (p150/95, CR4)</td>
<td>CD11c/CD18</td>
<td>FG, C3bi</td>
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<tr>
<td></td>
<td>α6β2</td>
<td>CD10/CD18</td>
<td>ICAM-3</td>
</tr>
<tr>
<td>III 83 (cytoadhesins)</td>
<td>αvBS3</td>
<td>CD51/CD61</td>
<td>FG, FN, wVF, VN, TSP</td>
</tr>
<tr>
<td></td>
<td>αvβ63</td>
<td>CD41/CD61</td>
<td>FG, FN, wVF, VN, TSP</td>
</tr>
<tr>
<td>IV Other integrins</td>
<td>αvβ54</td>
<td>CD49f/CD104</td>
<td>LM</td>
</tr>
<tr>
<td></td>
<td>αvBS5</td>
<td>CD51/-</td>
<td>VN</td>
</tr>
<tr>
<td></td>
<td>αvBS6</td>
<td>CD51/-</td>
<td>VN</td>
</tr>
<tr>
<td></td>
<td>α9β6</td>
<td>CD49d/-</td>
<td>FN, VCAM-1, MadCAM-1</td>
</tr>
<tr>
<td></td>
<td>αa8β8</td>
<td>CD51/-</td>
<td>FN</td>
</tr>
<tr>
<td>Immunoglobulin superfamily</td>
<td>ICAM-1</td>
<td>CD54</td>
<td>LFA-1, Mac-1, CD43</td>
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<tr>
<td></td>
<td>ICAM-2</td>
<td>CD102</td>
<td>LFA-1</td>
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<td></td>
<td>ICAM-3</td>
<td>CD50</td>
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<td>VCAM-1</td>
<td>CD106</td>
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<td>CD58</td>
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<tr>
<td></td>
<td>CD4</td>
<td>CD4</td>
<td>MHc class II</td>
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<td></td>
<td>CD8</td>
<td>CD8</td>
<td>MHc class I</td>
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<tr>
<td></td>
<td>PECAM-1</td>
<td>CD31</td>
<td>PECAM-1, α4β8, V93, heparin</td>
</tr>
<tr>
<td></td>
<td>MadCAM-1</td>
<td>-</td>
<td>α4β7, L-selectin</td>
</tr>
<tr>
<td></td>
<td>N-CAM</td>
<td>CD66</td>
<td>N-CAM, heparan sulphate, heparin</td>
</tr>
<tr>
<td></td>
<td>C-CAM</td>
<td>-</td>
<td>C-CAM</td>
</tr>
<tr>
<td></td>
<td>CEA</td>
<td>CD66e</td>
<td>CEA, integrins</td>
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<tr>
<td></td>
<td>MUC18</td>
<td>-</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>DCC</td>
<td>-</td>
<td>?</td>
</tr>
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</table>

### Caderhins
- E-cadherin
- N-cadherin
- P-cadherin

### Selectins
- P-selectin (GMP-140) | CD62P | CD15S, PSGL-1 |
| E-selectin (ELAM-1) | CD62E | CD15S, CD66, ESL-1 |
| L-selectin (Leu8, LECAM-1) | CD62L | CD15S, PNA, MadCAM-1, E-selectin, CD34, glycan-1, P-selectin |

### Cell surface proteoglycan
- H-CAM | CD44 | HA, Coll, FN |


sequence Arg-Gly-Asp (RGD) present in FN, VN and a variety of other adhesive proteins is a major recognition site of several integrins such as αvβ3, αvβ6, αvβ1, αvβ5, αvβ6, αvβ8, and αvβB3 (Akiyama et al., 1995). Other recognition sequences have been identified in FN. The cell surface integrin adhesion receptors also recognize Leu-Asp-Val (LDV) and Arg-Glu-Asp-Val (REDV) in FN. The Tyr-Ile-Gly-Ser-Arg (YIGSR) sequence in LM mediates the binding of LM to the αvβ3 integrin receptor (Humphries et al., 1987; Komoriya et al., 1991).

A number of studies have suggested that interactions of integrins with their ligands are associated with tumorigenicity and tumor progression (Akiyama et al., 1995; Buck, 1995) and altered expression of integrins on tumor cells can change their adhesive properties and biological behavior (Buck, 1995; Glukhovo et al., 1995). Signaling through integrin engagement can both protect and promote apoptosis of tumor cells (Brooks et al., 1994; Montgomery et al., 1994; Ruoslahti, 1995). In invasive and metastatic melanoma the αvβ3, (receptor of VN, FN and LM) and αvβ3 (VCAM-1(CD106) and FN receptor) molecules are upregulated. αvβ3 has been implicated in enhancing the invasiveness of melanoma cells in vitro and in increasing melanoma growth in vivo (Felding-Habermann et al., 1992; Juliano and Varner, 1993). αvβ3 mediates the binding of melanoma cells to endothelial cells and may be involved in promoting metastasis (Albelda et al., 1990; Albelda, 1993).

A systematic study of integrin expression in normal colon, adenomas and carcinomas within the same patient has shown that as cells transit from adenomas to carcinomas there is a progressive loss in expression of both αvβ1, receptors for collagen and LM and αvβ1 receptors for FN (Pignatelli et al., 1990; Stallmach et al., 1992). It has also been suggested that αvβ1 may function as a negative growth regulator when it is not bound to its ligand, whereas when the receptor is occupied, the negative signal is relieved and/or positive growth signal is generated (Juliano and Varner, 1993). A decrease in expression of αvβ1 increases the tumorigenicity of Chinese hamster ovary (CHO) cells in nude mice (Ruoslahti, 1995). In contrast, increased expression of the αvβ1 in CHO and human colon cancer cells inhibits their tumorigenicity in vivo (Giancotti and Ruoslahti, 1990; Ruoslahti, 1995). However, in the absence of serum and growth factors, the binding of αvβ1 to FN might prevent apoptosis of tumor cells by enhancing the expression of bcl-2 (Zhang et al., 1995). Studies using human prostate cancer cells indicate that expression of αvβ3 and the loss of αvβ4 in tumor cells might confer an invasive phenotype (Cress et al., 1995). The αv integrins also appear to be important in tumor growth. For example, Agrez et al. (1994) have demonstrated that αvβ6 enhances the growth of colon cancer cells in vitro and in vivo, while Friedlander et al. (1996) reported that anti-αv and β1 antibodies completely inhibited the migration of astrocytoma cells. Antibodies against αvβ3 blocked intercellular adhesion and organoid formation of colon carcinoma cells, resulting in rapid apoptosis of these tumor cells (Bates et al., 1994). The survival and
growth of human melanoma cells within a three-dimensional dermal collagen matrix also required ligation of $\alpha_3\beta_1$ to dermal collagen. Disruption of this interaction with an anti $\alpha_3\beta_1$ MAb induced cell death (Montgomery et al., 1994). Moreover, $\alpha_3\beta_1$ on tumor cells can bind to matrix metalloproteinase MMP-2 in a proteolytically active form and facilitate cell-mediated collagen degradation and thus invasion (Brooks et al., 1996). In addition, it has been demonstrated that $\alpha_3\beta_1$ is necessary for proliferation and maturation of newly forming blood vessels, an event essential for the growth and metastasis of human tumors (Drake et al., 1995). Recently, Kostenuik et al. (1996) reported that human prostatic carcinoma cells adhere to bone matrix via the $\alpha_3\beta_1$ integrin collagen receptor, and that collagen-derived peptides and antibodies against the $\alpha_3$ or $\beta_1$ integrin subunits inhibit this interaction. Therefore, the integrins may be involved at several levels in both tumor development and progression.

The Ig superfamily includes molecules which function in cellular immunity (i.e., the MHC antigens, CD2, CD4, CD8 and the T cell receptor) and leukocyte trafficking [ICAM-1 (CD54), ICAM-2 (CD102), PECAM-1 (CD31) and VCAM (CD106)], as well as neural cell adhesion molecule (N-CAM, CD56), epithelium-specific adhesion molecule C-CAM, carcinoembryonic antigen (CEA), «deleted in colorectal carcinoma» (DCC), vascular addressin, MAdCAM-1, epithelial-specific adhesion molecule C-CAM, carcinoembryonic antigen (CEA), «deleted in colorectal carcinoma» (DCC), vascular addressin, MAdCAM-1, PECAM-1 (CD31) and VCAM (CD106), as well as neural cell adhesion molecule (N-CAM, CD56), epithelium-specific adhesion molecule C-CAM, carcinoembryonic antigen (CEA), «deleted in colorectal carcinoma» (DCC), vascular addressin, MAdCAM-1 and MUC18 (Johnson, 1991; Zhu et al., 1991; Kleinerman et al., 1995a,b). These molecules contain Ig homology units in their extracellular domain and they can mediate homotypic and heterotypic adhesion. Many reports have suggested that de novo expression or secretion of CD54 may be involved in the pathogenesis and progression of many types of tumors including hematopoietic and epithelial neoplasms (Johnson et al., 1989; Natali et al., 1990; Huang et al., 1995; Santarosa et al., 1995). Indeed, increased expression of CD54 on melanoma and lymphoma cells correlates with an increased risk of metastasis and a reduced number of disease-free remissions (Johnson et al., 1989; Stauder et al., 1989; Natali et al., 1990). CD106, expressed on endothelial cells, can mediate the attachment of $\alpha_3\beta_1^+$ tumor cells to endothelium and facilitate metastasis (Albelda et al., 1990). MUC18 has been identified as a progression-associated molecule in melanoma (Lehmann et al., 1989) and there is a significant correlation between MUC18 expression in melanoma cells and their ability to form metastases (Luca et al., 1993; Edward, 1993). DCC is a transmembrane protein with many similarities to the N-CAM family: 1) it is encoded by a gene that is deleted in colorectal carcinoma (Fearon et al., 1990); 2) decreased or absent DCC expression is a common alteration in several types of tumors (Fearon and Pierceall, 1995); 3) inactivation of this gene may lead to abnormalities in cell-cell interaction and the malignant phenotype. Increased CEA expression is associated with malignant transformation and high levels of CEA have been found in many human adeno-carcinomas. CEA mediates homotypic aggregation of tumor cells as well as the homing of colorectal cancer cells to liver (Johnson, 1991; Jothy et al., 1995). Kleinerman and colleagues (1995a,b) have demonstrated that C-CAM, an androgen-regulated cell adhesion molecule, acts as a tumor suppressor in prostate cancer. Transfection of an antisense C-CAM vector into a nontumorigenic prostate epithelial cell line, results in tumor formation in nude mice, while expression of C-CAM in a human prostate cancer cell line suppressed tumor growth in vitro and tumorigenicity in vivo (Hsieh et al., 1995). More recently, Zhu et al. (1992) showed that a lung-specific endothelial cell adhesion molecule (Lu-ECAM-1) which is constitutively present on lung endothelial cells, mediated metastasis of murine melanoma cells to the lung. Anti-Lu-ECAM-1 MAb markedly reduced lung metastasis.

Cadherins are calcium-dependent cell-cell adhesion molecules. There are at least three subclasses of cadherins including epithelial cadherin (E-cadherin), neural and muscular cadherin (N-cadherin) and placental cadherin (P-cadherin). E-cadherin is expressed in almost all cell types and plays a key role in the maintenance of epithelial structure. Inactivation of E-cadherin causes the disruption of cell-cell adhesion, and over-expression of E-cadherin by genetic manipulation induces tighter cell adhesion (Shiozaki, 1996). E-cadherin has been implicated as a suppressor of invasion since a decrease or absence of this adhesion molecule leads to an increased invasive potential of epithelial tumor cells and is associated with the progression of several kinds of epithelial neoplasms (Frixen et al., 1991; Matsuura et al., 1992; Giroldi et al., 1994; Shiozaki et al., 1996). Transfection of an E-cadherin-expressing vector into highly malignant epithelial tumor cells abrogated their invasiveness, while treatment with anti-E-cadherin antibodies rendered invasiveness of these transfectants (Vleminkx et al., 1991). Moreover, noninvasive ras-transformed epithelial cells were rendered invasive by down-regulating E-cadherin expression following introduction of a plasmid encoding E-cadherin-specific antisense RNA (Vleminkx et al., 1991). These studies suggest that impaired functions of E-cadherin may contribute to the release of cancer cells from the primary lesion and trigger invasion and metastasis (Shiozaki et al., 1996).

Selectins are glycoproteins that have a lectin-like domain which binds to specific carbohydrate structures, such as the sialyl Lewis$^x$ (SL$^x$, CD15s) and sialyl Lewis$^b$ (SL$^b$) antigens. Three types of selectins have been described, i.e., E-selectin (ELMA-1, CD62E), L-selectin (Leu-8, CD62L) and P-selectin (GMP-140, CD62P). These molecules mediate cellular interactions with the vascular endothelium and are involved in lymphocyte rolling, in recruiting leukocytes to sites of inflammation, in the activation of neutrophils and in lymphocyte homing (Crook-Torabi and Fantone, 1995). Tumor cells show increased expression of CD15s and SL$^x$ (Fukuda, 1996). Highly metastatic colonic
carcinoma cells bind more avidly to CD62E on activated human endothelial cells than on low-metastatic counterparts (Fukuda, 1996). Patients with higher levels of CD15s on their tumors have a poorer prognosis than those with lower levels of CD15s (Nakamori et al., 1993). Furthermore, Saiki et al. (1996) demonstrated that anti-CD62E antibodies or synthetic CD15s inhibit tumor cell attachment to layers of activated ECs, suggesting that E-selectin on ECs may be important for the adhesive interactions of the endothelium with CD15s-expressing tumor cells in target organs to form metastasis. P-selectin is also expressed on endothelium and may facilitate the arrest of tumor cells in microvessels by mediating the binding of platelets to certain tumor cells, forming tumor cell clumps and aggregates in the circulation (Stone and Wagner, 1993).

CD44 is a broadly distributed cell surface proteoglycan which is expressed in a variety of isoforms with different molecular weights. CD44 interacts primarily with hyaluronate in the extracellular environment and pericellular layer and mediates cell-cell and cell-matrix binding. It may also bind to FN and collagen (Yamaguchi et al., 1996). It is involved in hematopoiesis, lymphocyte homing and leukocyte activation (Lazar and Pure, 1995). CD44 has also been associated with tumor cell proliferation and metastasis (Lokeshwar et al., 1995). The upregulation of CD44 or the expression of certain isoforms of CD44 have been linked to the increased aggressiveness and metastatic potential of many human tumors (Koopman et al., 1993; Tanabe et al., 1993; Lokeshwar et al., 1995; Ermak et al., 1996; Yamaguchi et al., 1996). In rat pancreatic and mammary adenocarcinomas, expression of CD44v6, a splice variant of CD44, correlates with their metastatic properties. Hence, overexpression of this variant in several non-metastasizing tumor cell lines confers full metastatic behavior to these cells (Gunthert et al., 1991; Rudy et al., 1993). Expression of a hyaluronate-binding form of CD44 (CD44H) in human tumors significantly enhances their rate of local growth and hematogenous dissemination in nude mice (Sy et al., 1991) since the capacity of CD44 to mediate tumor cell attachment to hyaluronate determines the rate of formation of the resulting tumor mass (Bartolazzi et al., 1994). It has been thought that hyaluronate might serve as a molecular bridge, promoting tumor cell interactions with host tissue ECM components which are critical for growth of both primary and metastatic tumors (Bartolazzi et al., 1994). Alternatively it may be important in the initial adhesion step leading to extravasation from the blood, as recently shown (DeGrendele et al., 1996).

Tumor progression is a dynamic process likely to be determined by the interactions of tumor cells with each other, with host cells and with the ECM. Adhesion receptors may also transmit growth stimulatory and/or inhibitory signals to tumor cells. Therefore, alterations in their expression or function may contribute to the uncontrolled proliferation and metastasis of malignant cells (Pignatelli and Wilding, 1996). Loss in expression or function of some adhesion molecules, such as E-cadherin and certain integrins, in tumor cells may promote the detachment of the cells from the primary tumors. Upregulation of certain adhesion molecules (i.e., CD44, integrins containing αv or α6) may enhance tumor invasion through adjacent stroma and extravasation through endothelial basement membrane and between endothelial cells. In the circulation, integrins and members of Ig superfamily mediate the adhesion of tumor cells to each other and activate platelets to form tumor-platelet aggregates. Fibronogen, FN and thrombospondin in plasma may bridge tumor cells to platelets or endothelial cells through their adhesion receptors. The αIIbβ3 receptor and P-selectin on platelets are also important in the formation of tumor emboli (Honn et al., 1995). The attachment of tumor cells to the endothelium in selective target organs is directed by integrins, selectins, organ-specific endothelial adhesion molecules and members of the Ig superfamily (Santarosa

![Diagram](image-url)
et al., 1995; Kleinerman et al., 1995b). Finally, adhesion molecules are required in cellular extravasation, invasion of the subendothelial matrix, migration into the tissue parenchyma, neovascularization and the formation of metastasis. These processes represent potential targets for antiadhesion therapy (Fig. 1).

The development of new therapies involving anti-adhesive molecules

Knowing the importance of adhesion molecules in tumor growth, invasion, and metastasis has provided a rationale for developing new therapies. It is believed that most malignant cells use adhesion molecules to promote their growth and guide their dissemination into particular organs. Thus, by preventing tumor cells from interacting with each other or with their microenvironments, tumor growth and metastasis should be suppressed. In this regard, several approaches aimed at inhibiting the activities of adhesion molecules have been studied in vitro and in experimental animals and some have been evaluated in clinical trials for inflammatory diseases (Davis et al., 1995; Kavanaugh et al., 1994), transplantation (Mauff et al., 1996) and cardiovascular diseases (Jordan et al., 1996). Due to their specificity and unlimited availability, the most common approach is to use monoclonal antibodies (MAbs) which recognize adhesion molecules. Many studies have shown that neutralizing MAbs which target adhesion molecules are effective in inhibiting invasion, dissemination and/or proliferation of tumor cells in animal systems (Ruiz et al., 1993; Saiki et al., 1993; Zahalka et al., 1993; Edward, 1995; Newton et al., 1995). By directly interfering with cell-cell or cell-ECM interactions, these antibodies may disrupt invasion processes of tumor cells or induce adhesion-dependent apoptosis (Bates et al., 1994, 1995). Many adhesion molecules can also serve as signal transducing molecules and, thus, antibodies directed against adhesion molecules may induce negative signals in tumor cells resulting in apoptosis or growth arrest (Lokeswar et al., 1995; Newton et al., 1995). Other attractive approaches to inhibit tumor growth and metastasis involve the development of simple synthetic peptides (Humphries et al., 1986, 1988; Kleinerman et al., 1989; Kumagai et al., 1991), non-peptidic antagonists of adhesion molecules (Greenspoon et al., 1993; Harden et al., 1993) as well as soluble adhesion molecules including recombinant forms and proteolytic fragments (McCarthy et al., 1986, 1988; Barsky et al., 1988; Sy et al., 1992; Bartolazzi et al., 1994). These bind to recognition sites on adhesion receptors and compete with cell or matrix-associated natural adhesion molecules.

Angiogenesis is also necessary for tumor development and growth. Recently, some adhesion molecules have been found to play crucial roles in tumor neovascularization (Brooks et al., 1994). Antagonists of these adhesion molecules can induce apoptosis of proliferating angiogenic blood vessels without affecting preexisting quiescent blood vessels. They may thus disrupt ongoing angiogenesis in tumors, and consequently suppress tumor progression (Brooks et al., 1994, 1995). Cytokines can alter the expression of adhesion molecules on tumors and change their biological behavior (Garofalo et al., 1995; Herzberg et al., 1996). Hence, they may enhance tumor metastasis by upregulating the expression of certain adhesion molecules on endothelial cells or tumor cells. These effects can be blocked by specific cytokine antagonists. On the other hand, some cytokines may diminish the metastatic potential of tumors by changing the patterns of expression of adhesion molecules (Herzberg et al., 1996). Other approaches includes restoring the functions of tumor-suppressive adhesion molecules or specifically downregulating the expression of progression-associated adhesion molecules in tumor cells with pharmacologic agents or by genetic approaches (Chiang et al., 1991; Lallier and Bronner-Fraser, 1993; Bennett et al., 1994; Jiang et al., 1995; Kleinerman et al., 1995a,b). Finally, combinations of anti-adhesion and chemotherapeutic agents are also being explored (Saiki et al., 1993).

Current status of anti-adhesion molecule therapy in cancer

Due to the importance of FN-integrin interactions in tumor cell migration, invasion and metastasis, interruption of these interactions may have significant antitumor effects. Several anti-integrin antibodies inhibit experimental metastasis in different tumor models by different mechanisms (Yamada et al., 1990; Newton et al., 1995). Thus, Akiyama et al. (1995) showed that a monoclonal anti-β1 integrin antibody was very effective in blocking the invasion of both fibrosarcoma cells and breast cancer cells and completely inhibited invasion through reconstituted basement membrane Matrigel even when added after the cells were allowed to attach to the membrane. This suggests that the antibody might inhibit a later step in the invasion process, such as migration through the Matrigel (Yamada et al., 1990). Both anti-β1 and anti-α5 MAbs also inhibit experimental metastasis of breast carcinoma cells when coadministered with tumor cells to nude mice (Newton et al., 1995). Pretreating tumor cells with Fab fragments of the antibodies was as effective as co-injection of intact antibodies with tumor cells, indicating that the antibodies might inhibit the initiation of adhesion during tumor cell arrest and cell migration. Antibody against LM-specific α6β4-containing integrins inhibited experimental metastasis of B16/129 murine melanoma cells to lung (Ruiz et al., 1993; Edward, 1995). Direct examination of tissues showed that the antibody inhibited the adhesion of melanoma cells to the vascular endothelium in the lungs within five minutes of injection. IL-1 could increase lung metastasis of melanoma by inducing CD106 expression on endothelial cells. Pretreatment of tumor cells with a MAb against the CD106 ligand, α4β1, completely abrogated IL-1-augmented lung metastasis

Adhesion molecules as targets for therapy

Due to the importance of FN-integrin interactions in tumor cell migration, invasion and metastasis, interruption of these interactions may have significant antitumor effects. Several anti-integrin antibodies inhibit experimental metastasis in different tumor models by different mechanisms (Yamada et al., 1990; Newton et al., 1995). Thus, Akiyama et al. (1995) showed that a monoclonal anti-β1 integrin antibody was very effective in blocking the invasion of both fibrosarcoma cells and breast cancer cells and completely inhibited invasion through reconstituted basement membrane Matrigel even when added after the cells were allowed to attach to the membrane. This suggests that the antibody might inhibit a later step in the invasion process, such as migration through the Matrigel (Yamada et al., 1990). Both anti-β1 and anti-α5 MAbs also inhibit experimental metastasis of breast carcinoma cells when coadministered with tumor cells to nude mice (Newton et al., 1995). Pretreating tumor cells with Fab fragments of the antibodies was as effective as co-injection of intact antibodies with tumor cells, indicating that the antibodies might inhibit the initiation of adhesion during tumor cell arrest and cell migration. Antibody against LM-specific α6β4-containing integrins inhibited experimental metastasis of B16/129 murine melanoma cells to lung (Ruiz et al., 1993; Edward, 1995). Direct examination of tissues showed that the antibody inhibited the adhesion of melanoma cells to the vascular endothelium in the lungs within five minutes of injection. IL-1 could increase lung metastasis of melanoma by inducing CD106 expression on endothelial cells. Pretreatment of tumor cells with a MAb against the CD106 ligand, α4β1, completely abrogated IL-1-augmented lung metastasis...
Anti-LM containing the LM receptor-binding region inhibited because pulmonary metastasis (Terranova et al., 1982; Barsky et al., 1984; Komoriya et al., 1991; Yamamura et al., 1993). This pentapeptide may not only block tumor cells binding to basement membranes by competing with LM for the LM receptor on tumor cells, but also suppress tumor-induced angiogenesis. Many synthetic peptides containing the YIGSR sequence are effective in inhibiting the growth and dissemination of different types of tumors (Yamamura et al., 1993). A \(\alpha_\beta_3\)-specific peptide has been isolated and can induce apoptosis of tumor cells under serum-free condition (Koivunen et al., 1994; Ruoslahti, 1995). It has been demonstrated that synthetic CD15s inhibits tumor-cell arrest in the lungs following i.v. injection of B16-BL6 melanoma cells while the FN-derived RGDS peptide analogues [Ar(DRGDS)\(_3\)] inhibit the invasion of tumor cells into basement membranes. Therefore, different adhesion molecule antagonists can target cells at different stages of the metastasis processes.

Morla et al. (1994) have found that soluble FN can be converted into fibrils (superfibronection) following treatment with a small recombinant fragments derived from the III\(_1\)-C domain of FN. Superfibronection is ten-fold more adhesive to cells than native FN and effectively inhibits cell migration in vitro and tumor growth in vivo (Matsumoto et al., 1991; Saiki et al., 1991, 1995; Yoneda et al., 1994; Ruoslahti, 1995) reported that a recombinant fusion polypeptide CH271 containing both cell- and heparin-binding domains of FN is very effective in inhibiting liver and lung metastasis of three different types of tumors. Hence, it reduced the arrest and retention of tumor cells in target organs, blocked their adhesion to subendothelial matrix and inhibited invasion of the basement membrane. Murata et al. (1989) demonstrated that 6-O-carboxyl-methyl-chitin (SCM-chitin), which structurally mimics heparan and heparin sulfate but does not have heparin-like anticoagulant properties, inhibited lung colonization of murine melanoma cells. The antimetastatic activity of SCM-chitin might be due to the suppression of tumor cell invasion and tumor-induced angiogenesis by specific binding to LN and FN and/or by inhibiting the enzymatic activities of cell-derived heparanase and type-IV collagenase (Saiki et al., 1990; Murata et al., 1991).

A new synthetic compound SCM-chitin-RGDS, in which the cell-adhesive RGDS peptide was conjugated to SCM-chitin has great therapeutic potential in cancer metastasis (Komazawa et al., 1993). This conjugate effectively inhibited liver metastasis of lymphomas and colon carcinomas in mice, and increased survival rates of tumor-bearing animals. Combined treatment with CH271 and the anti-cancer drugs, doxorubicin or mitomycin-C, resulted in enhanced inhibitory effects on
tumor metastasis and invasion, and significantly prolonged the survival of mice with lymphomas (Saiki et al., 1993). This study suggested that anti-adhesion therapy in combination with chemotherapy might result in additive antitumor activity.

Because altered expression of variant forms of CD44 is associated with proliferation and metastasis of tumor cells, blocking the ability of CD44 to interact with its ligands has been investigated as a means of suppressing the growth of tumors in vitro and in vivo. Coinjection of an anti-CD44 antibody with metastatic tumor cells led to retardation or even complete blockade of lymph node and lung metastases in mice (Seiter et al., 1993). A neutralizing anti-CD44 antibody, IM7.8.1, inhibited proliferation of human prostate cancer cells and significantly decreased their invasive activity (Lokeshwar et al., 1995). Zahalka et al. (1993, 1995) also demonstrated that the IM7.8.1 prevented lymph node invasion by subcutaneous (s.c.) murine lymphoma LB cells but not spleen infiltration, which was blocked by anti-LFA-1 MAbs. Administration of the anti-human CD44, which completely inhibits the binding of the human melanoma cell line SMMU-2 to hyaluronic acid in vitro, suppressed the growth and metastatic potential of SMMU-2 tumor cells in vivo (Guo et al., 1994). Hence, early i.v. administration of this antibody significantly inhibited the growth of s.c. melanomas. Furthermore, when antibody treatment was initiated one week after tumor inoculation, it did not suppress local tumor development but did inhibit the formation of metastatic tumors leading to prolongation of survival. Sy et al. (1992) have shown that a soluble recombinant CD44-Ig fusion protein, which binds to hyaluronic acid in ECM, effectively suppressed hematogenous dissemination of CD44H+ human B-lymphoma cells in nude mice. Bartolazzi et al. (1994) also showed that the soluble fusion protein blocked local development of murine melanomas without affecting the growth of the tumor cells in vivo. These studies indicated that interference with CD44-hyaluronic acid interaction can suppress tumor growth and metastasis.

The interaction of CD54 with its ligand (LFA-1 (q3-B2), CD11a/CD18) might be involved in the pathogenesis of lymphoma and multiple myeloma (Van Riet and van Camp, 1993). Anti-CD18 and anti-CD54 MAbs inhibit invasion and metastasis of murine and human lymphomas (Harning et al., 1993; Rocha et al., 1996). One anti-CD54 antibody had strong antitumor activity in SCID mice with disseminated human myeloma although it was not cytotoxic to tumor cells in vitro. This antibody also suppressed the growth of advanced tumors, suggesting that the antibody may interfere with invasion and/or the homing of tumor cells to anatomical sites crucial for their growth in vivo (Huang et al., 1995).

Cell-cell interaction mediated by carbohydrate components of major tumor-associated carbohydrate antigens has been suggested to play a role in tumor progression (Hakomori, 1991). In this regard, glycosphingolipid-containing liposomes, oligosaccharide derivatives of glycosphingolipids or MAbs against carbohydrates on tumor cells inhibit tumor metastasis of mouse melanomas, most likely by interfering with the early stages of interaction between tumor cell surface glycosphingolipids or carbohydrates and endothelial cell glycosphingolipids or carbohydrates (Hakomori, 1991; Honn et al., 1992). Modified citrus pectin, a soluble component of a plant fiber derived from citrus fruit, interferes with cell-cell interactions mediated by cell surface carbohydrate-binding galectin-3 molecules. An in vitro study showed that the modified citrus pectin inhibited both the adhesion of prostate cancer cells to rat endothelial cells and colony formation in semisolid media. Oral administration of the modified citrus pectin markedly reduced spontaneous metastasis of prostate cancer in rats. The effect of modified citrus pectin might be manifested in the early stages of metastasis, possibly by inhibiting the formation of tumor cell emboli as well as by inhibiting the interactions between tumor cells and the endothelium of a target organ, thus, acting as anti-adhesion agent (Pienta et al., 1995).

Several approaches aimed at restoring or enhancing the expression and functions of tumor-suppressive adhesion molecules or downregulating progression-associated adhesion molecules in tumor cells have been investigated (Kleinerman et al., 1995b; Jiang et al., 1995; Rummel et al., 1996). Using a recombinant adenoviral delivery system, Kleinerman and coworkers (1995a,b) demonstrated that expression of tumor suppressor C-CAM slowed the growth of human prostate tumors in nude mice. Vleminkx et al. (1991) showed that introducing the E-cadherin gene into highly invasive epithelial tumor cells significantly suppressed their invasive behavior in vivo. Jiang et al. (1995) have also reported that gamma-linolenic acid, a n-6 polyunsaturated fatty acid, upregulated E-cadherin expression in a range of human cancer cells, increased cell aggregation, and inhibited their motility and invasion. More recently, Rummel et al. (1996) have demonstrated that exposure to PMA reduced MUC18 expression in tumor cells. Antisense oligonucleotides or expression of antisense RNA in tumor cells by gene therapy can also specifically inhibit the expression of metastasis-associated proteins in tumor or host cells (Vleminkx et al., 1991; Bennett et al., 1994). In addition, several cytokines such as tumor necrosis factor (TNF) and IL-4 can induce changes in integrin expression and adhesive properties of tumor cells and decrease the metastatic potential of colon carcinoma cells (Herzberg et al., 1996). These studies strongly suggest that it may be possible to devise strategies to regulate the expression of certain adhesion molecules in tumor cells and thereby influence tumor growth and/or metastatic behavior.

Conclusions

The mechanisms controlling tumor growth and metastasis are extremely complex and involve numerous biochemical processes. These include adhesion
molecule-mediate signaling and cell-cell and cell-matrix interactions which are essential biological processes in tumor development and dissemination. A number of preclinical studies have demonstrated the feasibility of using agents aimed at altering adhesion processes in controlling tumor growth and metastasis. In particular, anti-adhesion therapy holds promise as an adjuvant therapy, specifically in metastasis. It may also be used to enhance the cytotoxic effects of conventional chemotherapeutic agents and reverse drug resistance (Bates et al., 1995; Kerbel, 1995).

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References


Adhesion molecules as targets for therapy


Adhesion molecules as targets for therapy


