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Abstract: In recent years, cell adhesion and cell adhesion molecules have been shown to be important for many normal biological processes, including embryonic cell migration, immune system functions and wound healing. It has also been shown that they contribute to the pathogenesis of a large number of common human disorders, such as rheumatoid arthritis and tumor cell metastasis in cancer.

In this review, the basic mechanisms of cellular adhesion and the structural and functional features of adhesion molecules are summarized.

Introduction

Cells in vivo must form contacts with their neighbours or with an extracellular matrix (ECM) in order to form tissues or organs. The macromolecular components of ECM, which are secreted by resident cells, include proteglycans, glycoproteins and collagens, which may function as tracks, directing migrating cells along a particular route. Other members of the ECM, including adhesive molecules such as laminin, vitronectin and fibronectin, facilitate the adherence of cells to their substratum as they migrate. ECM not only fills intercellular spaces, shaping and strengthening many tissues, but also influences celluar functions such as state of differentiation and proliferation (1, 2, 4). Evidence originally obtained from studies with antisera against cell surface proteins revealed that the morphology of cells bound to the ECM could be modified and that these cells could become de-attached by such treatments, suggesting that specific receptors regulated the process (2). In the last 20 years, the nature of many of these cell adhesion receptors has been elucidated, while the use of synthetic peptides or proteolytic fragments of adhesive proteins has revealed the nature of cell-binding sites on these receptors (3, 4).

Cell adhesion receptors identified to date mediate both homophilic adhesion (which involves binding of an adhesion molecule on one cell to the same adhesion molecule on a second cell) and heterophilic adhesion (in which an adhesion molecule on one cell type binds to a different type of cell adhesion molecule on a second cell). The T-cell interaction with antigen-presenting target cells in the immune system is the best known example of heterophilic adhesion (4). Many different molecules have been identified by using specific monoclonal antibodies (mAbs) and the subsequent identification of genes responsible for encoding these molecules has shown that they are structurally different from each other. These cell adhesion molecules can be divided into 4 major families: the cadherin superfamily, the selectins, the immunoglobulin superfamily and the

integrins (2-5). The interactions of these cell adhesion with the ECM are important for development processes as diverse as the differentiation of tissues, morphogenesis and the development of metastases. During embryogenesis, for example, adhesion mediated by cell adhesion receptors to fibronectin is essential for cell motility, which is involved in the migration of neural crest and primordial germ cells (1). When mammary epithelial cells were cultured only on reconstituted basement membrane or on collagen gels, they became polarised and produced milk proteins, suggesting that ECM-receptor interactions also are involved in determining the differentiation of tissues (6). In malignant disease, the adhesive interactions of tumour cells with other cells or with the ECM are thought to regulate invasive and metastatic behaviour. Several lines of evidence have been used to demonstrate the involvement of altered expression of adhesion molecules in some of the events of the metastatic process. For example, down-regulation or loss of $\alpha5\beta1$ integrin expression from neoplastic cells seems to be associated with increased tumorigenicity in nude mice (7). In addition, down-regulation of E-cadherin was found in many carcinomas, such as in those of the head and neck region (8, 9), the thyroid (10), the lungs (11) and the prostate (12, 13).

The Cadherins

One group of cell adhesion molecules implicated in tissue formation are the Ca^{2+}– depentent, developmentally regulated, transmembrane proteins termed cadherins (8-14). Cadherins expressed on one cell can bind to a matching cadherin expressed on a neighbouring cell, co cadherins interact in a homophilic fashion (5). However, more recent studies have revealed that various types of cadherin can also interact with other cell adhesion family members, such as integrins and proteglycans, in a heterophilic fashion. For example, E-cadherin on epithelial cells binds to the $\alpha E\beta7$ integrin expressed on T-lymphocytes (15). Cadherins contain a short transmembrane domain and a relatively long extracellular domain containing four cadherin repeats (EC1-EC4), each of which contains calcium binding sequences. The structural features of cadherins are demonstrated in Figure 1. The cytoplasmic domain is highly conserved region between cadherin molecules, implying that it has an important function. Cadherins interact with specific cytoplasmic proteins, e.g., catenins (α, β and γ) (16), as a means of being linked to the actin cytoskeleton. The binding of cadherins to the catenins is crucial for cadherin function, and the deletion of specific sites in the cytoplasmic domain of the cadherins inhibits the interaction between cadherins and catenin, with the result that the cadherins become nonadhesive. As a consequence of this interaction with catenins, the cadherins are able to form cell junctions, which are important for epithelial cell polarity (17, 18, 20). Many different cadherins have been described, the main ones being neural cadherin (N-cadherin), placental cadherin (P-cadherin) and epithelial cadherin (E-cadherin). Each cadherin shows a specific tissue distribution during development and adult life. For example, N-cadherin is the predominant cadherin of neural tissues, but is also expressed on cardiac and skeletal muscle cells, where it maintains the stucture of intercalated discs between neighbouring muscle cells (19). The permanent expression of P-cadherin is limited to the epidermis, mesothelium and corneal epithelium (20), and E-cadherin expression is restricted to non-neural epithelial tissues (21).

E-cadherin is thought to be important during embryonic development, and is also involved in generating and maintaining epithelial layers in adult tissues (22). Furthermore, the loss of E-cadherin expression has been linked to the invasive behaviour of tumour cells. When kidney epithelial cells, which express E-cadherin and are non-invasive, are transfected with oncogenes, they become invasive and show the loss of E-cadherin expression on their cell surface. Similar results have been obtained by using anti-E-cadherin antibodies to inhibit E-cadherin activity on non-transformed kidney epithelial cells (17, 18). Many cancer types, such as breast, stomach and colorectal cancer, have been shown by immunohistochemical techniques to exhibit loss or down-regulation of E-cadherin expression (23). In prostate cancer, E-cadherin expression is down-regulated or absent in approximately 50% of tumours. However, there are many reports indicating that some epithelial tumours show no indication of down-regulation or loss of E-cadherin expression (24, 25). Certain metastatic deposits of prostate carcinoma have been shown to exhibit high surface expression of E-cadherin, and the levels of E- and P-cadherins expression are unchanged in the primary tumors or their metastases. However, down-regulation at the protein level is not the only way that cadherin function can be impaired. Interaction of cadherins with abnormal catenins may cause the loss of cadherin mediated cell adhesion, while mutations in the cadherin can also result in a similar loss of function (25).

The Selectins

Selectins, a family of Ca^{+2}–dependent carbohydrate–binding proteins, mediate the initial attachment of leukocytes to the endothelium on the blood vessel wall during the rolling step of leukocyte extravasation in inflammation (2, 4). Selectins recognise fucosylated carbohydrate ligands, especially structures containing Sialyl–Lewis[x] (sLe[x]) and Sialyl–Lewis[a] (sLe[a]), which are heavily expressed on neutrophils and monocytes (26) and also found on natural killer cells. These selectin/carbohydrate interactions permit leukocytes to roll along the vascular endothelium in the direction of blood flow as a prelude to integrin–mediated adhesion.

Structural features of selectins (Figure 2) include the presence of NH_2–terminal C–type Ca^{2+}–dependent lectin–like binding domain, which determines the ability of each selectin to bind to specific carbohydrate lingands, an epidermal growth factor–like region and a number of repeat sequences similar to those found in complement regulatory proteins (CRP). This is followed by a membrane–spanning region and a short cytoplasmic region. The lectin and EGF–like domains are shown to have 60% to 70% homology at the nucleotide and protein level to each other (26, 27). The selectins include a group of three related molecules. E (endothelial)–selectin in expressed on endothelial cells where its synthesis is increased rapidly after cell stimulation by cytokines (TNF–α and IL–1) or endotoxin and then is translocated to the luminal surface of the venular endothelium (28). Because carbohydrate ligands such as sLe[a], a ligand for E–selectin, are expressed on some tumour cells but are not usually found on leukocytes, this interaction between E–selectin and sLe[a] is more relevant to tumour metastases than to leukocyte trafficking. For example, E–selectin has been found to regulate adhesion of human colon cancer cells to the endothelium by binding to sLe[a] and sLe[x] carbohydrate ligands (26, 27).
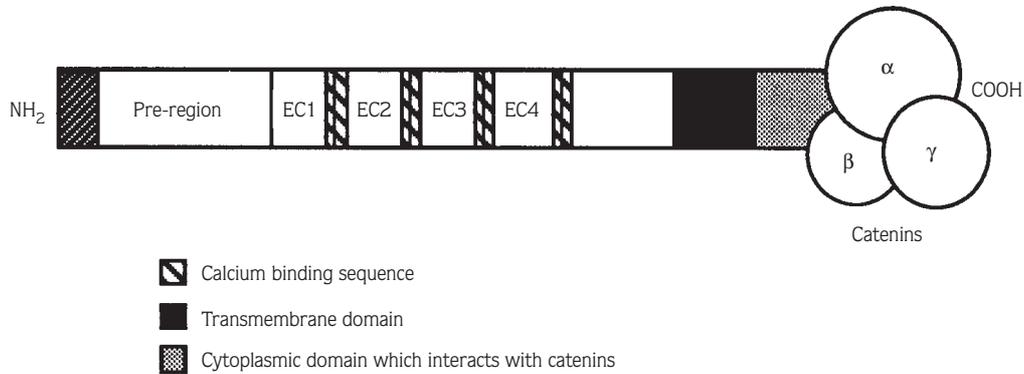
	Calcium binding sequence					

Calcium binding sequence

Transmembrane domain

Cytoplasmic domain which interacts with catenins

Fig. 1.   Structural features of cadherin molecules.

Lectin domain

EGF-like domain

Complement regulatory-like domain

Transmembrane domain
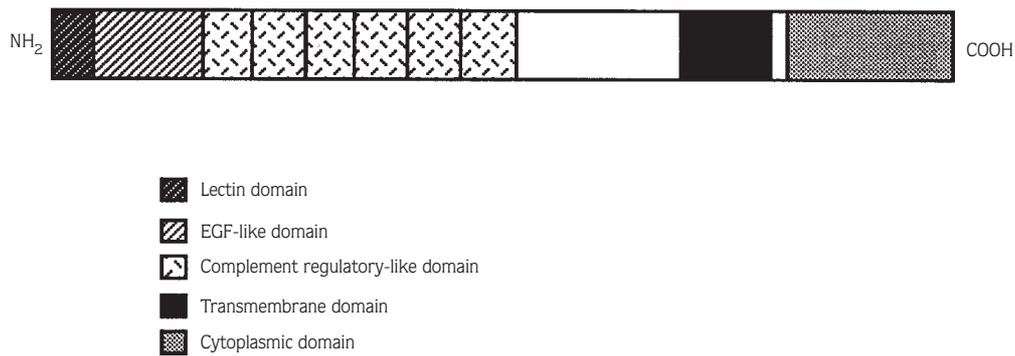
Cytoplasmic domain

Fig. 2.   Schematic diagram of selectin molecule.

P–selectin is another type of selectin adhesion protein that initially was found in platelets and also is constitutively expressed in endothelial cells (29, 30). In both cell types, P–selectin is synthesised and stored in cytoplasmic granules; in platelets P–selectin is contained in the α–granules, whereas in endothelial cells it is found in Wiebel–Palade bodies. P–selectin is mobilised rapidly to the external plasma membrane of endothelial cells and platelets in response to activation with cytokines such as thrombin (30). Expression of P–selectin on the cell surface generally is short–lived, which supports the idea that this selectin mediates early leukocyte–endothelial interactions and also mediates the binding of activated B–cells, and a subset of T–cells, to stimulated endothelium in vitro. Recently it has been shown that P–selectin expressed on platelets regulates their binding to tumour cells and that this phenomenon can

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prevent tumour cell destruction by immune mechanisms owing to the formation of aggregates (29, 30, 31).

Unlike E– and P–selectins, L–selectin is found only on leukocytes and is expressed continuously throughout myeloid differentiation and on early erythroid progenitor cells but not on mature erythrocytes (30). Although originally L–selectin was reported to mediate lymphocyte binding to high endothelial venules (HEV) of peripheral lymph nodes during lymphocyte homing, it subsequently was shown to be expressed on most other peripheral blood leukocytes and is thought to be involved in regulating leukocyte traffic in the systemic microcirculation (28). Some blood cells, such as lymphocytes and neutrophils, have shown a loss of L–selectin expression after activation (32) due to proteolytic cleavage near the site of membrane insertion. Loss of L–selectin from the surface of leukocytes inhibited leukocyte adhesion to cytokine–stimulated endothelium and was able to prevent leukocytes homing to inflammatory sites in vivo (33). Recently elevated levels of L–selectin have been observed in the serum of patients with AIDS and leukemia (34) and it may be that the presence of this molecule has an impact upon the trafficking of normal and neoplastic cells.

Immunoglobulin Superfamily Adhesion Molecules

The immunoglobulin superfamily contains many cell adhesion molecules (Figure 3). The structure of this family of adhesion receptors is characterised by repeated domains, similar to those found in immunoglobulins. By mutation and deletion analysis these immunoglobulin domains have been shown to mediate many different functions, including acting as receptors for growth factors and mediating cell–cell adhesion rather than cell–ECM interactions (35, 36). Though not all immunoglobulin–superfamily adhesion molecules mediate cell–cell interactions, many which belong to this family do function as adhesion receptors, including intercellular
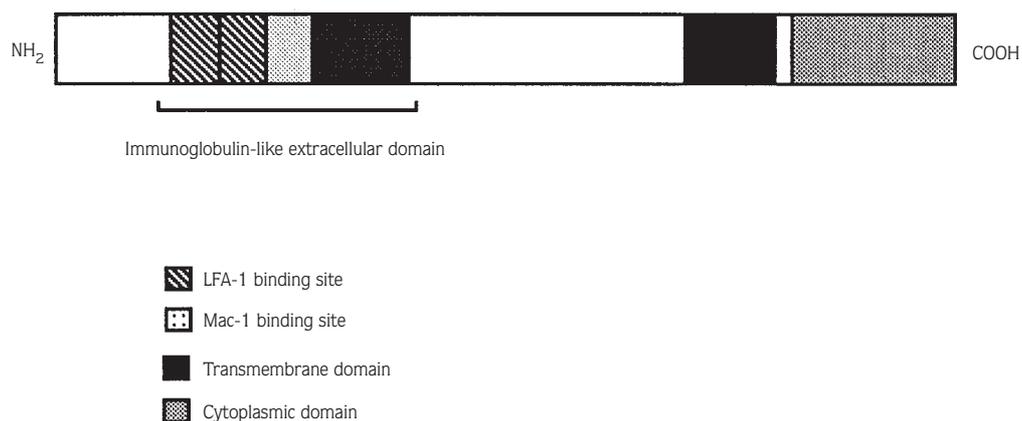

Immunoglobulin-like extracellular domain

LFA-1 binding site

Mac-1 binding site

Transmembrane domain

Cytoplasmic domain

Fig. 3.   A member of immunoglobulin superfamily was shown as a schematic diagram.

adhesion molecule–1 (ICAM–1; CD54), intercellular adhesion molecule–2 (ICAM–2), vascular cell adhesion molecule–1 (VCAM–1; CD106), platelet–endothelial cell adhesion molecule–1 (PECAM–1; CD31) and the mucosal addressin cell adhesion molecule–1 (MAdCAM–1). ICAM–1, ICAM–2 and VCAM–1 are involved in the adhesion of T cells to endothelial cells by serving as surface ligands for the integrins LFA–1 (leukocyte–function antigen–1; $\alpha L\beta 2$) and $\alpha 4\beta 1$ (36). Some adhesion receptors of the immunoglobulin superfamily are very restricted in their patterns of expression. Thus the neural cell adhesion molecule (CEA) is found on cells of the gastrointestinal tract. However, other members of this immunoglobulin superfamily are not restricted. Thus ICAM,1 is expressed on a variety of haematopoietic and nonhaematopoietic cells, including B and T cells, fibroblasts, keratinocytes and endothelial cells, where the level of expression can be upregulated by various cytokines (37, 38).

(i) ICAM-1 and ICAM-2

The adhesion molecules ICAM-1 and ICAM-2 (CD102) are counter-receptors for the leukocyte $\beta 2$ integrin, LFA-1 (CD11a/CD18). Amino acid substitutions in the extracellular domains have indicated that the primary binding site for LFA-1 is located in the NH_2-terminal first domain of ICAM-1 (38). A recent report has shown that a second ligand-binding site for another $\beta 2$ integrin on leukocytes (CD11b/CD18, Mac-1) is localised to the third immunoglobulin-like domain. Because ICAM-2 has only two extracellular immunoglobulin-like domain. Because ICAM-2 has only two extracellular immunoglobulin-like domains and, as mentioned above, the binding site for Mac-1 is localised to the third immunoglobulin-like domain of ICAM-1, it appears that ICAM-2 does not serve as an endothelial ligand for this leukocyte integrin (38, 39). ICAM-1 is expressed on leukocytes, fibroblasts, epithelial cells and endothelial cells where its expression can be induced by cytokines such as TNF-α and IL-1β (40). ICAM-2 also has a similar tissue distribution to ICAM-1, but apparently is expressed constitutively and is not regulated by cytokines. A portion of the cytoplasmic region of ICAM-1 has been shown to bind to the cytoskeleton of COS cells transfected with the cDNA of human ICAM-1 (38, 40, 41). Linkage with the cytoskeleton may localise ICAM-1 within regions of the endothelial cell membrane in order to facilitate leukocyte adherence and transmigration (41). The expression of ICAM-1 in primary melanoma is related to the presence of distant metastases (42). The precise involvement of ICAM-1 in the process of metastasis is not yet clear. Elevated levels of soluble ICAM-1, which still retains the binding site for LFA-1 in its extracellular domain, have been found in the serum of melanoma and ovarian cancer patients (43). It has been suggested that this active form of ICAM-1 can inhibit binding sites on cytotoxic T-cell and natural killer cells and that in its presence therefore tumour cells might better be able to escape immune destruction (42, 43). Because human melanoma cells have been shown to release ICAM-1, and its increased level in serum results in a non-specific inflammatory response, it has been suggested that circulating levels of ICAM-1 reflect the formation of metastases, possibly as a consequence of facilitating disseminating tumour cell binding (43).

(ii) VCAM-1

Another member of the immunoglobulin gene superfamily, VCAM-1, is a 90-110 kDa glycoprotein expressed on the surface of activated endothelium and a variety of other cell types,

including dendritic cells, tissue macrophages and bone marrow fibroblasts. VCAM-1 expression on endothelial cells can be up-regulated by several cytokines, such as IL-1β, IL-4, TNF-α and interferon-γ (IFN-γ) (36, 44). VCAM-1 interacts with the leukocyte integrin α4β1 on many different cells including eosinophils, monocytes (and also certain tumour cells, as will be discussed below) and with α4β7 on activated peripheral T cells (45). Thus α4β1/VCAM-1 interactions, like LFA-1/ICAM-1 interactions, may regulate the movement of lymphocytes out of blood vessels to inflammatory sites. Furthermore, an α4β1/VCAM-1 interaction has been shown to be crucial for the binding of haematopoietic precursor cells to bone marrow stroma (46, 47), the binding of lymphocytes to dendritic cells (47) and the generation of secondary myoblasts (48). Interaction of VCAM-1 with α4β1 integrin expressed on certain tumour types has also been suggested to be an important mechanism for the development of metastases in cancers such as melanomas, osteosarcomas, neuroblastomas and rhabdomyosarcomas (49).

(iii) PECAM-1

The platelet-endothelial cell adhesion molecule PECAM-1, also knows as CD31 or endoCAM, is a 130kDa glycoprotein found on endothelial cells, on platelets and on some leukocytes such as monocytes and neutrophils (50). Several observations suggest that PECAM-1 could be involved in leukocyte adhesion and particularly in leukocyte transmigration and particularly in the preferential migration of naive and CD8^{+} T cells across HEV (36). PECAM-1 is homologous to both CEA and ICAM-1 proteins and has been shown to contribute to both homotypic and heterotypic cell adhesion by interaction with either itself or the integrin αvb3 (51, 52). Unlike ICAM-1, which is expressed over the entire surface of resting endothelial cells, PECAM-1 is expressed at intercellular junctions of endothelial cells and the surface expression of PECAM-1 is not increased by treatment with cytokines, such as TNF-α and IL-1 or by combinations of TNF-α and IFN-γ (50). Binding of mAbs to PECAM-1 enhanced CD8^{+} T-cell adhesion to fibronectin or VCAM-1, but not to fibrinogen or collagen, suggesting that it may cause activation of integrins containing α4 subunits such as α4β1 or α4β7 (51, 53). Inhibition of PECAM-1 expression on leukocytes or endothelial cells by treatment with soluble PECAM-1 or blocking PECAM-1 mAbs has been shown to inhibit monocyte or neutrophil transmigration in vitro. Treatment of either the endothelium or the leukocytes separately is equally effective, suggesting that homophilic adhesive interaction is involved (54).

Integrins

Integrins are a major family of cell surface receptors that are responsible for anchoring cells to ECM, and that function as cell-cell adhesion molecules. They also act as regulatory receptors that can initiate intracellular signal pathways (55, 56). Several recent studies have shown that integrins influence a variety of dynamic processes during embryonic development, tissue organisation and inflammation by affecting cell migration, proliferation, differentiation and gene expression. These molecules also might serve as targets for the therapy of certain diseases, such as leukocyte adhesion deficiency (LAD), resulting from a structural defect in the β2 subunit (57), and Glanzmann's thrombasthenia, which is a defect or deficiency in αIIbβ3 (58).

The integrin family is composed of heterodimers consisting of two non-covalently associated subunits, α and β, both of which are necessary for adhesive binding. The integrins can be classified into four distinct subfamilies based on a common β subunit: β1 integrin (very late activation antigens (VLA) proteins), β2 integrin (Leu CAMs), β3 integrins (cytoadhesins) and β7 integrins (homing). Fifteen different α and eight different β subunits give rise to over twenty different αβ heterodimeric combinations at cell surfaces (Figure 4). Both the α and β subunit
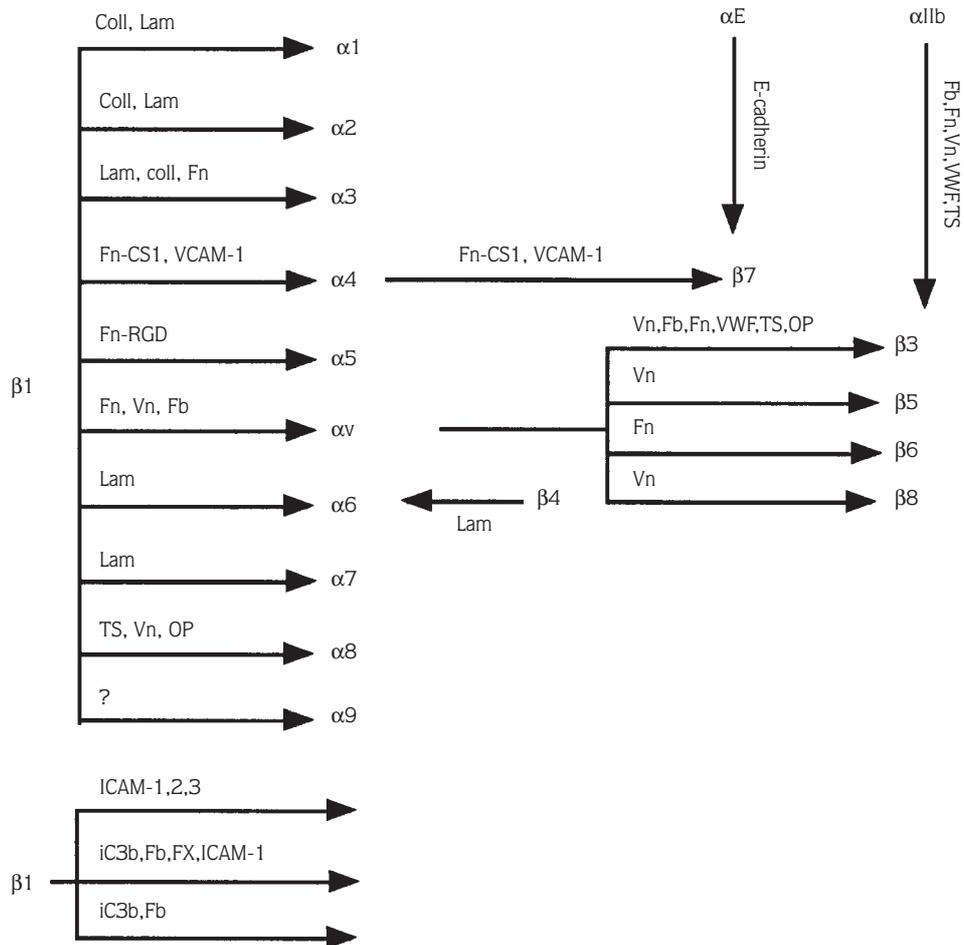
Fig. 4.   Structure of **α** and **β** subunits of integrins.
Lam, laminin; Coll, collagen; Fn, fibronectin; Fn-RGD, RGD binding site in Fn; Fn-CS1 denotes binding to the CS1 splice insert of fibronectin; VCAM-1, vascular cell adhesion molecule 1; Vn, vitronectin; Fb, fibrinogen; VWF, von willebrand factor; TS, thrombospondin; OP, osteopontin; ICAM-1,2,3, intercellular cell adhesion molecules; iC3b, inactivated C3b component of comlement; FX, coagulation factor X.

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of integrins are membrane glycoproteins with a large extracellular domain, a single transmembrane domain and a short cytoplasmic domain. Typically, the α subunits, which have a molecular weight range from 150 to 200 kDA, display lower sequence homology than do the β subunits. The N-terminal of the α subunit contains 3 or 4 divalent cation binding sites which resemble the "EF hand" consensus structure found in other calcium-binding proteins, e.g., calmodulin or troponin-C (59). These divalent cation binding sites are essential for ligand binding and regulation and for maintaining the association between the α and β subunits (60).

The α subunits can be divided into two groups: the first group of α subunits undergoes post-translational α subunit cleavage (e.g., α5 and αv), whereas the other group contains an extra 180-200 amino acids inserted between repeats 2 and 3 (Figure 5), known as the I domain or inserted domain (e.g., α1, α2, αL, αM and αX). Except for the α4 subunit, which will be discussed later, the α subunits in group one have four putative cation sites. The group two α subunit, however, has three divalent cation sites (61).

The C-terminal cytoplasmic domains of α subunits are small (15 to 77 amino acids). Apart from the membrane-proximal sequence GFFKR, which is highly conserved between α subunits, the subunits of remaining sequence have limited homology to one another, suggesting that each type of subunit has unique cytoskeletal interactions. However, various species can show a high
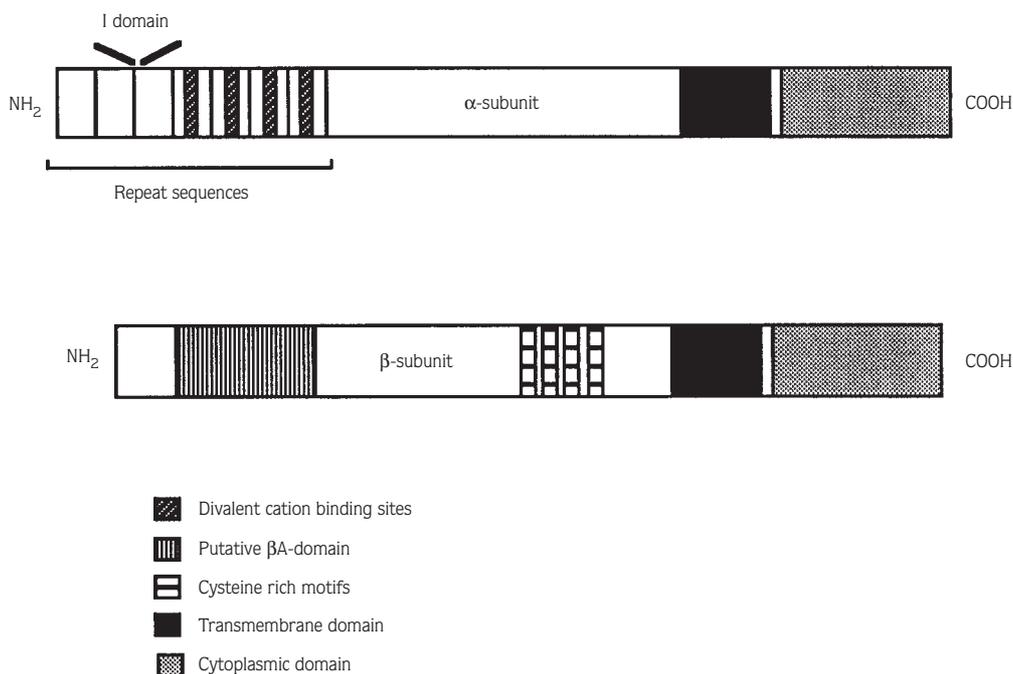

Fig. 5.   Association between the known α and β integrin subunits and the ligands with which they interact.

degree of homology between the C-terminal cytoplasmic domains of similar α subunits. For instance, 31 of the 36 C-terminal amino acids of α3 from the human have been found to be identical to α3 from the chicken.

Cloning and sequencing studies of the human integrin β1 (62), β2 (63) and β3 (64) have revealed strong homology at amino acid levels of 40-48%. All β subunits, which molecular weights of between 90 and 130kDa, except for β4 (210kDa), contain 56 conserved cysteines. Many of these cysteines are in four repeating motifs within a cysteine-rich region in the extracellular domains of β1, β2 and β3 subunits. The cytoplasmic domain of the β subunits is short (40-50 amino acids), with the exception again being β4, which contains a long cytoplasmic domain of 1018 amino acids containing four fibronectin type III repeats (65).

Quantitative analyses of cell adhesion have implicated the cytoplasmic region of α and β subunits, which are anchored to cytoskeletal structures in the cell, as contributing to the regulation of adhesion. Recent studies have revealed that integrin subunits transmit signals from the extracellular matrix to the cell interior (outside-in) and from the inside of the cell to the outside of the cell (inside-out), similar to those transduced by growth factors, hormones and cytokines (66). Integrin signaling regulates cell proliferation, differentiation and survival as well as cell adhesion. Mutation studies of the cytoplasmic domain of β1 integrins (67) have shown that this region of the integrin is important for integrin-mediated cell adhesion and the localisation of integrins to the focal contacts. In platelets, fibroblasts and carcinomas, the binding of soluble ligands, e.g., fibrinogen to activate αIIbβ3 integrin, causes tyrosine phosphorylation of several different proteins, including focal adhesion kinase (FAK) (55, 67). Changes in intracellular pH and calcium, the release of lipid second messengers, the activation of PKC and the activation of phosphatidyinositol-3-kinase (PI3-kinase) (68) all are caused by integrin engagement during cell adhesion. In addition to these effects, the integrin-mediated activation of mitogen-activated protein kinase (MAPK) (69), the activation of p21 Ras (70) and the expression of immediate early genes by α5β1 integrin have also been demostrated, thus tying integrin occupancy to the cell proliferation machinery. Integrin-mediated signaling has been shown to be an important phenomenon in the context of cancer cell growth and behaviour (71). Oncogenic transformation of cells tends not to show a complete loss of adhesion but rather a change in the expression of certain integrins. Melanoma obeys this rule in that integrins such as αv and β3 are shown to be expressed at high levels in malignant melanoma cells, where it is suggested that they participate in increased invasion or metastasis (71). Blocking αvβ3 function with anti-αv antibody inhibited both the migration of melanoma cells on vitronectin and xenograft formation in nude mice (72, 73). In summary, it has been documented that changes in various integrin-ligand interactions permit melanoma cells to become invasive both on extracellular matrix substrates and in distant tissues during tumour progression.

Discussion

Cell adhesion and adhesion molecules have been shown to contribute to the pathogenesis of a large number of common human disorders and tumor cell metastasis in cancer. Recent studies

have demostrated that cell adhesion moleculas are involved in signal transduction pathways. These molecules transmit signals from the extracellular matrix on the cell interior (outside-in) and from the inside of the cell to the outside of the cell (inside-out) similar to those transduced by growth factors, hormones and cytokines. These results might be extremely significant in metastatic spread and the treatment of a large number of human disorders.

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