MINIREVIEW

The Regulation of Expression of Integrin Receptors (44078)

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Abstract. **The integrins are a family of cell surface receptors that mediate cell-extracellular matrix and cell-cell interactions. The quantities and activities of these receptors are modulated during a wide variety of biological processes. A variety of agents have been found to affect expression of integrins and their function. These include cytokines, hormones, and pharmacologic agents. Mechanisms regulating integrin expression and function include regulation of protein levels by transcriptional or posttranscriptional mechanisms, alteration of protein structure by alternative splicing of mRNA, mobilization to the cell surface of preexisting intracellular stores of integrins, and modulation of receptor activity (inside-out signaling). We review studies that assess the effects of external agents on integrin levels using the cytokine TGFβ as an example. We also review studies that analyze integrin regulation with an emphasis on the control of integrin gene transcription. This review shows that the strategies for integrin modulation are quite complex. This regulatory sophistication is likely necessary, given the critical role that integrins play in the myriad social interactions of cells.** [P.S.E.B.M. 1997, Vol 214]

Integrins are a family of cell surface receptors which mediate cell-extracellular matrix and cell-cell adhesion. They are heterodimers made up of one larger α and one smaller β subunit (for a review see Ref. 1). They are generally grouped into families based on the β subunit. One β subunit can generally bind one of several different α subunits to yield a unique receptor. However the α_v subunit is unique. It is able to bind one of several different β subunits, so it is often considered as defining its own family. Since the initial characterization of the integrin family in the late 1980s, there have been numerous reports of integrin modulation during such processes as development, wound healing, inflammation, thrombosis, tumorigenesis, and metastasis. The mechanisms of regulation have also been investigated, yielding insights into their complexity. This review is intended to summarize and synthesize the results of these studies. We will first discuss, using transforming growth factor–β (TGFβ) as an example, mediators that can signal a cell to up- or downregulate integrin receptors. We will then discuss the mechanisms by which a cell can control the presence of an active integrin molecule on its surface. These mechanisms can be broadly characterized as (i) regulation of protein levels by transcriptional or posttranscriptional mechanisms, (ii) alternative splicing of mRNA, (iii) mobilization of preexisting intracellular stores, and (iv) conformational control (inside-out signaling).

Mediators That Regulate Integrin Levels

Many studies have examined the effects of signaling molecules, drugs, or other agents on integrin levels. Changes at the protein level are most commonly shown by FACS analysis, immunoprecipitation, or immunostaining. Parallel changes are also commonly shown at the mRNA level. In this section, we will review in detail the effects of

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TGFβ on integrins. We will then briefly cover other agents that can mediate changes in integrins.

TGFβ. A number of peptide growth factors have been shown to regulate integrin levels. The best studied of these regulatory molecules are members of the transforming growth factor–β family, referred to here collectively as TGFβ. Even as the first studies demonstrating the structure of integrins were being completed, the effects of TGFβ on integrins were being investigated (2). TGFβ increases β_1 integrin expression on several cell types at both the protein and mRNA level (2–7). In some cases, however, increases of β_1 integrin dimers occur not due to increased synthesis of β_1 but due to increases of its α subunit partner (3, 8) or to faster maturation of the β_1 subunit (2). In these cases, it has been suggested that the β subunits are normally expressed in excess and that stimulation by TGFβ increases assembly with the limiting α partner. Indeed, Jaspers *et al.* showed that overexpressing α_4 by transfection with α_4 cDNA increased the rate of maturation of the β_1 integrin precursor as well as the quantity of β_1 integrins on the cell surface (9). Other examples of integrins that are increased by TGFβ stimulation include α_1 (10), α_2 (6–8, 11), α_3 (7, 8), α_5 (5, 6, 8, 12), α_v (12), β_3 (13), β_5 (6, 12), and β_6 (6). In many cases TGFβ is found only to increase the expression of integrins that are already present on cells. In other cases, TGFβ is found to initiate synthesis of a particular integrin. For example Janat *et al.* (13) reported *de novo* synthesis of β_3 upon stimulation with TGFβ1 in rabbit vascular smooth muscle cells. Likewise, Zambruno *et al.* (6) reported *de novo* expression of β_6 mRNA in keratinocytes upon stimulation with TGFβ1. Many of the effects of TGFβ are cell-type specific. For example, α_3 is increased on guinea pig airway epithelial cells after stimulation with TGFβ1 (8) but is decreased on keratinocytes (6). Additionally α_5 is increased on several cells by TGFβ1 but decreased on *ras*-transformed hepatocytes (10). TGFβ can also inhibit the activity of other cytokines which may increase a particular integrin. Rinaldi *et al.* showed that, in synovial cells, the increase in α_3 induced by γ-interferon (IFN-γ) can be inhibited by TGFβ (14). Although most of these studies used exogenously added TGFβ, at least one example has been offered of autocrine TGFβ inducing integrin expression (5).

It is apparent from these studies that the control of integrin expression by TGFβ is complex. Given that TGFβ has been shown to induce extracellular matrix molecules themselves, a recurring theme appears to be that TGFβ induces an increase in extracellular matrix and enhances the ability of the cells to respond to this increase. However, the above examples of cell-type specificity and varying mechanisms of regulation, such as increases in mRNA, changes in assembly of dimers, and cooperative effects with other cytokines, indicates a complex system which may be influenced by numerous factors.

Other Growth Factors and Cytokines. A number of other growth factors can regulate integrin levels. Most of these have not yet been sufficiently studied to compare effects on different cell types or on many different integrin subunits. These growth factors include PDGF-AB (15); PDGF-BB (16); EGF (17); NGF (18); acidic FGF (18); basic FGF (7); IL-4 (19); IL-1β (14, 20–22); IL-6 (23); β family chemokines (MCP-1, MIP-1α, RANTES) (24); tumor necrosis factor–α (TNF-α) (14, 25, 26); TNF-β (27); IFN-γ (14, 26); M-CSF (28, 29); and GM-CSF (29). Several signaling molecules and hormones such as retinoic acid (30, 31), 1,25-dihydroxyvitamin D_3 (32), and corticosterone (33, 34) have also been shown to have effects.

Pharmacologic Agents. Several pharmacologic agents have the ability to regulate integrin levels. This is often in the context of interruption of a known signaling pathway, or in the pharmacologic induction of differentiation. Examples include phorbol esters (25, 35–39), the tyrosine kinase inhibitor genistein (40), forskolin (which increases cAMP levels) (41), gossypol (a biphenolic compound from the Portia tree which has been used as an anti-inflammatory and anti-tumor agent) (42), thalidomide (43), and dexamethasone (18).

Mechanical Factors. Mechanical stress can also alter integrin levels. Carvalho *et al.* showed that mechanical strain on human osteosarcoma cells can increase β_1 integrin mRNA and cause changes in protein distribution (44). Somewhat paradoxically, stress deprivation of rabbit anterior cruciate ligaments increased staining for β_1 integrin (45).

Infectious Agents. Infectious agents which have so far been found to have an effect on integrin levels include *Pneumocystis carinii* (46), HIV (47, 48), and cytomegalovirus (49).

Table I summarizes mediators found to regulate integrin levels.

Control of Gene Expression

A long-term modulation of integrin functions can occur with changes in integrin protein levels. This can be controlled by modulation of gene transcription, or by posttranscriptional mechanisms. Studies of regulatory regions of integrin genes have begun to unravel the complex control mechanisms that regulate integrin gene transcription. A number of integrin promoter regions have been characterized, including α_2 (50), α_4 (51–53), α_5 (54), α_L (CD11a) (55), α_M (CD11b) (56–59), α_X (CD11c) (60), α_v (61), α_{IIb} (62), β_1 (63), β_2 (CD18) (64, 65), β_3 (66), avian β_3 (67), and mouse β_7 (68) (Table II). All of these promoters lack both TATA and CAAT boxes except α_{IIb}, which contains a CAAT box (69), and α_4 which contains both TATA and CAAT boxes.

Sp1. All of the characterized promoters except α_4 and mouse β_7 have been shown to contain Sp1-binding sites. In most eukaryotic promoters the TATA box binds the complex TFIID, which plays a central role in the initiation of mRNA synthesis. Sp1 has been suggested to serve to anchor TFIID in the absence of TATA boxes (70). Chen *et al.* (59) showed that in the case of α_M (CD11b), Sp1 binding at one

Table I. Reported Integrin Regulatory Molecules

Integrin	Mediator	Cell type	How shown	References
α_1	IL-1β, TNF-α, IFN-γ	Synovial cells	Staining, FACS	14
	NGF, aFGF, dexamethasone (decreases)	PC 12 pheochromocytoma	Northern, I.P.	18
	TGFβ	*ras*-transformed hepatocytes	I.P., Northern	10
	Retinoic acid, PMA, TNF-α	Endothelial cells	I.P.	25
α_2	PDGF ab	Normal fibroblasts	I.P.	15
	PDGF bb	Normal fibroblasts	Northern	16
	EGF	Squamous cell carcinoma	I.P., ELISA	17
	IL-1β	MG-63 osteosarcoma	RT-PCR	22
	TGFβ	Endothelial cells, colon carcinoma	I.P., Northern	7, 11
	bFGF	Endothelial cells	I.P., Northern	7
	PMA	K562 leukemic cells	Northern, FACS, nuclear run-on	37, 114
α_3	PDGF ab	Normal fibroblasts	I.P.	15
α_4	M-CSF	Macrophages	I.P.	28
	PMA (decreases)	Myeloid cell lines U937 and HL60	FACS, Northern, nuclear run-on (transcription constant)	35, 38
α_5	PDGF ab	Normal fibroblasts	I.P.	15
	IL-1β	Synovial cells, osteosarcoma lines	RT-PCR	14, 20–22
	Il-6	Corneal epithelium	RT-PCR	23
	TGFβ	Colon carcinoma, keratinocytes, endothelial cells	RNAse protection, I.P., Northern	5–7
	bFGF	Endothelial cells	I.P.	7
	M-CSF	Macrophages	I.P.	28
	PMA	Myeloid cell lines U937 and HL60	FACS, Northern	35, 38
α_v	Retinoic acid	Melanoma	Northern	30
	1α,25-Dihydroxyvitamin D_3	Osteoclasts	Northern, nuclear run-on	32
	IL-4	Bone marrow macrophages	Northern	19
	TGFβ	Keratinocytes	Northern	6
α_L	Polyunsaturated fatty acids	Neutrophils	FACS	115
	PMA	Myeloid cell lines U937 and HL60	Northern, nuclear run-on	35
α_M	β family chemokines (MCP-1, MIP-1α, RANTES)	Monocytes	FACS	24
	PMA	Myeloid cell lines U937 and HL60	Northern, nuclear run-on	35
α_X	β family chemokines (MCP-1, MIP-1α, RANTES)	Monocytes	FACS	24
	PMA	Myeloid cell lines U937 and HL60	FACS, Northern, nuclear run-on	35, 36
α_{IIb}	PMA	K562 leukemic cells	Northern, FACS, nuclear run-on	37, 114
β_1	PDGF ab	Normal fibroblasts	I.P.	15
	IL-6	Corneal epithelium	RT-PCR	23
	TGFβ	Endothelial cells	I.P., Northern	7
	Retinoic acid	Teratocarcinoma	I.P.	31
	Corticosterone	Osteoblasts, bone	I.P., Northern, staining	33, 34
β_2	Genistein	Myelomonocytic cells THP-1 and HL60	FACS	40
	PMA	Myeloid cells HL60	Northern, nuclear run-on (no change in transcription)	35, 36
	Gossypol	Neutrophils	FACS	42
	Thalidomide (decreases)	Neutrophils	FACS	43
β_3	bFGF	Endothelial cells	I.P.	7
	GM-CSF	Macrophages	I.P., Northern	29
	PMA	K562 leukemic cells	Northern, FACS, nuclear run-on	114
	TNF-α, IFN-γ (decreases)	Endothelial cells	FACS, Northern	26
β_4	Forskolin	Schwann cells	Northern	41
β_5	M-CSF	Macrophages	I.P., Northern	29
β_6	TGFβ	Keratinocytes	Northern	6
β_7	PMA	Myeloid cell lines U937 and HL60	Northern, nuclear run-on	35
	TNFβ	Lymphocytes	FACS	27

Note. Many of the reported effects are complex and may be related to the individual experimental conditions reported. The reader is cautioned to refer to individual references for details. All mediators increase the integrin except where noted. I.P., immunoprecipitation; RT-PCR, reverse transcriptase–polymerase chain reaction; ELISA, enzyme-linked immunosorbent assay.

Table II. Reported Integrin Promoter Regions and Putative Consensus Binding Sites

Subunit	Promoter characterized?	Consensus sequences in promoter
α_1	No	
α_2	Yes (50)	Sp1, Ap-1, AP-2, GATA, PU.1, possible estrogen receptor–binding site
α_3	No	
α_4	Yes (51–53)	TATA, CAAT, Sp1, AP-1, AP-2, PU, MyoD, ets
α_5	Yes (54)	Sp1, AP-1, AP-2, ets
α_6	No	
α_v	Yes (61)	Sp1, ets, GATA
αL (CD11a)	Yes (55)	Sp1, oct, PU
α_M (CD11b)	Yes (56–59)	Sp1, AP-2, PU, ets, RAR
α_X (CD11c)	Yes (60)	Sp1, AP-1, AP-2, PU, c-*myc*, NFκβ, oct, hept, RA
α_{IIb}	Yes (human and mouse) (62, 69, 71, 116–118)	CAAT, Sp1, CP-2, GATA, ets
β_1	Yes (63)	Two independent promoters. Sp1, NF-1, AP-1, oct
β_2 (CD18)	Yes (64, 65)	SP1, RAR, ets
β_3	Yes (66)	Sp1, PU, two putative megakaryocytic elements
β_4	No	
β_5	No	
β_6	No	
β_7	Yes (mouse) (68)	AP-2, myeloid motifs, PU, E (myoD), ets, NF-AT, GATA-3, HMG, RAR

of the Sp1-binding sites was necessary for promoter activity. Additionally this factor was found to bind only in U937 myeloid cells which express α_M, but not in HeLa cells, which do not express this integrin subunit. These authors proposed that binding of the transcription factor PU.1, which is myeloid specific, allows binding of Sp1, which then results in transcription.

Ets. Another putative transcription factor–binding site which is common to multiple integrin promoters is that of the ets family of transcription factors. Ets consensus binding sites have been described in the promoters of α_{IIb} (71), α_v (61), α_4 (52), α_5 (54), α_M (56), and β_2 (65). These sequences have been shown to be important in control of transcription of integrins. Rosen *et al.* carried out a detailed analysis of the α_4 promoter (52). There is a short sequence −42 to −76 bp from the transcription start site that is necessary for transcription in Jurkat cells which express α_4. This sequence showed no activity in HeLa cells which do not express α_4. This sequence contains three ets-binding sequences. Gel retardation assays showed two complexes: one, which showed slower electrophoretic mobility, was found only in Jurkat cells, while a faster migrating complex was found in both Jurkat and HeLa cells. The faster moving complex contained the ets family proteins GABPα and GABPβ. Using a panel of antibodies, the authors found evidence to suggest that the additional protein in the slower band was an ets-related protein but was not Ets-1, Ets-2, PU.1, or GABPα. The two downstream sites were sufficient to bind ets proteins, while the upstream site alone was not. However, the presence of the upstream site was required for the full, slower-moving complex to form. Deletion of this 5′ site also caused formation of another complex which was shown to contain Ets-1. In summary, the ets site farthest downstream is sufficient to bind GABPα/GABPβ and does have some promoter activity. Including the adjacent upstream site causes binding of Ets-1, which causes more efficient transcription. If the third ets site, farther upstream is included, Ets-1 does not bind, an unidentified ets protein does bind, and transcription is further stimulated.

Ets recognition sequences have also been implicated in the activity of the β_2 (CD18) promoter. Böttinger *et al.* used deletion analysis to find a short sequence from −81 to −35 that showed promoter activity (65). DNA footprint analysis showed that this region had two protected segments, suggesting binding of at least two transcription factors. Both segments contained ets-binding sequences, with the upstream sequence being inverted. This short promoter sequence was sufficient for tissue-specific expression and phorbol ester inducibility. The authors noted two strong bands on gel-shift assays. One complex is likely GABPα/GABPβ based on immunologic data and binds both ets regions. The other complex forms only in myeloid cells and also binds to both regions. This second transcription factor is ets related but otherwise yet unknown. The upstream segment binds GABPα/GABPβ more strongly, while the downstream segment binds the myeloid-specific factors more strongly.

Tissue-specific gene transcription was also attributed to presence of an ets-binding sequence in the promoter of the megakaryocyte/platelet integrin α_{IIb} gene (71). These authors showed that megaryocyte-specific α_{IIb} expression was due to a cooperative interaction between GATA-1 (an erythroid and megakaryocyte specific transcription factor) and Ets-1. Transfection of a −75-bp promoter fragment into megakaryocytic cells resulted in reporter activity. The same construct had no activity in HeLa cells. However, if HeLa cells were co-transfected with plasmids expressing Ets-1 or GATA-1, activity of the promoter was restored. This effect was additive when both Ets-1 and GATA-1 were included.

In summary, putative Ets binding sites have been found in a number of integrin promoters. In the cases of α_4, α_{IIb}, and β_2, these sites have further been shown to be functional in transcriptional regulation. For α_{IIb}, the ets site was found to be important in controlling tissue-specific expression of the gene product.

PU.1. Another member of the ets family which has tissue-specific activity is the lymphoid and myeloid-specific transcription factor PU.1. It is found primarily in macrophages and B cells (72). Its binding sequence has been noted

in the promoters of α_L (55), α_M (56), α_X (60), α_2 (50), α_4 (51), β_3 (66), and mouse β_7 (68) genes. Pahl *et al.* studied the role of PU.1 in transcriptional control of α_M (CD11b) in myeloid versus non-myeloid cells (58). They showed that a PU.1 site at −20 bp relative to the transcriptional start site is functional and necessary for promoter activity. Another consensus PU.1 site at −130 does not bind PU.1. The active PU.1 site appears to be responsible for much of the tissue-specific activity. However, it cannot be solely responsible, since PU.1 is also expressed in B cells though α_M is not.

Other Consensus Sites. A number of other consensus sequences for DNA-binding proteins have been identified in integrin promoters. Many of these putative sites have not yet been tested directly for activity in controlling integrin expression. However, there are intriguing possibilities. AP-1 sites are known to mediate transcriptional stimulation by phorbol esters (73) and by TGFβ (74). The promoter regions of α_2 (50), α_4 (51), α_5 (54), α_X (60), and β_1 (63) have consensus AP-1 sites. Expression of most of these genes have been shown to be responsive to one or both of these molecules. The responses however, are complex. For example, although α_4 and α_5 both contain AP-1 sites, phorbol ester–induced differentiation of U937 promonocytic cells causes an increase in $\alpha_5\beta_1$ and a decrease in $\alpha_4\beta_1$ (35, 38), though the decrease in α_4 may be due to posttranscriptional mechanisms (35). T cells (75) or MG-63 osteosarcoma cells (39) also showed no change or a decrease in α_4 in response to phorbol ester treatment. Although the β_1 promoter has several elements which could be responsive to TGFβ stimulation, when Cervella *et al.* transfected reporter constructs into MG-63 osteosarcoma cells the constructs showed no responsiveness to TGFβ (63).

Several integrin promoters have retinoic acid response elements. α_M (CD11b) (56), α_X (CD11c) (60), β_2 (CD18) (64), and mouse β_7 (68) have all been noted to contain these sites. α_M (CD11b) has been shown to be responsive to retinoic acid in the HL-60 myeloid cell line. However, the α_M promoter also contains an AP-2–binding site. AP-2 can itself be stimulated by retinoic acid (76). In addition, α_v and β_1, which have not been noted to have retinoic acid response elements in their promoters, are in fact increased by retinoic acid (30, 31, 77). Neither α_v nor β_1 have AP-2 consensus sites. Clearly, the effects are complex, and responsiveness to retinoic acid cannot be predicted simply on the presence or absence of a putative binding site.

Alternative Splicing

Another mechanism by which cells can regulate integrin function is by alternative splicing. Alternative splicing has been found in several integrins including α_3 (78), α_6 (78–81), mouse α_6 (82), α_7 (83, 84), α_{IIb} (85), drosophila PS2α (86), β_1 (87–92), β_3 (93, 94), human β_4 (95, 96), and mouse β_4 (97). Changes in splicing have been noted during development (82, 83) and tumorigenesis (98). Alternative splicing has also been noted to be tissue specific (78, 87, 88, 99, 100). Functional differences in alternatively spliced forms have been investigated. Niessen *et al.* found no change in ligand specificity with different isoforms of α_6 (101). Delwel *et al.* showed that PMA stimulation of α_{6A} or α_{6B} transfected cells resulted in better adhesion in α_{6B} transfectants than in α_{6A} transfectants, though PMA-induced phosphorylation of the α subunit was much stronger in α_{6A} variants (102). Hogervorst *et al.* showed that PMA-induced phosphorylation of α_{6A} resulted in decreased adhesion to laminin (103). Balzac *et al.* investigated the function of the β_{1B} isoform. Using an antibody against the unique peptide region, they were able to demonstrate tissue specific expression. They found no difference in the ability of β_{1A} and β_{1B} isoforms to bind ligand, but they did show that, while β_{1A} was localized to focal adhesion, β_{1B} was not (104). In follow-up studies, Balzac *et al.* transfected the β_{1B} isoform into CHO cells. They found that this subunit was not capable of inducing tyrosine phosphorylation as was the endogenous or transfected human β_{1A}. Transfection of the β_{1B} subunit resulted in reduced adhesion and migration suggesting a dominant-negative effect (89). Fornaro *et al.* showed that cells expressing the β_{1C} variant showed less ability to proliferate in response to serum stimulation (105). Meredith *et al.* showed that when this β_{1C} subunit was transfected into mouse fibroblasts, it inhibited cell cycle progression in late G1 near the G1/S transition (106).

Most of the alternative splicing events that have been reported affect the cytoplasmic domain of the protein. One exception is the alternatively spliced Drosophila PS2 α protein. Zavortink reported that the splice event occurs in the extracellular domain and may be important in determining ligand specificity (107). Ziober also reported alternative splicing in the ligand-binding domain of human α_7 (84).

In summary, changes in integrin structure due to alternative splicing appear to affect the protein's function. Alternative splicing of the cytoplasmic domain results in altered responsiveness to posttranslational events, such as phosphorylation, as well as altered intracellular signaling by that integrin subunit. Splicing of the extracellular domain may affect ligand binding.

Mobilization of Intracellular Stores

Neutrophils and monocytes express integrins of the β_2 (CD 18) family. Miller *et al.* reported that when monocytes were stimulated with FMLP or other mediators the cell surface expression of $\alpha_M\beta_2$ (Mac-1 or CD11b/CD18) and $\alpha_X\beta_2$ (p150, 95, or CD11c/CD18) increased rapidly with a half-maximal time of 2 min. Using detergent permeabilization studies and electron microscopy it was shown that those molecules were held in intracellular vesicles and then mobilized to the cell surface after stimulation (108). Likewise in neutrophils $\alpha_M\beta_2$ and $\alpha_X\beta_2$ are found in intracellular granules (109, 110). When neutrophils are stimulated by chemoattractant molecules such as C5a, IL-8, or FMLP, or by ligation of the Fcγ receptor, the cell surface expression of $\alpha_M\beta_2$ is increased due to exocytosis (111). This mecha-

nism provides a means of rapid modulation of integrin function, occurring within minutes.

Intracellular Control of Ligand Binding

This type of regulation, termed inside-out signaling, has been recently reviewed (1, 112, 113) and will not be discussed further here. Inside-out signaling is characterized by the presence of integrin molecules on the cell-surface that either do not bind ligand or bind with lower affinity. An intracellular change can then activate these molecules to produce an active receptor. This mechanism is also capable of yielding a very rapid increase in adhesion after appropriate stimulation.

Summary

The regulation of integrins has been studied in many different cell types. Regulation of these molecules has turned out to be far more complex than a simple stimulus-response function. A given cell type can respond to multiple exogenous signals, and the same signal has different effects on different cells. Even at a single point of regulation, such as control of transcription, the mechanisms are complicated. In sum, it is clear that the regulation of integrins is complex and affords the cell many possible levels of control. This regulatory sophistication is likely necessary, given the critical role that integrins play in the myriad social interactions of cells.

1. Hynes RO. Integrins: Versatility, modulation, and signaling in cell adhesion. Cell **69:**11–25, 1992.
2. Ignotz RA, Massague J. Cell adhesion protein receptors as targets for transforming growth factor–beta action. Cell **51:**189–197, 1987.
3. Heino J, Ignotz RA, Hemler ME, Crouse C, Massague J. Regulation of cell adhesion receptors by transforming growth factor–beta. Concomitant regulation of integrins that share a common beta 1 subunit. J Biol Chem **264:**380–388, 1989.
4. Roberts CJ, Birkenmeier TM, McQuillan JJ, Akiyama SK, Yamada SS, Chen WT, Yamada KM, McDonald JA. Transforming growth factor beta stimulates the expression of fibronectin and of both subunits of the human fibronectin receptor by cultured human lung fibroblasts. J Biol Chem **263:**4586–4592, 1988.
5. Wang D, Zhou GH, Birkenmeier TM, Gong J, Sun L, Brattain MG. Autocrine transforming growth factor beta 1 modulates the expression of integrin alpha 5 beta 1 in human colon carcinoma FET cells. J Biol Chem **270:**14154–14159, 1995.
6. Zambruno G, Marchisio PC, Marconi A, Vaschieri C, Melchiori A, Giannetti A, De Luca M. Transforming growth factor-beta 1 modulates beta 1 and beta 5 integrin receptors and induces the de novo expression of the alpha v beta 6 heterodimer in normal human keratinocytes: Implications for wound healing. J Cell Biol **129:**853–865, 1995.
7. Enenstein J, Waleh NS, Kramer RH. Basic FGF and TGF-beta differentially modulate integrin expression of human microvascular endothelial cells. Exp Cell Res **203:**499–503, 1992.
8. Sheppard D, Cohen DS, Wang A, Busk M. Transforming growth factor beta differentially regulates expression of integrin subunits in guinea pig airway epithelial cells. J Biol Chem **267:**17409–17414, 1992.
9. Jaspers M, de Meirsman C, Schollen E, Vekemans S, Cassiman JJ. Stable expression of VLA-4 and increased maturation of the beta 1-integrin precursor after transfection of CHO cells with alpha 4m cDNA. FEBS Lett **353:**239–242, 1994.
10. Serra R, Carbonetto S, Lord M, Isom HC. Transforming growth factor beta 1 suppresses transformation in hepatocytes by regulating alpha 1 beta 1 integrin expression. Cell Growth Differ **5:**509–517, 1994.
11. Hafez MM, Hsu S, Yan Z, Winawer S, Friedman E. Two roles for transforming growth factor beta 1 in colon enterocytic cell differentiation. Cell Growth Differ **3:**753–762, 1992.
12. Gailit J, Welch MP, Clark RAF. TGF-β1 stimulates expression of keratinocyte integrins during re-epithelialization of cutaneous wounds. J Invest Dermatol **103:**221–227, 1994.
13. Janat MF, Argraves WS, Liau G. Regulation of vascular smooth muscle cell integrin expression by transforming growth factor beta 1 and by platelet-derived growth factor–BB. J Cell Physiol **151:**588–595, 1992.
14. Rinaldi N, Barth T, Henne C, Mechterscheimer G, Moller P. Synoviocytes in chronic synovitis in situ and cytokine stimulated synovial cells in vitro neo-express alpha 1, alpha 3, and alpha 5 chain of beta 1 integrins. Virchows Arch **425:**171–180, 1994.
15. Kirchberg K, Lange TS, Klein EC, Jungtaubl H, Heinen G, Meyer-Ingold W, Scharffetter-Kochanek K. Induction of beta 1 integrin synthesis by recombinant platelet-derived growth factor (PDGF-AB) correlates with an enhanced migratory response of human dermal fibroblasts to various extracellular matrix proteins. Exp Cell Res **220:**29–35, 1995.
16. Ahlen K, Rubin K. Platelet-derived growth factor–BB stimulates synthesis of the integrin alpha 2-subunit in human diploid fibroblasts. Exp Cell Res **215:**347–353, 1994.
17. Fujii K, Dousaka-Nakajima N, Imamura S. Epidermal growth factor enhancement of HSC-1 human cutaneous squamous carcinoma cell adhesion and migration on type I collagen involves selective up-regulation of alpha 2 beta 1 integrin expression. Exp Cell Res **216:**261–272, 1995.
18. Zhang Z, Tarone G, Turner DC. Expression of integrin alpha 1 beta 1 is regulated by nerve growth factor and dexamethasone in PC12 cells. Functional consequences for adhesion and neurite outgrowth. J Biol Chem **268:**5557–5565, 1993.
19. Kitazawa S, Ross FP, McHugh K, Teitelbaum SL. Interleukin-4 induces expression of the integrin alpha v beta 3 via transactivation of the beta 3 gene. J Biol Chem **270:**4115–4120, 1995.
20. Dedhar S. Regulation of expression of the cell adhesion receptors, integrins, by recombinant human interleukin-1 beta in human osteosarcoma cells: inhibition of cell proliferation and stimulation of alkaline phosphatase activity. J Cell Physiol **138:**291–299, 1989.
21. Dedhar S. Signal transduction via the beta 1 integrins is a required intermediate in interleukin-1 beta induction of alkaline phosphatase activity in human osteosarcoma cells. Exp Cell Res **183:**207–214, 1989.
22. Milam SB, Magnuson VL, Steffensen B, Chen D, Klebe RJ. IL-1 beta and prostaglandins regulate integrin mRNA expression. J Cell Physiol **149:**173–183, 1991.
23. Ohashi H, Maeda T, Mishima H, Otori T, Nishida T, Sekiguchi K. Up-regulation of integrin alpha 5 beta 1 expression by interleukin-6 in rabbit corneal epithelial cells. Exp Cell Res **218:**418–423, 1995.
24. Vaddi K, Newton RC. Regulation of monocyte integrin expression by beta-family chemokines. J Immunol **153:**4721–4732, 1994.
25. Defilippi P, van Hinsbergh V, Bertolotto A, Rossino P, Silengo L, Tarone G. Differential distribution and modulation of expression of alpha 1/beta 1 integrin on human endothelial cells. J Cell Biol **114:**855–863, 1991.
26. Defilipi P, Truffa G, Stefanuto G, Altruda F, Silengo L, Tarone G. Tumor necrosis factor alpha and interferon gamma modulate the expression of the vitronectin receptor (integrin beta 3) in human endothelial cells. J Biol Chem **266:**7638–7645, 1991.
27. Ni J, Porter AG, Hollander D. Beta 7 integrins and other cell adhesion molecules are differentially expressed and modulated by TNF beta in different lymphocyte populations. Cell Immunol **161:**166–172, 1995.
28. Shima M, Teitelbaum SL, Holers VM, Ruzicka C, Osmack P, Ross FP. Macrophage-colony-stimulating factor regulates expression of the integrins alpha 4 beta 1 and alpha 5 beta 1 by murine bone marrow macrophages. Proc Natl Acad Sci U S A **92:**5179–5183, 1995.
29. De Nichilo MO, Burns GF. Granulocyte-macrophage and macrophage colony-stimulating factors differentially regulate alpha v integrin expression on cultured human macrophages. Proc Natl Acad Sci U S A **90:**2517–2521, 1993.
30. Santos CL, Giorgi RR, Frochtengarten F, Elias MC, Chammas R,

Brentani RR. Regulation of vitronectin receptor expression by retinoic acid on human melanoma cells. Int J Clin Lab Res **24:**148–153, 1994.
31. Ross SA, Ahrens RA, De Luca LM. Retinoic acid enhances adhesiveness, laminin and integrin beta 1 synthesis, and retinoic acid receptor expression in F9 teratocarcinoma cells. J Cell Physiol **159:**263–273, 1994.
32. Medhora MM, Teitelbaum S, Chappel J, Alvarez J, Mimura H, Ross FP, Hruska K. 1 alpha,25-dihydroxyvitamin D3 up-regulates expression of the osteoclast integrin alpha v beta 3. J Biol Chem **268:**1456–1461, 1993.
33. Gronowicz GA, McCarthy MB. Glucocorticoids inhibit the attachment of osteoblasts to bone extracellular matrix proteins and decrease beta 1-integrin levels. Endocrinology **136:**598–608, 1995.
34. Doherty WJ, DeRome ME, McCarthy MB, Gronowicz GA. The effect of glucocorticoids on osteoblast function. The effect of corticosterone on osteoblast expression of beta 1 integrins. J Bone Joint Surg Am **77:**396–404, 1995.
35. Bellon T, Lopez-Rodriguez C, Rubio MA, Jochems G, Bernabeu C, Corbi AL. Regulated expression of p150,95 (CD11c/CD18; alpha X/beta 2) and VLA-4 (CD49d/CD29; alpha 4/beta 1) integrins during myeloid cell differentiation. Eur J Immunol **24:**41–47, 1994.
36. Noti JD, Reinemann BC. The leukocyte integrin gene CD11c is transcriptionally regulated during monocyte differentiation. Mol Immunol **32:**361–369, 1995.
37. Burger SR, Zutter MM, Sturgill-Koszycki S, Santoro SA. Induced cell surface expression of functional alpha 2 beta 1 integrin during megakaryocytic differentiation of K562 leukemic cells. Exp Cell Res **202:**28–35, 1992.
38. Ferreira OC Jr., Valinsky JE, Sheridan K, Wayner EA, Bianco C, Garcia-Pardo A. Phorbol ester–induced differentiation of U937 cells enhances attachment to fibronectin and distinctly modulates the alpha 5 beta 1 and alpha 4 beta 1 fibronectin receptors. Exp Cell Res **193:**20–26, 1991.
39. Chen D, Magnuson V, Hill S, Arnaud C, Steffensen B, Klebe RJ. Regulation of integrin gene expression by substrate adherence. J Biol Chem **267:**23502–23506, 1992.
40. Tiisala S, Majuri ML, Carpen O, Renkonen R. Genistein enhances the ICAM-mediated adhesion by inducing the expression of ICAM-1 and its counter-receptors. Biochem Biophys Res Commun **203:**443–449, 1994.
41. Feltri ML, Scherer SS, Nemni R, Kamholz J, Vogelbacker H, Scott MO, Canal N, Quaranta V, Wrabetz L. Beta 4 integrin expression in myelinating Schwann cells is polarized, developmentally regulated and axonally dependent. Development **120:**1287–1301, 1994.
42. Benhaim P, Mathes SJ, Hunt TK, Scheuenstuhl H, Benz CC. Induction of neutrophil Mac-1 integrin expression and superoxide production by the medicinal plant extract gossypol. Inflammation **18:**443–458, 1994.
43. Nogueira AC, Neubert R, Helge H, Neubert D. Thalidomide and the immune system. 3. Simultaneous up- and down-regulation of different integrin receptors on human white blood cells. Life Sci **55:**77–92, 1994.
44. Carvalho RS, Scott JE, Yen EH. The effects of mechanical stimulation on the distribution of beta 1 integrin and expression of beta 1-integrin mRNA in TE-85 human osteosarcoma cells. Arch Oral Biol **40:**257–264, 1995.
45. AbiEzzi SS, Gesink DS, Schreck PJ, Amiel D, Akeson WH, Woods VL Jr. Increased expression of the beta 1, alpha 5, and alpha v integrin adhesion receptor subunits occurs coincident with remodeling of stress-deprived rabbit anterior cruciate and medial collateral ligaments. J Orthop Res **13:**594–601, 1995.
46. Pottratz ST, Weir AL, Wisniowski PE. Pneumocystis carinii attachment increases expression of fibronectin-binding integrins on cultured lung cells. Infect Immun **62:**5464–5469, 1994.
47. Weeks BS, Klotman ME, Dhawan S, Kibbey M, Rappaport J, Kleinman HK, Yamada KM, Klotman PE. HIV-1 infection of human T lymphocytes results in enhanced alpha 5 beta 1 integrin expression. J Cell Biol **114:**847–853, 1991.
48. Lafrenie RM, Wahl LM, Epstein JS, Hewlett IK, Yamada KM, Dhawan S. HIV-1-Tat modulates the function of monocytes and alters their interactions with microvessel endothelial cells. A mechanism of HIV pathogenesis. J Immunol **156:**1638–1645, 1996.
49. Ito M, Watanabe M, Ihara T, Kamiya H, Sakurai M. Increased expression of adhesion molecules (CD54, CD29 and CD44) on fibroblasts infected with cytomegalovirus. Microbiol Immunol **39:**129–133, 1995.
50. Zutter MM, Santoro SA, Painter AS, Tsung YL, Gafford A. The human alpha 2 integrin gene promoter. Identification of positive and negative regulatory elements important for cell-type and developmentally restricted gene expression. J Biol Chem **269:**463–469, 1994.
51. Rosen GD, Birkenmeier TM, Dean DC. Characterization of the alpha 4 integrin gene promoter. Proc Natl Acad Sci U S A **88:**4094–4098, 1991.
52. Rosen GD, Barks JL, Iademarco MF, Fisher RJ, Dean DC. An intricate arrangement of binding sites for the Ets family of transcription factors regulates activity of the alpha 4 integrin gene promoter. J Biol Chem **269:**15652–15660, 1994.
53. Audet JF, Masson JY, Rosen GD, Salesse C, Guerin SL. Multiple regulatory elements control the basal promoter activity of the human alpha 4 integrin gene. DNA Cell Biol **13:**1071–1085, 1994.
54. Birkenmeier TM, McQuillan JJ, Boedeker ED, Argraves WS, Ruoslahti E, Dean DC. The alpha 5 beta 1 fibronectin receptor. Characterization of the alpha 5 gene promoter. J Biol Chem **266:**20544–20549, 1991.
55. Cornwell RD, Gollahon KA, Hickstein DD. Description of the leukocyte function-associated antigen 1 (LFA-1 or CD11a) promoter. Proc Natl Acad Sci U S A **90:**4221–4225, 1993.
56. Hickstein DD, Baker DM, Gollahon KA, Back AL. Identification of the promoter of the myelomonocytic leukocyte integrin CD11b. Proc Natl Acad Sci U S A **89:**2105–2109, 1992.
57. Pahl HL, Rosmarin AG, Tenen DG. Characterization of the myeloid-specific CD11b promoter. Blood **79:**865–870, 1992.
58. Pahl HL, Scheibe RJ, Zhang DE, Chen HM, Galson DL, Maki RA, Tenen DG. The proto-oncogene PU.1 regulates expression of the myeloid-specific CD11b promoter. J Biol Chem **268:**5014–5020, 1993.
59. Chen HM, Pahl HL, Scheibe RJ, Zhang DE, Tenen DG. The Sp1 transcription factor binds the CD11b promoter specifically in myeloid cells in vivo and is essential for myeloid-specific promoter activity. J Biol Chem **268:**8230–8239, 1993.
60. Lopez-Cabrera M, Nueda A, Vara A, Garcia-Aguilar J, Tugores A, Corbi AL. Characterization of the p150,95 leukocyte integrin alpha subunit (CD11c) gene promoter. Identification of cis-acting elements. J Biol Chem **268:**1187–1193, 1993.
61. Donahue JP, Sugg N, Hawiger J. The integrin alpha v gene: Identification and characterization of the promoter region. Biochim Biophys Acta **1219:**228–232, 1994.
62. Prandini MH, Denarier E, Frachet P, Uzan G, Marguerie G. Isolation of the human platelet glycoprotein IIb gene and characterization of the 5′ flanking region. Biochem Biophys Res Commun **156:**595–601, 1988.
63. Cervella P, Silengo L, Pastore C, Altruda F. Human beta 1-integrin gene expression is regulated by two promoter regions. J Biol Chem **268:**5148–5155, 1993.
64. Agura ED, Howard M, Collins SJ. Identification and sequence analysis of the promoter for the leukocyte integrin beta-subunit (CD18): A retinoic acid-inducible gene. Blood **79:**602–609, 1992.
65. Bottinger EP, Shelley CS, Farokhzad OC, Arnaout MA. The human beta 2 integrin CD18 promoter consists of two inverted Ets cis elements. Mol Cell Biol **14:**2604–2615, 1994.
66. Villa-Garcia M, Li L, Riely G, Bray PF. Isolation and characterization of a TATA-less promoter for the human beta 3 integrin gene. Blood **83:**668–676, 1994.
67. Cao X, Ross FP, Zhang L, MacDonald PN, Chappel J, Teitelbaum SL. Cloning of the promoter for the avian integrin beta 3 subunit gene and its regulation by 1,25-dihydroxyvitamin D3. J Biol Chem **268:**27371–27380, 1993.
68. Leung E, Mead PE, Yuan Q, Jiang WM, Watson JD, Krissansen GW. The mouse beta 7 integrin gene promoter: transcriptional regulation of the leukocyte integrins LPAM-1 and M290. Int Immunol **5:**551–558, 1993.
69. Uzan G, Prenant M, Prandini MH, Martin F, Marguerie G. Tissue-specific expression of the platelet GPIIb gene. J Biol Chem **266:**8932–8939, 1991.
70. Pugh BF, Tjian R. Mechanism of transcriptional activation by Sp1: Evidence for coactivators. Cell **61:**1187–1197, 1990.
71. Lemarchandel V, Ghysdael J, Mignotte V, Rahuel C, Romeo PH.

GATA and Ets cis-acting sequences mediate megakaryocytic-specific expression. Mol Cell Biol **13:**668–676, 1993.
72. Klemsz MJ, McKercher SR, Celada A, Van Beveren C, Maki RA. The macrophage and B cell-specific transcription factor PU.1 is related to the ets oncogene [see comments]. Cell **61:**113–124, 1990.
73. Angel P, Imagawa M, Chiu R, Stein B, Imbra RJ, Rahmsdorf JH, Jonat C, Herrlich P, Karin M. Phorbol ester-inducible genes contain a common cis element recognized by a TPA-modulated trans-acting factor. Cell **49:**729–739, 1987.
74. Kim SJ, Angel P, Lafyatis R, Hattori K, Kim KY, Sporn MB, Karim M, Roberts AB. Autoinduction of transforming growth factor beta 1 is mediated by the AP-1 complex. Mol Cell Biol **10:**1492–1497, 1990.
75. Kohn FR, Grigg ME, Klingemann HG. Differential regulation of fibronectin receptor subunit gene and cell surface expression in human peripheral blood T lymphocytes. J Immunol **146:**1484–1489, 1991.
76. Luscher B, Mitchell PJ, Williams T, Tjian R. Regulation of transcription factor AP-2 by the morphogen retinoic acid and by second messengers. Genes Dev **3:**1507–1517, 1989.
77. Dedhar S, Robertson K, Gray V. Induction of expression of the alpha v beta 1 and alpha v beta 3 integrin heterodimers during retinoic acid-induced neuronal differentiation of murine embryonal carcinoma cells. J Biol Chem **266:**21846–21852, 1991.
78. Tamura RN, Cooper HM, Collo G, Quaranta V. Cell type-specific integrin variants with alternative alpha chain cytoplasmic domains. Proc Natl Acad Sci U S A **88:**10183–10187, 1991.
79. de Curtis I, Gatti G. Identification of a large complex containing the integrin alpha 6 beta 1 laminin receptor in neural retinal cells. J Cell Sci **107:**3165–3172, 1994.
80. Hogervorst F, Kuikman I, van Kessel AG, Sonnenberg A. Molecular cloning of the human alpha 6 integrin subunit. Alternative splicing of alpha 6 mRNA and chromosomal localization of the alpha 6 and beta 4 genes. Eur J Biochem **199:**425–433, 1991.
81. Cooper HM, Tamura RN, Quaranta V. The major laminin receptor of mouse embryonic stem cells is a novel isoform of the alpha 6 beta 1 integrin. J Cell Biol **115:**843–850, 1991.
82. Hierck BP, Thorsteinsdottir S, Niessen CM, Freund E, Iperen LV, Feyen A, Hogervorst F, Poelmann RE, Mummery CL, Sonnenberg A. Variants of the alpha 6 beta 1 laminin receptor in early murine development: distribution, molecular cloning and chromosomal localization of the mouse integrin alpha 6 subunit [published erratum appears in Cell Adhes Commun 1993 Sept; 1(2): following 190]. Cell Adhes Commun **1:**33–53, 1993.
83. Song WK, Wang W, Sato H, Bielser DA, Kaufman SJ. Expression of alpha 7 integrin cytoplasmic domains during skeletal muscle development: Alternate forms, conformational change, and homologies with serine/threonine kinases and tyrosine phosphatases. J Cell Sci **106:**1139–1152, 1993.
84. Ziober BL, Vu MP, Waleh N, Crawford J, Lin CS, Kramer RH. Alternative extracellular and cytoplasmic domains of the integrin alpha 7 subunit are differentially expressed during development. J Biol Chem **268:**26773–26783, 1993.
85. Bray PF, Leung CS, Shuman MA. Human platelets and megakaryocytes contain alternately spliced glycoprotein IIb mRNAs. J Biol Chem **265:**9587–9590, 1990.
86. Brown NH, King DL, Wilcox M, Kafatos FC. Developmentally regulated alternative splicing of Drosophila integrin PS2 alpha transcripts. Cell **59:**185–195, 1989.
87. Zhidkova NI, Belkin AM, Mayne R. Novel isoform of beta 1 integrin expressed in skeletal and cardiac muscle. Biochem Biophys Res Commun **214:**279–285, 1995.
88. van der Flier A, Kuikman I, Baudoin C, van der Neut R, Sonnenberg A. A novel beta 1 integrin isoform produced by alternative splicing: Unique expression in cardiac and skeletal muscle. FEBS Lett **369:**340–344, 1995.
89. Balzac F, Retta SF, Albini A, Melchiorri A, Koteliansky VE, Geuna M, Silengo L, Tarone G. Expression of beta 1B integrin isoform in CHO cells results in a dominant negative effect on cell adhesion and motility. J Cell Biol **127:**557–565, 1994.
90. Altruda F, Cervella P, Tarone G, Botta C, Balzac F, Stefanuto G, Silengo L. A human integrin beta 1 subunit with a unique cytoplasmic domain generated by alternative mRNA processing. Gene **95:**261–266, 1990.
91. Languino LR, Ruoslahti E. An alternative form of the integrin beta 1 subunit with a variant cytoplasmic domain. J Biol Chem **267:**7116–7120, 1992.
92. Belkin AM, Zhidkova NI, Balzac F, Altruda F, Tomatis D, Maier A, Tarone G, Koteliansky VE, Burridge K. Beta 1D integrin displaces the beta 1A isoform in striated muscles: localization at junctional structures and signaling potential in nonmuscle cells. J Cell Biol **132:**211–226, 1996.
93. Djaffar I, Chen YP, Creminon C, Maclouf J, Cieutat AM, Gayet O, Rosa JP. A new alternative transcript encodes a 60 kDa truncated form of integrin beta 3. Biochem J **300:**69–74, 1994.
94. van Kupevelt TH, Languino LR, Gailit JO, Suzuki S, Ruoslahti E. An alternative cytoplasmic domain of the integrin beta 3 subunit. Proc Natl Acad Sci U S A **86:**5415–5418, 1989.
95. Clarke AS, Lotz MM, Mercurio AM. A novel structural variant of the human beta 4 integrin cDNA. Cell Adhes Commun **2:**1–6, 1994.
96. Tamura RN, Rozzo C, Starr L, Chambers J, Reichardt LF, Cooper HM, Quaranta V. Epithelial integrin alpha 6 beta 4: Complete primary structure of alpha 6 and variant forms of beta 4. J Cell Biol **111:**1593–1604, 1990.
97. Kennel SJ, Foote LJ, Cimino L, Rizzo MG, Chang LY, Sacchi A. Sequence of a cDNA encoding the beta 4 subunit of murine integrin. Gene **130:**209–216, 1993.
98. Tennenbaum T, Belanger AJ, Glick AB, Tamura R, Quaranta V, Yuspa SH. A splice variant of alpha 6 integrin is associated with malignant conversion in mouse skin tumorigenesis. Proc Natl Acad Sci U S A **92:**7041–7045, 1995.
99. Shaw LM, Lotz MM, Mercurio AM. Inside-out integrin signaling in macrophages. Analysis of the role of the alpha 6A beta 1 and alpha 6B beta 1 integrin variants in laminin adhesion by cDNA expression in an alpha 6 integrin–deficient macrophage cell line. J Biol Chem **268:**11401–11408, 1993.
100. Hogervorst F, Admiral LG, Niessen C, Kuikman I, Janssen H, Daams H, Sonnenberg A. Biochemical characterization and tissue distribution of the A and B variants of the integrin alpha 6 subunit. J Cell Biol **121:**179–191, 1993.
101. Niessen CM, Hogervorst F, Jaspars LH, de Melker AA, Delwel GO, Hulsman EH, Kuikman I, Sonnenberg A. The alpha 6 beta 4 integrin is a receptor for both laminin and kalinin. Exp Cell Res **211:**360–367, 1994.
102. Delwel GO, Hogervorst F, Kuikman I, Paulsson M, Timpl R, Sonnenberg A. Expression and function of the cytoplasmic variants of the integrin alpha 6 subunit in transfected K562 cells. Activation-dependent adhesion and interaction with isoforms of laminin. J Biol Chem **268:**25865–25875, 1993.
103. Hogervorst F, Kuikman I, Noteboom E, Sonnenberg A. The role of phosphorylation in activation of the alpha 6A beta 1 laminin receptor. J Biol Chem **268:**18427–18430, 1993.
104. Balzac F, Belkin AM, Koteliansky VE, Balabanov YV, Altruda F, Silengo L, Tarone G. Expression and functional analysis of a cytoplasmic domain variant of the beta 1 integrin subunit. J Cell Biol **121:**171–178, 1993.
105. Fornaro M, Zheng DQ, Languino LR. The novel structural motif Gln795–Gln802 in the integrin beta 1C cytoplasmic domain regulates cell proliferation. J Biol Chem **270:**24666–24669, 1995.
106. Meredith J Jr., Takada Y, Fornaro M, Languino LR, Schwartz MA. Inhibition of cell cycle progression by the alternatively spliced integrin beta 1C. Science **269:**1570–1572, 1995.
107. Zavortink M, Bunch TA, Brower DL. Functional properties of alternatively spliced forms of the Drosophila PS2 integrin alpha subunit. Cell Adhes Commun **1:**251–264, 1993.
108. Miller LJ, Bainton DJ, Borregard N, Springer TA. Stimulated mobilization of monocyte Mac-1 and p150,95 adhesion proteins from an intracellular vesicular compartment to the cell surface. J Clin Invest **80:**535–544, 1987.
109. Bainton DF, Miller LJ, Kishimoto TK, Springer TA. Leukocyte adhesion receptors are stored in peroxidase-negative granules of human neutrophils. J Exp Med **166:**1641–1653, 1987.
110. Singer II, Scott S, Kawka DW, Kazazis DM. Adhesomes: Specific granules containing receptors for laminin, C3bi/fibrinogen, fibronectin, and vitronectin in human polymorphonuclear leukocytes and monocytes. J Cell Biol **109:**3169–3182, 1989.
111. Molad Y, Haines KA, Anderson DC, Buyon JP, Cronstein BN. Immunocomplexes stimulate different signalling events to chemoat-

tractants in the neutrophil and regulate L-selectin and beta 2-integrin expression differently. Biochem J **299:**881–887, 1994.
112. Ginsberg MH. Integrins: dynamic regulation of ligand binding. Biochem Soc Trans **23:**439–446, 1995.
113. Diamond MS, Springer TA. The dynamic regulation of integrin adhesiveness. Curr Biol **4:**506–517, 1994.
114. Zutter MM, Fong AM, Krigman HR, Santoro SA. Differential regulation of the alpha 2 beta 1 and alpha IIb beta 3 integrin genes during megakaryocytic differentiation of pluripotential K562 cells. J Biol Chem **267:**20233–20238, 1992.
115. Bates EJ, Ferrante A, Harvey DP, Poulos A. Polyunsaturated fatty acids increase neutrophil adherence and integrin receptor expression. J Leukoc Biol **53:**420–426, 1993.
116. Martin F, Prandini MH, Thevenon D, Marguerie G, Uzan G. The transcription factor GATA-1 regulates the promoter activity of the platelet glycoprotein IIb gene. J Biol Chem **268:**21606–21612, 1993.
117. Prandini MH, Uzan G, Martin F, Thevenon D, Marguerie G. Characterization of a specific erythromegakaryocytic enhancer within the glycoprotein IIb promoter. J Biol Chem **267:**10370–10374, 1992.
118. Denarier E, Martin F, Martineau S, Marguerie G. PCR cloning and sequence of the murine GPIIb gene promoter. Biochem Biophys Res Commun **195:**1360–1364, 1993.