

**Integrins.**

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## Integrins

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### Introduction

Integrins are a family of cell surface proteins that mediate cell adhesion. Adhesion is of fundamental importance to a cell; it provides anchorage, cues for migration, and signals for growth and differentiation. There are two principal types of cell adhesion: cell–extracellular matrix adhesion and cell–cell adhesion. Integrins appear to be the primary mediators of cell–extracellular matrix adhesion, and they also serve as one of the many families of molecules active in cell–cell adhesion.

The past couple of years have seen a virtual explosion of work done on the integrins, and this effort has made them the best understood cell adhesion molecules. A number of factors contributed to this fast progress. First, the discovery of integrins brought together a large number of separate observations. The integrin family of receptors was discovered in the mid-1980s when it was realized that a group of chicken adhesion proteins, the platelet protein gp IIb/IIIa, a group of lymphocyte adhesion proteins, the VLA family of cell surface antigens, and receptors for fibronectin and vitronectin all had related structures and activities. Secondly, the integrin work was preceded by many years of detailed work on the extracellular matrix proteins that integrins are the receptors for and, thirdly, the obvious importance of integrins for a number of aspects of biology and medicine brought many new investigators into the field. The name integrin was coined to signify the presumed role of these proteins in integrating the intracellular cytoskeleton with the extracellular matrix.

Aside from their biological importance to fundamental cellular processes, the medical importance of the integrins is rapidly being realized as well; integrins have been found to play a role in platelet aggregation, immune functions, tissue repair, and tumor invasion, and some diseases are already known to be caused by mutations in integrin genes. Moreover, knowledge of the target amino acid sequence for many integrins, the Arg-Gly-Asp (RGD)<sup>1</sup> sequence, can be exploited to design compounds controlling cell adhesion for therapeutic purposes. This review summarizes some of the latest developments in the field.

### Integrin diversity

Integrins are a family of membrane glycoproteins consisting of two subunits,  $\alpha$  and  $\beta$ . The primary structure of many of these

subunits has been deduced from sequencing of complementary DNA (reviewed in reference 1). This sequence information is the basis of the general model for the structure and interactions of integrins depicted in Fig. 1. The ligand-binding site of integrins appears to be formed by sequences from both subunits (see reference 2, 3), and their cytoplasmic domains form connections with the cytoskeleton (see reference 4). These properties endow integrins with the ability to serve as a link between the cytoskeleton and the extracellular matrix.

There are 11  $\alpha$  subunits and 6  $\beta$  subunits known at this time that have been at least partially sequenced and thereby shown to be distinct (1, 5–7). The  $\alpha$  and  $\beta$  subunits in various combinations form at least 16 integrins (Fig. 2). It is likely that more will be discovered.

It has recently become clear that in addition to each  $\beta$  being able to associate with multiple  $\alpha$ 's, a single  $\alpha$  subunit can become paired with more than one  $\beta$ . The  $\alpha_v$  subunit appears to be particularly versatile; it combines with different  $\beta$  subunits (see reference 3) to comprise as many as four integrins. This diversity of the integrins provides cells with varied capabilities to recognize adhesive substrates.

### Integrin expression in cells

The complement of integrins expressed by different cell types varies greatly. Cultured mammalian cell lines possess from two to 10 different integrins (e.g., reference 3).

Some integrins are clearly cell type-specific. The most striking examples are gp IIb/IIIa, which is expressed exclusively by megakaryocytes and platelets (8), and LFA-1, Mac-1, and p150/95, which are expressed only by leukocytes (9). The  $\alpha_6\beta_4$  integrin is specific for epithelial cells and tumors derived from them (10).

The expression of individual integrins appears to be regulated during development in *Drosophila* (11) and in vertebrate species; agents that affect growth and differentiation can modulate integrin expression. Transforming growth factor- $\beta$  (TGF- $\beta$ ), for example, causes a striking upregulation of certain integrins (12). The proper temporal expression of the correct complement of integrins may make it possible for cells to find their appropriate adhesive substrates in the body.

### Integrin ligands and the RGD sequence

Many integrins bind to extracellular matrix proteins and thereby mediate cell–extracellular matrix interactions. Among the extracellular matrix ligands for integrins are fibronectin, fibrin(ogen), laminin, various collagens, entactin, tenascin, thrombospondin, von Willebrand factor, and vitronectin (1, 13).

Other integrins bind to cell membrane proteins (“counter receptors”), mediating cell–cell adhesion. The intercellular adhesion proteins ICAM-1 and ICAM-2 have been identified as “counter receptors” for the leukocyte integrin LFA-1 (also known as CD11a/CD18 or  $\alpha_L\beta_2$ ) (9), and the counter receptor

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1. Abbreviations used in this paper: LAD, leukocyte adhesion deficiency; RGD, Arg-Gly-Asp sequence; TGF- $\beta$ , transforming growth factor- $\beta$ .

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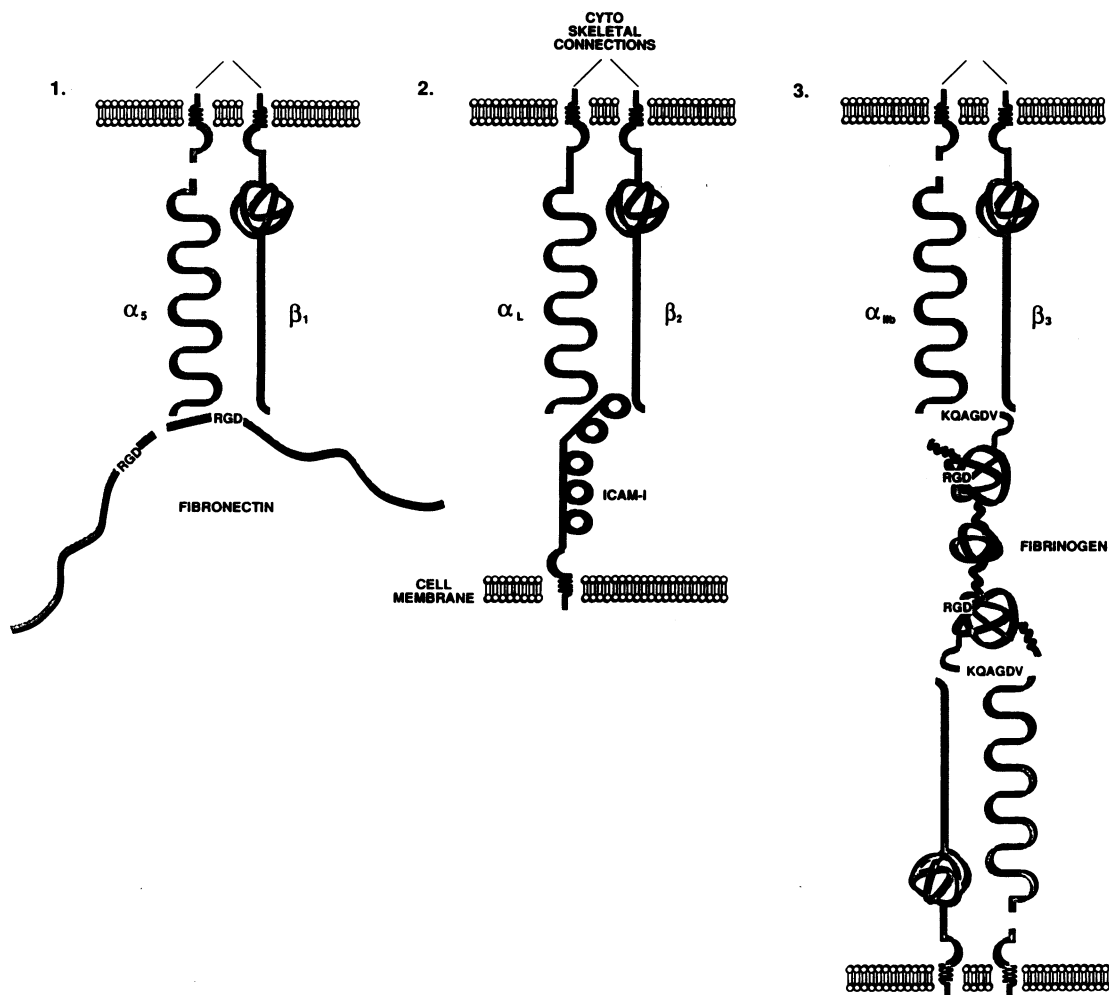


Figure 1. Integrin-structure, interactions, and the three binding modes of various integrins.

for the  $\alpha_4\beta_1$  integrin is VCAM-1 (14). The  $\alpha_4\beta_1$  integrin shows an interesting dual specificity in that it can also bind to fibronectin (15). ICAM-1, ICAM-2, and VCAM-1 are members of the immunoglobulin superfamily, many of which are adhesion proteins.

In a third mode of interaction, the major integrin in platelets, gp IIb/IIIa, promotes the binding of platelets to one another through soluble, multivalent mediator molecules. Fibrinogen and von Willebrand factor function as the primary ligands for gp IIb/IIIa in platelet aggregation, but this integrin also binds to fibronectin and vitronectin (8). These latter interactions may be important for the adhesion of activated platelets to the subendothelial matrix.

The recognition site for many of the integrins that bind to extracellular matrix and platelet adhesion proteins is the tripeptide RGD (13). First identified in fibronectin, it has since been shown to be a cellular recognition sequence in many extracellular matrix and platelet adhesion proteins (Fig. 2). The conformation of the RGD site appears to determine which integrin an RGD protein or RGD peptide will bind (13). Short synthetic peptides containing the RGD sequence can be designed to exhibit varying integrin specificities by restricting the conformation of the peptide through cyclization. An RGD-related sequence in the fibrinogen  $\gamma$  subunit KQAGD may form a structure that resembles RGD, because peptides containing

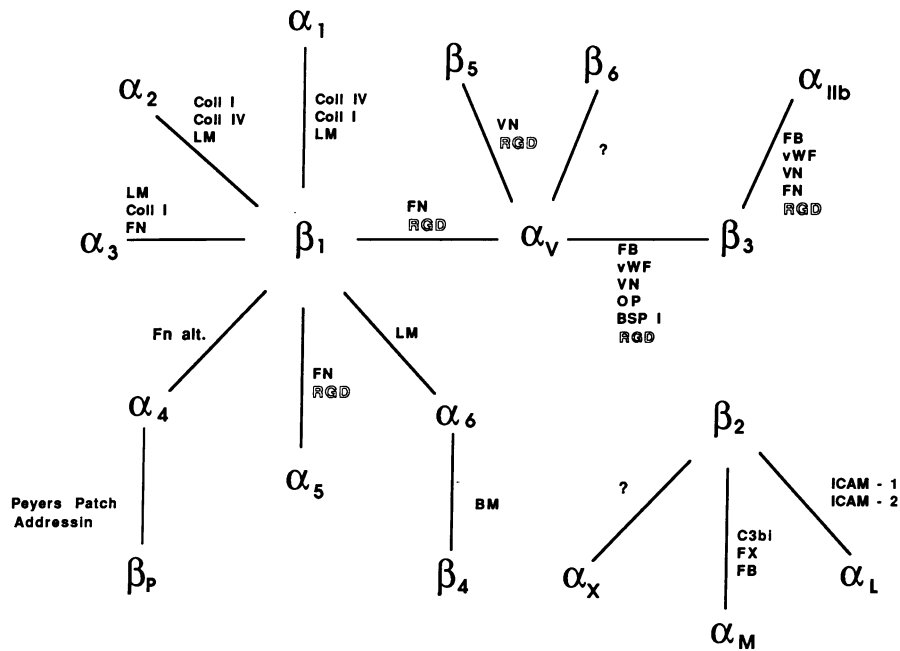
these sequences bind essentially interchangeably to platelet gp IIb/IIIa (8).

A sequence entirely different from RGD and KQAGD has been identified as the target sequence of the  $\alpha_4\beta_1$  integrin in fibronectin (15). This sequence is present in one of the alternatively spliced segments of fibronectin (16). As discussed below, the peptides reproducing the integrin binding sites may provide a novel class of therapeutic agents.

#### Regulation of integrin activity and specificity

The main platelet integrin gp IIb/IIIa requires activation to bind to its ligands. This integrin is present at the surface of resting platelets, but no aggregation results, even though fibrinogen and other ligands are available (8, 17). It is not known how activation of the platelets arouses the binding activity of gp IIb/IIIa. The other platelet integrins may not require activation, because unactivated platelets attach to fibronectin, laminin, and collagen.

The leukocyte integrin LFA-1 is also activatable. Interestingly, the ligation of the T cell receptor causes the activation of this integrin in lymphocytes (18). Other integrins such as the  $\alpha_5\beta_1$  fibronectin and  $\alpha_6\beta_1$  laminin receptor, which are constitutively activated in many types of cells, are also controlled by activation in leukocytes (19). It may be important for blood cells to control their activation in this manner, so that their



**Figure 2.** Integrin family. The known subunits, the subunit combinations that form the known integrins, and the known ligands for these integrins are shown. Also shown is the RGD specificity of those integrins that bind to this sequence. The newly identified  $\beta_6$  subunit has been tentatively assigned to the  $\alpha_V$  group because its amino acid sequence is most homologous with  $\beta_3$  (8). *FN*, fibronectin; *VN*, vitronectin; *FB*, fibrinogen; *LM*, laminin; *vWF*, von Willebrand factor; *COLL*, collagen; *OP*, osteopontin; *BSP 1*, bone sialoprotein 1; *ICAM-1*, *ICAM-2*, intercellular adhesion molecules; *FX*, factor X; *BM*, basement membrane; *C3bi*, complement component C3bi; *Fn alt.*, fibronectin alternatively spliced domain.

circulation through the body is not impeded until they become stimulated at the site of an injury or by some other activating event.

Cells may also regulate integrin specificity. The  $\alpha_2\beta_1$  integrin in platelets is a collagen receptor, but in some other cells, it binds to laminin and fibronectin in addition to collagen (20). Elucidation of the molecular mechanisms of integrin activation is one of the most important goals of research on these proteins.

#### *The gp IIb/IIIa integrin in platelet function*

The role of gp IIb/IIIa is most vividly illustrated by the disease that is caused by a hereditary deficiency of this receptor, Glanzmann's thrombasthenia (reference 8, 17). Platelets from individuals with this trait fail to aggregate in response to activation. This establishes the role of gp IIb/IIIa as the primary mediator of platelet aggregation.

Gp IIb/IIIa is an attractive target for therapeutic manipulation of platelet aggregation. Monoclonal antibodies that neutralize the activity of gp IIb/IIIa provide a possible inhibitor of platelet aggregation (21). RGD peptides, or perhaps peptides containing the related KQAGDV sequence (8), may offer an alternative for anti-gp IIb/IIIa antibodies in therapeutic suppression of the gp IIb/IIIa activity. Cyclization of certain synthetic RGD-containing peptides has yielded compounds that have up to 5,000-fold increased affinities for gp IIb/IIIa relative to the linear peptides with a concurrent decrease in affinity for other RGD-dependent integrins (reference 22, Pierschbacher, M.D., personal communication). Such peptides, therefore, can serve as efficient and specific inhibitors of platelet aggregation.

Highly active RGD peptides also exist in nature. Certain snake venoms contain short proteins that have an active RGD sequence in a highly conserved disulfide loop and that are very potent inhibitors of platelet aggregation (23). These proteins have been named "disintegrins" to denote their ability to inhibit gp IIb/IIIa and other integrins. The disintegrins would appear less suitable as therapeutic agents than the synthetic

peptides, because they lack the specificity of the peptides designed as inhibitors of gp IIb/IIIa.

#### *Leukocyte integrins*

Integrins, along with other types of adhesion molecules, play an important role in the functions of the various types of leukocytes; in general they appear to mediate the attachment that accompanies the conversion of leukocytes from circulating cells to adherent tissue cells. This typically happens in a tissue injury. Leukocytes bind to the endothelium in an injured tissue as a result of increased adhesiveness induced by the injury; the  $\beta_2$  integrins are activated in the leukocytes, and the endothelium expresses increased amounts of ICAM-1. Mac-1 ( $\alpha_M\beta_2$ , CD11b/CD18) binds to fibrinogen and some other proteins not necessarily present on endothelial cells (24). However, this integrin and p150/95 ( $\alpha_x\beta_2$ , CD11c/CD18) probably have cell surface ligands as well and are important in neutrophil and monocyte adhesion and extravasation.

The most concrete demonstration of the important role the  $\beta_2$  integrins play in leukocytes comes from the hereditary condition known as leukocyte adhesion deficiency or LAD (9). This disease is caused by the lack of a functional  $\beta_2$  subunit, the common subunit of LFA-1, Mac-1, and p150/95. The disease is primarily characterized by a defect in leukocyte extravasation, resulting in an inability of the patient to fight infections. Because at least LFA-1 is also involved in various aspects of immune recognition, lack of such a function must also play a role in LAD.

Leukocytes also have integrins other than those of the  $\beta_2$  family. The  $\beta_1$  family of integrins that includes fibronectin, laminin, and collagen receptors was identified as a protein family of unknown function in lymphocytes. The name VLA for very late antigens was given to this group of proteins because they were greatly elevated in lymphocytes that had been subjected to long-term stimulation (1). Moreover, lymphocyte stimulation through the CD3 system results in the activation of the  $\alpha_5\beta_1$  fibronectin receptor and  $\alpha_6\beta_1$  laminin receptor within

minutes from the activation (19), suggesting that these integrins also play a role in the earliest phases of an immune response. In macrophages, the ligation of the fibronectin receptor causes upregulation of the complement-binding integrin, Mac-1 (25), suggesting transmission of a signal into the cell by the  $\alpha_5\beta_1$  integrin.

An integrin specific for lymphocytes that has a unique  $\beta$  subunit mediates lymphocyte homing. This integrin,  $\alpha_4\beta_p$ , recognizes an unknown ligand on the high endothelia of lymph node venules allowing the lymphocytes to enter lymph nodes (26).

Leukocytes also possess one or more  $\alpha_v$  integrins; the  $\alpha_v$  subunit can become associated with a number of  $\beta$  subunits to form integrins with related but distinct specificities (3, 27). Their function is not well understood, but interestingly the  $\alpha_v\beta_3$  integrin, or a closely related integrin, appears to bind osteoclasts to bone by interacting with an RGD-containing protein known as osteopontin (28).

The leukocyte integrins offer new therapeutic possibilities. Restoration of the  $\beta_2$  integrin function by gene therapy may some day become a treatment for LAD (9). On the other hand, at times it appears to be beneficial to suppress the function of the  $\beta_2$  integrins. Preventing leukocyte migration to the areas of injury and inflammation after reperfusion of tissues is an example of one such situation (29) in which tissue damage can be reduced. This can be accomplished by administering monoclonal antibodies against  $\beta_2$ .

The counterreceptor for LFA-1, ICAM-1, is also a receptor for rhinoviruses, the viruses that cause the common cold. Soluble pieces of ICAM-1 can inhibit viral entry into cells through competition with the binding of the virus to the cell surface ICAM-1, suggesting a new therapy for the common cold (9). The leukocyte integrins and integrins in other cells can also serve as entry receptors for viruses as well as for bacteria (30, 31). In the case of foot-and-mouth disease, the entry can be inhibited with RGD-containing peptides (30).

The transactivating protein, tat, of the human immunodeficiency virus (HIV) also contains an RGD sequence and binds to cells in an RGD-dependent manner (32). This may be important, because the tat protein can enter a cell and activate the expression of a resident viral genome as well as act as a growth factor for Kaposi's sarcoma cells (33). If RGD-dependent binding plays a role in these tat protein functions, inhibitors could be readily designed. Finally, it may be possible to block the binding of osteoclasts to the bone with RGD-containing peptides. This might prevent bone resorption in diseases such as osteoporosis.

#### *Integrins in tissue repair*

There is increasing evidence that the cell movements that take place during tissue repair such as wound healing depend on integrin-mediated interactions. Keratinocytes freshly isolated from normal skin do not express fibronectin receptors and do not attach to fibronectin-coated dishes. However, if kept in culture longer, or if isolated from wound tissue, these cells do express receptors and do attach to fibronectin (34). It appears that keratinocytes, when they close a wound, use the fibronectin receptors to attach to and migrate on the provisional, fibronectin-containing wound matrix. This thinking agrees well with the extensive literature that implicates fibronectin and its receptors in various cell migrations during embryonal development (see references 13 and 16).

Emerging applications of the role of the extracellular matrix in wound healing include the use of fibronectin to facilitate the healing of corneal ulcers (see reference 34) and the use of synthetic materials that reproduce the fibronectin cell attachment sites as a wound healing "glue" (Pierschbacher, M.D., personal communication).

A particularly intriguing effect of an extracellular matrix molecule is the ability of laminin to promote the outgrowth of cellular processes, neurites, by neurons (13). The lack of regenerative capacity in the adult central nervous system could be, at least in part, due to the fact that laminin is not expressed in the fully developed brain, although it is present in the developing fetal brain. Indeed, implantation of a laminin-containing device into a brain lesion can improve the restoration of anatomical connections across the lesion (35) suggesting therapeutic potential in this approach.

#### *Integrins in cancer*

Normal cells deposit fibronectin, laminin, collagens, and other extracellular matrix components around themselves as a network of insoluble protein. They can then attach to this matrix through their cell surface integrins. For reasons that are only partially understood, most tumorigenic cells, at least in culture, fail to deposit such a matrix or do so to a lesser degree than normal cells. It is known that the "classical" fibronectin receptor, the  $\alpha_5\beta_1$  integrin is needed for the matrix deposition and its expression is often reduced in tumor cells (36). Moreover, increasing the expression of the  $\alpha_5\beta_1$  integrin by gene transfer increases the deposition of fibronectin by tumorigenic Chinese hamster ovary cells (37). However, at least one other factor, a "matrix assembly receptor", is also needed for fibronectin deposition (38). This factor, which is absent in matrix-deficient cells, has not been characterized yet, but will obviously be an important object of future studies.

A consequence of the lack of matrix deposition is that the tumor cells have an added degree of freedom; their mobility is not limited by adhesion to their own matrix. The importance of this constraint in normal cellular behavior is suggested by the  $\alpha_5\beta_1$  gene transfer experiment mentioned above. The cells expressing high levels of this integrin from the transfected genes not only deposit more fibronectin matrix, but have become less migratory than the control cells, grow less well in soft agar, and, unlike the parental cells, fail to form tumors in nude mice (37). The expression of fibronectin receptors and the assembly of a fibronectin matrix may therefore be very closely associated with the expression of the tumorigenic phenotype.

There is another aspect of fibronectin in malignancy, however. It appears that fibronectin (and extracellular matrix in general) play a dual role malignancy: as discussed above, a tumor cell should lack its own extracellular matrix to be able to proliferate fast and migrate optimally. However, such a cell needs some matrix adhesion to be able to derive traction for migration from the matrices of other cells. This is suggested by the fact that tumor cells and other migratory cells preferentially migrate on surfaces coated with adhesive extracellular matrix proteins. Moreover, the RGD peptides can inhibit migration of tumor cells through tissue in invasion assays (reviewed in reference 39).

The RGD peptides can also affect tumor cells in vivo. Several laboratories have published experiments in which dissemination of intravenously injected tumor cells in mouse tissues has been inhibited by a simultaneous injection of an RGD

peptide (reviewed in reference 39). The loss of adhesion resulting from the peptide treatment may deny the cells anchorage and traction for growth and migration. Alternatively, the RGD peptides may be capable of inducing the receptors to deliver a growth inhibitory signal into the cell; an indication of the ability of the peptides to deliver a signal is that they have been shown to induce expression of proteases in fibroblast cultures and that at high doses they also stop the proliferation of cells (39, 40). Thus, the peptides may be receptor agonists with regard to signaling, in addition to being inhibitors of adhesion.

These observations suggest new modes of cancer therapy; the peptides already at hand allow modulation of invasiveness and metastasis through control of integrins. Research along these lines could prove extremely rewarding in that it would target invasion and metastasis rather than the properties of cancer cells targeted by more traditional therapies.

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