Integrin $\alpha 1\beta 1$

2

Humphrey Gardner

Abstract

Integrin $\alpha 1\beta 1$ is widely expressed in mesenchyme and the immune system, as well as a minority of epithelial tissues. Signaling through $\alpha 1$ contributes to the regulation of extracellular matrix composition, in addition to supplying in some tissues a proliferative and survival signal that appears to be unique among the collagen binding integrins. $\alpha 1$ provides a tissue retention function for cells of the immune system including monocytes and T cells, where it also contributes to their long-term survival, providing for peripheral T cell memory, and contributing to diseases of autoimmunity. The viability of $\alpha 1$ null mice, as well as the generation of therapeutic monoclonal antibodies against this molecule, have enabled studies of the role of $\alpha 1$ in a wide range of pathophysiological circumstances. The immune functions of $\alpha 1$ make it a rational therapeutic target.

Keywords

Integrin · Collagen · Knockout mouse · Phenotype

2.1 Introduction

The integrin $\alpha 1$ subunit was first discovered by Hemler et al. as the α component of the Very Late Antigen I (VLA1) expressed on a subset of T cells in the joints of patients with rheumatoid arthritis [57], as well as in a subset of lymphocytes after long term in vitro culture. $\alpha 1$ is the largest of the α subunits, with an apparent mw of 190 kDa nonreduced and 210 kDa reduced [60]. $\alpha 1$'s larger size compared to $\alpha 2$ is due to a higher degree of glycosylation [59]. At the C terminus, the intracellular portion of $\alpha 1$ is the shortest of the α subunits, at 13 residues. Functionally, $\alpha 1$ is one of four collagen binding I-domain containing $\beta 1$ partners, along with $\alpha 2$, $\alpha 10$ and $\alpha 11$. None of the four are known to partner with any β subunit other than $\beta 1$. The $\alpha 1$ I domain shows, like $\alpha 2$, 10 and 11, affinity modulation of ligand binding activity in the same way as has been described for αL [89, 133].

H. Gardner (✉)
Translational Medicine, Astrazeneca, 35 Gatehouse Drive, Waltham, MA 02451, USA
e-mail: humphrey.gardner@astrazeneca.com

D. Gullberg (ed.), *I Domain Integrins*, Advances in Experimental Medicine and Biology 819,
DOI: 10.1007/978-94-017-9153-3_2,

2.2 Tissue Distribution and Gene Regulation

$\alpha1\beta1$, like $\alpha11\beta1$, is predominantly present in mesenchyme. In the adult $\alpha1$ is most abundant in vascular and visceral smooth muscle. This smooth muscle expression has been shown, in the chicken, to be due to a unique combination of transcription factors, GATA6, SRF, and Nkx3.2 [101]. The latter is not found in mammals, but similar factors such as Bapx1 and its family members may play the same role. $\alpha1$ expression is switched off during megakaryocytic differentiation and this appears to be due to gene methylation [20]. The regulation of $\alpha1$ baseline expression in other tissues has not been extensively explored. Other sites of $\alpha1$ expression include fibroblasts [136, 142] and, particularly, specialized fibroblast related cells such as hepatic stellate (Ito) cells [112], pericytes [142] and mesangial cells [60, 96]; bone marrow mesenchymal stem cells [36, 54]; chondrocytes [85], in concert with integrin $\alpha10$ [18] and $\alpha2$ [152]; neural cells including undifferentiated Schwann cells [139] and neurons [37]; and many white blood cells [44, 59]. Microvascular endothelium shows abundant $\alpha1$ expression [33], which is upregulated during angiogenesis. Surprisingly, immunoelectron microscopy shows the presence of abundant $\alpha1\beta1$ on the luminal, as well as abluminal, endothelial surface [16], where no canonical $\alpha1$ ligand would be expected to be. $\alpha1$ is generally absent from normal epithelia, other than the endoderm derived hepatocytes [55, 86, 137], retinal pigment epithelium [99], and endometrial glands [10], where it is cyclically expressed.

Although SNPs in *ITGA1* have been associated with osteoporosis in Korean populations [80], these are synonymous and do not have associated expression data to corroborate their relevance.

2.3 Expression During Development

During development, there is abundant and dynamic expression of $\alpha1$ in embryonic tissues. It is first seen at the leading edge of invading trophoblast shortly after implantation [140], and antibody blockade of $\alpha1$ inhibits trophoblast invasion in vitro [32]. During early to mid embryogenesis $\alpha1$ is expressed transiently by neurons of the CNS [37], by maturing skeletal and cardiac muscle [144], in the skin [61], throughout the developing kidney [73], and in neural crest cells as they mature to dorsal root ganglia [37].

2.4 Expression in Malignancy

Dysregulation of $\alpha1$ has been noted in tumors. Some studies of melanoma have shown a correlation of worse clinical behavior with the presence of $\alpha1$ [124, 125], and others with the absence of $\alpha1$ [50]. Leiomyosarcomas often show loss of $\alpha1$ and gain of $\alpha2$ [94]. Bronchoalveolar [75] and gastric [46] carcinomas sometimes show gain of $\alpha1$ expression, as do squamous cell carcinomas of the head and neck [114]. Survey of RNAseq signatures of the GATC database shows that $\alpha1$ is in general reduced in total expression in tumors compared to normal tissues, probably reflecting the increased epithelial to mesenchyme ratio of the tumors, whereas the reverse is seen for the more epithelially expressed $\alpha2$ (Fig. 2.1). The two exceptions to this finding are head and neck SCC, corroborating Ratzinger et al. [114], and clear cell carcinoma of the kidney (Fig. 2.1). Lastly, dermatotrophic T cell lymphomas show expression of $\alpha1$ [138] probably consistent with the ontogeny of their derivation in the T cell lineage. There is no consistent relationship between $\alpha1$ expression and tumor behavior, in contrast to, the well-characterized and functionally significant $\alpha6\beta4$ to $\alpha6\beta1$ switch seen in some epithelial malignancies.

2.5 Integrin $\alpha1$ Ligands

The best-known ligands for $\alpha1$ are the collagens, investigated mostly in fibroblast studies, and laminin 111, investigated primarily in studies of neural cells. Other $\alpha1$ ligands include matrilin-1,

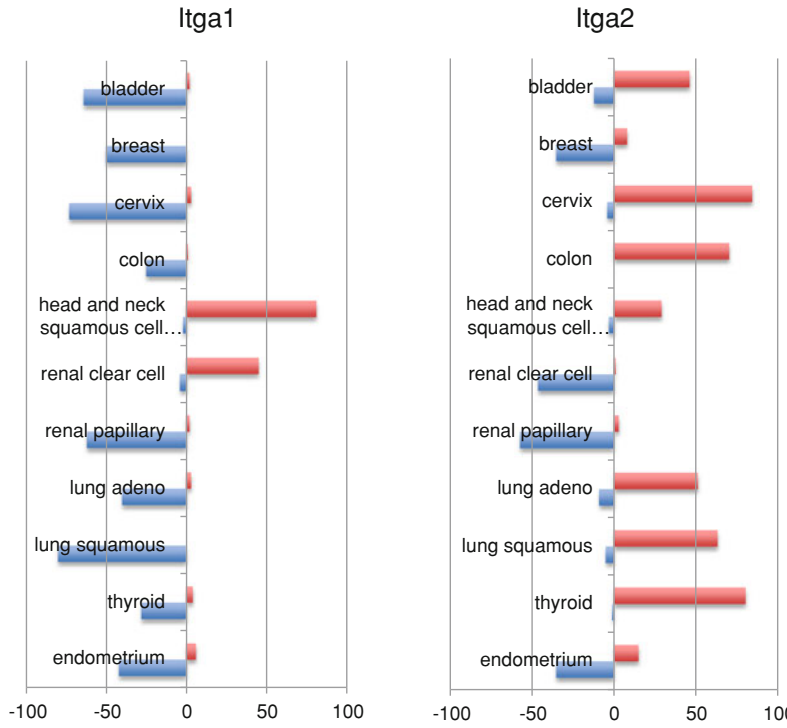

Fig. 2.1 Expression of Integrins alpha1 and 2 in different tumor types. Ratio of RNAseq counts for the gene in tumor versus matched normal was determined. Data taken from TCGA where total evaluable number of samples for the tumor type exceeded 100. Numbers of samples where the ratio of expression exceeded 2 were quantitated. *Red bars* indicate the proportion of cases where tumor expression is twofold or more greater than matched normal, and *blue bars* where tumor expression is twofold or more lower than matched normal. With the exception of renal tumors, Itga2 tended to be increased in expression in tumors in comparison to normal tissue. With the marked exception of clear cell carcinoma of the kidney and head and neck squamous cell carcinoma, Itga1 tended to be downregulated in tumors versus normal tissue

expressed in cartilage, galectins 1, 3 and 8, and the NC1 domain of collagen IV(1), which will be discussed in the context of endothelial regulation. Lastly, semaphorin 7A expressed on macrophages appears to be a counterreceptor to α1β1 [141]. Ligands are listed in Table 2.1.

2.5.1 Collagens

α1 and α2 β1 integrins have collagen binding preferences that are at first glance discordant with their tissue distributions. α1β1, predominantly expressed on connective tissue, has a higher affinity for collagen type IV than for type I; whereas α2β1, predominantly on epithelial cells, favors collagen I, which epithelial cells do not normally see, over the collagen IV abundant in epithelial basement membranes. α1 and α2 (and probably α10 and α11) bind the triple helical domains of the collagens with highest affinity, and biochemical, cell biological and crystallographic studies show that this binding is contributed to by more than one chain of the triple helix [39, 42]. As such, the binding is dependent on the chains being in register, and would thus be exquisitely sensitive to melting. As collagen melting occur at or below physiological temperatures in a very dynamic fashion [81], it is likely that α1 ligand binding, and hence signaling, can be affected by events distal to the receptor along the collagen fibril. This might be especially important in tissue remodeling.

The α1 I domain can bind the collagen triple helix at multiple different sites [117, 153], with the relative affinities being divisible into several

Table 2.1 Known ligands of Integrin $\alpha1\beta1$

Ligand	Likely cellular context	References
Collagen I	Fibroblasts	[39]
Collagen IV	Fibroblasts, myoepithelium	[39]
Collagen IX	Cartilage	[76]
Collagen XVI	Connetctive tissue	[40]
Arresten (Col4A1 NC1 domain)	Angiogenesis	[25]
Laminin 111	Neural tissue	[143]
Laminin 112	Neural tissue	[143]
Matrilin I	Cartilage	[91]
Galectin 8	T cells	[31]
Galectins 1, 3	Vascular smooth muscle	[98]
Jararhagin	Snake venom	[104]
Obtustatin	Snake venom	[92]
Ross River Virus	Viral infection	[82]
Semaphorin 7A	T cell macrophage interactions	[141]

classes. Among these there are approximately three of the highest binding affinity, with Kds of ~0.25 uM, and about 13 in the next affinity class, with Kds of ~14 uM. The highest binding class regions are adjacent to or overlap with the sites occupied by α2 I domain, and these can be competed off both α1 and α2 I domains by triple helical model molecules containing the core sequence GLOGER or GFOGER, the latter of which was also independently identified as an inhibitor of α1 and α2 binding to collagen I [72] as well as α11 [158]. This core peptide is not effective in blocking α1 binding to collagen IV, but is effective in blocking α2. Recently the peptide GFPGEN was identified as a sequence selective for binding α1 over α2 [130]. The collagen IV binding site for α1 is unique and of higher affinity [17], and has been shown by to require Asp 461 in the α1 chain of collagen IV and Arg 461 in the α2 chain [39]. The binding of integrin α1, α2 and α10 I domains to other collagens has also been explored [103, 147]. More recently α1 has been clearly identified as a receptor for the FACIT collagens IX (predominantly in cartilage) [76] and XVI (predominantly in connective tissue) [40], in a region close to that bound by α2. Mutation of Arg 218 to Asp in α1 causes loss of collagen IV and IX binding, but only partial reduction in collagen I binding [76]. Structural analysis based on modeling from the α2 subunit demonstrates the existence of closed and open states alternately blocking or enabling binding of RKKH type peptides. The two states are energetically very similar, allowing for the possibility of control by inside-out signaling [104]. Another mutation in α1, Glu 317 to Ala, causes increased affinity of the I domain for both collagens and laminin [146], and reveals the possibility that the activated integrin, and ligand bound open integrin, may be slightly different states [77]. Dramatically, this I domain mutation Glu 317 to Ala also causes increased activation of ERK, and enhanced downregulation of collagen synthesis [132], further affirming outside–in signaling and attributing it to the integrin itself. The relationship between the probable affinity modulation of α1, the multiplicity of sites on the collagen fibril along which α1 can bind, and the dynamic instability of the triple helix, suggest a highly dynamic interaction between integrin and collagen. For example, one could see how fibroblast motility along collagen I might be contributed to by detachment and reattachment of the integrin along the fibril. Another possibility is that collagen fibril assembly and extrusion from the fibroblast might be aided by $\alpha1\beta1$ protruding from the plasmamembrane

surrounding the fibril. Indeed, the α1 null mouse has narrower and less well formed collagen fibrils than the wild type animal (Gardner, unpublished). However, the relative importance of α1 binding to collagen I versus the basement membrane and facit collagens in vivo has not been established.

2.5.2 Laminins

Laminin 111 and 211 binding by α1 is seen in fibroblasts, and is particularly evident on neural cells, for which the pheochromocytoma line PC12 is used as a prototype [143, 159]. These cells show α1 dependent adhesion to domain VI of the laminin α chains 1 and 2, at sites adjacent to or congruent with α2, at the opposite end of the laminin molecule from the binding regions of the epithelial laminin receptor α3β1 and the hemidesmosome integrin α6β4 [24]. This seems reasonable in the context of an epithelial basement membrane, where epithelial cells would bind at one end of the molecule and mesenchymal cells at the other (although binding to laminin 332 by α1 is not seen). In vitro, α1 has been [13] found to be important for neurite outgrowth on laminin [145] and neural crest cell attachment to collagen [108]. Neural crest cell attachment to laminin can be inhibited by antisense oligonucleotides to α1 mRNA [78]. Further studies have shown that neural crest cells migrating on laminin 111 interact, via α1, with two distinct sites on the molecule. LN E8—α1 interaction drives FAK activation, focal adhesion formation, and migration, while LN E1—α1 interaction drives ERK activation and survival [35]. While it is tempting to suggest that this specificity is attributable to subtleties of outside in signaling, the work does not rule out the possibility of some essential coreceptor for one or other interaction. The α1 null mouse, however, has normal pigmentation on all genetic backgrounds and appears neurologically and neuroanatomically normal except for a sensitivity to ketamine/xylazine anesthesia (Davidson J, unpublished observations) which may have a neurological basis. Whether α2, possibly co-expressed on neurons, provides an adequate alternative for neurite outgrowth, will be seen in the α1/α2 double null animal.

2.5.3 Matrilin and Galectin

Matrilin-1 is found in cartilage, and appears to cause increased chondrocyte adhesion to collagen II, via its association with α1 [91]. Galectin 8 [31] binds several integrins including α1 but not α2, and induces Erk phosphorylation independently of cell attachment. Galectins 1 and 3, secreted by vascular smooth muscle, also appear to bind integrin α1, the latter in a lactose dependent manner [98]. These glycoproteins, in contrast to matrilin-1, appear to inhibit cell attachment to other matrix components.

2.5.4 Semaphorin 7A

The semaphorins are best known as guidance molecules in the CNS. Interestingly, Sema7A, a subset of semaphorins primarily found in the immune system, appears also to be a component of the immunological synapse in some activated T cells [141], where it interacts specifically with macrophages expressing integrin α1β1, inducing downstream effects of α1 activation. Similarly to α1 null mice, sema7A null animals are resistant to encephalitis and DTH models. α1β1 is widely expressed in the CNS. Whether it interacts with other semaphorins is to be seen.

2.6 Peptide Inhibitors of α1

While Jararhagin, a venom protein first noted to bind the alpha2 I domain, also binds the α1 I domain [104], Marcinkiewicz and colleagues also identified Obtustatin [92] as a specific inhibitor of α1 which does not bind to the I domain. Using blockade of FGF2 driven angiogenesis in the chick CAM model as an assay, they pinned down a specific inhibitory peptide

with affinities in the millimolar range, with sequence CWKTSLTSHYC. No further work has been published on this interesting molecule.

2.7 Co-receptors of α1

Many non-I domain containing integrins have been shown to associate in the membrane with other receptors, the best examples being the tetraspanins [8] and Integrin Associated Protein [15]. These may modulate integrin behavior and binding to ligands. α1 has not been shown to associate with such proteins, but this is an area meriting further exploration. On the other hand, α1 is one of a subset of integrins (including α5β1, αvβ3, and α6β4) which associate in the membrane with caveolin and stimulate the Erk pathway via Fyn and Shc [150, 151].

2.8 Integrin α1 Regulation by Cytokines

Most studies of regulation of α1 expression in the adult relate to expression during lymphocyte ontogeny, and in fibroblasts in response to a variety of cytokines. Like integrins α2, α3, α4, and α5β1, α1β1 is upregulated in fibroblast lineages by TGF-β [56], as well as interleukin-1β [123], TNF-α, and interferon gamma [47]. The only cytokine which appears to cause differential regulation of α1 is platelet derived growth factor—BB, which causes downregulation of α1 integrin and upregulation of α5 integrin in fibroblasts [47] and mesangial cells [68].

2.9 The α1 Null Mouse

Aspects of the α1 null mouse will be discussed in subsequent sections. A brief overview is provided here to provide perspective on the known and suspected roles of α1. α1 null mice are viable and fertile, and embryogenesis proceeds normally despite the broad and dynamic expression in trophoblast and developing nervous system. Initially, adult animals are remarkably normal with a mild decrease in weight, normal smooth muscle function, normal rates of wound healing, normal liver function, normal behavior, and no blatant immunodeficiency in a laboratory environment [48]. With ageing, the animals exhibit a series of progressive phenotypes, notably osteoarthritis [156], and retinal degeneration [107], as well as a variety of other vulnerabilities.

2.10 Integrin α1, Signaling, and the Cell Cycle

The potential role of α1 as a cell cycle regulator was suggested by studies showing that α1β1 was a member of a small group of integrins which could activate the adaptor protein Shc, resulting ultimately in MAP kinase activation [150]. Several observations from the α1 null mouse confirmed this, including a reduction in fibroblast proliferation rate in embryonic skin and dermal fibroblast number in the adult, as well as the observations that embryonic fibroblasts from the α1 null failed to activate Shc in response to adhesion to collagen, and that they failed to grow on collagen in conditions of limiting serum whereas growth on the α5 ligand fibronectin or the αv ligand fibrinogen, was normal [109]. As α2 and probably α11 are present on these cells, this suggests that α1 is unique among collagen binding integrins in mesenchyme in being able to stimulate proliferation. Fracture calluses are smaller in α1 null mice, concomitant with a deficiency in bone marrow derived mesenchymal stem cell proliferation [41]. Interestingly, the number and proliferation of mesenchymal stem cell derived hypertrophic chondrocytes in this model is normal—suggesting a specific and transient dependence on α1 for proliferation in the mesenchymal stem cell differentiation pathway. Indeed, α1 has been identified as a very effective tool for the isolation of mesenchymal stem cells [36], and more recently for the selection of the most proliferative subclones of mesenchymal stem cells with the highest multidifferentiation potential [120]. A role for α1 has also been described in osteoblast differentiation [66]. Similar phases of α1 dependence for

proliferation appear to be present at some stages of lymphocyte ontogeny [95]. Furthermore, tumor cells derived from Kras transgenic mice are less proliferative on an α1 null background [90]. Overall, the subtlety of the proliferative deficit in the α1 null mouse must be accounted for by the large number of overlapping proliferative pathways, ligands, and integrins present in the organism.

The α1 cytoplasmic domain is very short. It is required for α1β1 migration into focal adhesions [12], and has a role in binding cytoskeletal components [87, p. 125] FAK, and phospholipase C gamma [149]. A remarkable study by Abair et al. [1], taking advantage of α1 null endothelial cells, demonstrated very specific requirements of components of the tail for full activity. The lysine triplet is required for migration and adhesion, and for activation of the Akt and p38 pathways, but not for Erk activation. Furthermore, alanine scanning shows that the most membrane proximal lysine is required for endothelial tubulogenesis, and migration on collagen IV, and that Lys 1151 is required for all functions except for proliferation. It appears that the integrin α1 cytoplasmic tail is quite unique among the integrins in being able to bind and activate the small nuclear shuttling phosphatase TCPTP. This phosphatase has many targets, but in the context of collagen ligand binding, TCPTP acts to cause a reduction in EGFR signaling [93], either by dephosphorylating EGFR directly or by reducing the amount of phosphorylated caveolin available to activate EGFR [11]. Whatever the mechanisms, the implication that active ligand binding, which in general would cause Erk activation, can serve to dampen an alternative pro-mitotic signaling pathway is intriguing. The specificity to α1 is also intriguing. While the genomic region containing α1 is lost in some tumors, and thus α1 might be regarded as a candidate tumor suppressor [93], the molecule is not expressed in most epithelial tissues. One physiological site where α1 might usefully downregulate EGFR activity is in myoepithelial cells of the breast, where cells express α1 [74], as well as EGFR [100], and are juxtaposed to basement membrane.

2.11 Integrin α1, Fibroblasts, and Collagen and Collagenase Regulation

Many studies have shown that α1β1 is a negative feedback regulator of collagen synthesis by fibroblasts. These were initiated by Langholtz et al., who showed that an activating antibody to α1 accentuated the normal downregulation of collagen synthesis seen when fibroblasts are suspended in collagen gels [79]. It was also noted that α1 levels appeared to be reduced on scleroderma fibroblasts, in conjunction with their upregulation of collagen synthesis [64]. Data from the α1 null mouse lent strong support to this role: in vivo the mice show a 20 % increase in the rate of collagen incorporation into the skin, and fibroblasts from these animals are deficient in downregulating synthesis in response to gel suspension [49]. We subsequently examined keloids to determine whether loss of α1 could account for the increased collagen expression in these lesions [142]. A high proportion of lesional fibroblasts expressed α1 (in contrast to scleroderma lesions), although the levels expressed were somewhat lower than seen in chronic wounds with low collagen production. Thus, absence of α1 could not account for the excess collagen production in keloids, but there may be a relative deficiency compared to normal wounds, which show distinct peaks in α1 expression at 8 and 30 days [9].

The mechanism for downregulation of collagen synthesis mediated by α1 has been extensively dissected. α1β1 stimulation by ligand activates the MAP kinases Erk1 and 2 via Fyn and Shc [109, 150], and Erk1/2 activation reduces collagen synthesis [116]. Reciprocally, the Erk1/2 inhibitor PD98059 causes upregulation of fibroblast collagen synthesis [1]. This is the reverse of the effect of α2β1 stimulation, which activates p38 and causes induction of collagen synthesis [65]. Thus, in general, α1β1 and α2β1 are opponents in their effect on collagen synthesis, the former inhibitory and the latter activatory. More specific mechanisms of collagen regulation involving reactive oxygen

species in mesangial cells will be discussed in the kidney chapter.

The regulation of metalloproteases has similar themes but appears more complex and is probably very cell type specific. Firstly, the structure and function of the mouse and human collagenases is not congruent: MMP1, which is the major fibroblast collagenase in humans, is upregulated by Erk1/2 activation, but the mouse MMP1 structural equivalents, McolA and McolB, are not seen in skin fibroblasts, and have a restricted expression in the placenta and uterus [3]. On the other hand human MMP13, found in chronic ulcers [148], is downregulated by Erk1/2 activation as well as being upregulated by p38 activation [115], and MMP13 is the major fibroblast collagenase in mouse [83]. Although functionally equivalent to human MMP1, mouse MMP13 appears to be regulated like human MMP13, as it is markedly upregulated in α1 null mice where there is loss of Erk1/2 signaling but normal α2-p38 signaling. The α1 null animal shows an increase in expression of several other MMPs, including 7, 9 and 2 in endothelial cells, and 9 and 2 in fibroblasts [49, 111]. For want of other evidence, this may be attributed to reduced Erk1/2 activation. However, whereas α1 stimulation is always inhibitory to collagen synthesis, it is sometimes activatory to MMP synthesis. In some systems α1 activation by laminin [84] or by collagen IV (Pozzi and Gardner, unpublished) or collagen I [121] causes an increase in MMP synthesis.

In many studies of fibroblast collagen interaction, the complex process of collagen gel contraction is addressed. In dermal fibroblasts integrin $\alpha 2\beta 1$ is seen to be the dominant player in this process [79], which can be uncoupled from MMP synthesis [14], and is dependent on a functional cytoskeleton. However, in studies of specialized cardiac fibroblasts [19], smooth muscle cells [53], stellate cells [113] and mesangial cells [69], α1 blockade has been shown to prevent gel contraction, as has integrin $\alpha v\beta 3$ blockade in other cell types [27]. It is possible that whereas α2 is structurally more suited to gel contraction (having a far higher affinity for collagen I), α1 expression may be required for maintenance of the contractile myofibroblastoid phenotype. It is striking that α1 expression is upregulated in vivo in all activated contractile myofibroblastoid cells including myofibroblasts in wound repair, mesangial cells, pericytes, myoepithelial cells [74], and hepatic stellate cells.

In summary, there may be several roles for α1 and its interplay with α2 in the fibroblast during dermal wound healing and other episodes of mesenchymal repair. α1 upregulation in fibroblasts contributes to collagen stimulated cell proliferation, and probably to the myofibroblast transition. α2 is the major contributor to the synthetic phenotype, where it contributes the major part of collagen matrix contraction and activates collagen synthesis, as well as activating MMP synthesis for matrix remodeling. α1 fine tunes the MMP response, possibly providing general inhibition of MMP release, but allowing for specific activation near the epidermal boundary where there is a greater abundance of the α1 high affinity ligand, collagen IV. α1 also provides feedback inhibition against excessive collagen synthesis. Consistent with these suggestions, the α1 null shows excessive collagen and collagenase synthesis at overlapping phases of wound healing [49], and collagen fibrils are densely aggregated and irregular in the dermis of the α1 null, while being individually smaller (Gardner, unpublished observations). Some aspects of this paradigm appear to be different in mesangial cells, which are discussed in the kidney chapter.

2.12 Integrin α1 and Angiogenesis

Immunohistochemical analysis of murine and human tissue shows that α1 is present on at least some normal microvascular endothelium. α1 has also been shown to be upregulated on endothelia in MS lesions [135]. New tumor microvessels appear always to express α1, while a smaller proportion of them, predominantly the slightly larger ones, also express α2 [111]. Vascular endothelial growth factor (VEGF/VPF) can induce α1 on endothelial cells, and as the only

collagen receptors expressed, α1 and α2 are required for endothelial haptotaxis through collagen. Antibodies to α1 and α2 reduce angiogenesis in response to subcutaneously implanted gels of fibrin or collagen containing VEGF, or to tumor xenografts [128, 129]. However, tumor matrix contains a great variety of alternative integrin ligands. As we have learned from fibroblasts, α1β1 can activate an Erk1/2 proliferation pathway mediated by Shc. α2β1 can also positively regulate the progression through the cell cycle in epithelial cells by non overlapping mechanisms [71]. Thus, α1 and α2 blockade in vivo may cause a simple reduction in endothelial proliferation. With this in mind, there is no deficiency in normal vasculo- and angiogenesis in α1 null mice. Analysis of the null mice, however, reveals other, subtler roles for α1 in angiogenesis.

Detailed analysis of endothelial cells and tumor vasculature in α1 null animals [111] led to independent verification of the significance of plasminogen fragments, the angiostatins [105], in endothelial growth regulation. Pulmonary microvascular endothelial cells from α1 null mice grew poorly compared to wild type, regardless of the substratum on which they were grown. This growth deficiency could be completely rescued by frequent media change even if the cells were grown on collagen. Furthermore, media conditioned by α1 null endothelial cells was inhibitory to the growth of wild type cells. The growth deficiency in α1 null endothelial cells was also corrected by antibodies to angiostatin, or growth in media containing serum from plasminogen null mice (from which no angiostatin could be generated) instead of fetal calf serum. Lastly, the growth deficiency could be rescued by MMP9 blockade. Analysis of conditioned medium from α1 null endothelial cells as well as plasma from wounded (but not unwounded) or tumor bearing α1 null mice showed an increase in MMP9 and angiostatin compared to wild type animals. These findings in endothelial cells were consistent with the increased MMP expression seen in α1 null fibroblasts, due to loss of α1-Erk1/2 inhibitory signaling with normal α2-p38 activatory signaling. Thus, increased MMP9 released by the α1 null cells cleaves plasminogen [106] to yield the endothelial inhibitor, angiostatin.

In vivo, α1 null mice, with higher plasma MMP9 and angiostatin levels are less able to vascularize subcutaneous tumors than wild type, but this deficit can be reversed by oral treatment of the animals with the MMP9 inhibitor doxycycline, and consequent reduction of their angiostatin levels [110]. MMP9 levels in the vasculature correlate inversely with tumor vascularization even in wild type mice. These studies have been repeated in several tumor systems with essentially similar results, namely that tumors in the α1 null host are smaller and less vascular and the phenotype can be reversed by MMP inhibition [22, 23]. These studies showed that the interplay between α1 and α2 integrins has significant consequences in the vascular system. Thus, during vascular remodeling, upregulation of endothelial α1 and α2 occurs, and the balance between them regulates MMP release, and ultimately vessel number.

While plasminogen is an MMP9 target, and its cleavage product angiostatin was entirely responsible for endothelial growth inhibition in vitro, other MMP targets might be of importance in this feedback system in vivo. These include the collagens themselves. In this regard the finding that a collagen NC1 domain is a ligand for α1 may be of significance. The NC1 domain of collagen IV α3, also known as tumstatin, causes endothelial cytostasis and blocks angiogenesis by binding to integrin αvβ3, and a similar mechanism appears to exist for α1 binding to the collagen IV(1) NC1 domain (arresten) [25]. This might be an explanation for the presence of α1 on the luminal surface of endothelium, where it could act as a detector of collagen fragments released during remodeling, and provide negative feedback to angiogenesis. While in general α1 binding to collagen in fibroblasts causes activation of Erk1/2 via Shc, arresten may provide a growth inhibitory signal. In fact this has been strongly suggested by the work of Nyberg et al. where the arresten—α1 interaction appears to mediate an apoptotic response [102], and this interaction has been invoked in the blockade of

growth of HSC tongue carcinoma cells [2]. The absence of both signals—collagen IV driving growth and arresten being pro-apoptotic—in the α1 null could explain why normal angiogenesis is unaltered in α1 null mice.

2.13 Smooth Muscle and α1

α1 is extremely abundant on smooth muscle, both visceral and vascular [6], and, in vivo, expresses no other collagen binding integrin (explanted smooth muscle rapidly upregulates α2, complicating studies [134]). Furthermore, smooth muscle basal lamina has abundant collagen IV. There is no upregulation of α2 or α10 in the α1 null smooth muscle in vivo, as assessed by immunostaining [48]. Yet in the α1 null mouse digestion and parturition is entirely normal, and EM studies reveal no alterations in smooth muscle structure. Studies of mesenteric arteries have shown that α1 deficient vessels rupture at lower stresses than wild type, due to a deficiency in the hypertrophic response [88]. Integrin α8β1, a fibronectin receptor, is also abundant in smooth muscle, but the double knockout α1/α8 animal also had histologically normal smooth muscle (Gardner and Brandenburger, unpublished). Further collagen binding integrin double knockouts may reveal the answer to this mystery.

2.14 Integrin α1 and the Retina and CNS

Retinal pigment epithelium (REPE) cells have been shown to use α1 as one among other receptors for collagen gel contraction [99] but α1 signaling of MAP kinase activation is clearly of unique importance. Peng et al. [107] found that older α1 null mice become blind, with loss of retinal evoked potentials, degeneration of the peripheral retina, irregularities in basal lamina thickness, rod degeneration and synaptic malformation in rod and cone terminals, and failure of transducin α translocation to the outer rod segments upon light exposure.

Frasca et al. [45] have made observations on the role of α1 in contributing to the neurotoxicity of amyloid. This appears to be due to α1-ligand interaction, via Erk activation, being permissive to neuronal entry into the cell cycle after their stimulation by A-beta. Neurons, in contrast to other cell types, appear to meet their demise after cell cycle entry.

2.15 Integrin α1 as a Viral Receptor

Many integrins have been recognized as receptors for viruses. α1 appears to be one of several receptors for Ross River virus, a semliki forest type alphavirus one of whose coat proteins has a region which appears to mimic a collagen fold [82]. There is a possibility that α1 is also a receptor for rotavirus enterotoxin [131].

2.16 Integrin α1 and the Kidney

Expression of α1 by glomerular mesangial cells [30, 60] as well as the developing kidney [73] led to a great deal of interest in the role of this integrin in the kidney. α1 null mice showed no functional or anatomic renal abnormality alterations in α1 null glomeruli in the unperturbed state, but a variety of challenges have exploited the underlying mesangial alterations to create new models of renal disease. Ex vivo studies demonstrate alterations in mesangial homeostasis in the absence of α1, notably an alteration in MMP profile rather different from that seen in cutaneous α1 null fibroblasts [155]. α1 nulls also have poor osmolarity regulation [97]. Streptozocin treated α1 nulls get worse glomerular disease than wild type [157], and the diabetic Akita mouse gets dramatically accelerated renal dysfunction when crossed into an α1 null background [154].

Cross of the α1 null with the collagen IV α3 chain null (COL4A3/Alports) mouse [29] led to unexpected effects. Reduced glomerular basement membrane stiffness in the COL4A3 null leads to a progressive glomerulonephritis with mesangial expansion and secondary tubulointerstitial fibrosis. Surprisingly, the double null

animal lived twice as long as the COL4A3 null, due to a delay in the progression of renal failure. This unexpected result appears to be due to several mechanisms. Firstly, in the normal progression of murine Alports, there is a marked influx of monocytes into the interstitium in response to glomerular epithelial damage. α1 null monocytes are defective in migrating into the renal interstitium, possibly due to the monocyte requirement for α1 to adhere to the collagen XIII generated by endothelium during injury [34], and are therefore reduced in number in the double null kidney. This reduces delivery of TGFβ to the kidney, delaying the onset and progression of interstitial fibrosis [122]. Secondly, mesangial cells are dependent on α1 and Rac to invade the glomerular tuft [155], a key process in the initiation of renal repair and injury. In the α1/COL4A3 double null, the mesangial expansion is greatly reduced [29]. In another glomerulonephritis model, anti-Thy-1 GN in the rat [69], direct injection of anti-α1 in the renal artery caused a marked reduction in mesangial proliferation and matrix accumulation, an important in vivo validation of a series of studies of the role of α1 in mesangial cells [67–70]. The role of α1 in driving proliferation is complex in mesangial cells. In contrast to studies in most systems which ascribe a pro-proliferative role for α1 signaling, overexpression of α1 in mesangial cells leads to activation of p27Kip and cell cycle arrest [70]. In fact mesangial cells appear to be an exception in many aspects of α1 physiology, in that Erk phosphorylation is upregulated in α1 null mesangial cells and p38 is downregulated. Notwithstanding the increased Erk phosphorylation, collagen synthesis is increased, via a reactive oxygen species driven mechanism [21, 28]. This may be due to some kind of integrin crosstalk, where the excess integrin α1 activates a pathway normally associated with another integrin [127]. A potential corollary of this is that monomer and polymer collagen have different effects on mesangial cell growth; on the latter substrate growth is inhibited, α1 is excluded from focal contacts, and ERK1/2 phosphorylation is diminished [126].

2.17 Integrin α1 and the Immune System

Integrin α1 was first discovered as a very late antigen on cultured T cells, and being the largest of the α subunits, was named Very Late Antigen 1 (VLA1), a name which persists in immunological studies. Hemler et al. subsequently showed that VLA1 was present on a large proportion of T cells in the joints of rheumatoid arthritics, but was almost absent from the circulation, giving a first clue to a role for α1 in tissue migration and T cell activation [60, 58]. More detailed study of the immune system revealed that α1 is also expressed on a subset of NK-T cells as well as populations of activated monocytes and NK cells.

α1 deficiency generated by knockout or antibody blockade has dramatic consequences in the immune system. α1 null mice show no overt immunodeficiency, but they show resistance to many different disease models involving monocyte function or peripheral T cell memory. These include a resistance to anti collagen II antibody induced and mycobacterium induced arthritis [44, 62], colitis [43], DTH, contact hypersensitivity [44], and LCMV induced encephalopathy [7]. Inflamed tissues in these models, as well as the normal gut mucosal epithelium [95], show reduced infiltration by T cells and monocytes. Furthermore, cultured splenocytes from α1 null animals show reduced proliferation in response to collagen, and fail to express integrin α2 upon long-term culture.

In murine influenza models, α1 positive T cells tend to be CD4 and associate with basement membranes, while α2 T cells bias to CD4 and an interstitial location. Memory to influenza is maintained by the α1 positive T cells, as they are protected from TNF driven apoptosis [119, 118]. Treg cells are VLA1 negative, and stimulated PBMCs can be diverted from generating VLA1 + T effector cells into Treg cells if TNF signaling is blocked [51]. Taken together, the results suggest that α1 is needed both for lymphocyte migration into the collagen rich periphery, and for the proliferation of activated

T cells in those locations, or for their long term survival as mediators of peripheral T cell memory [38].

In rheumatoid arthritics, α1 positive T cells are far more abundant and tend to be found in the joints as oligoclonal populations, probably responding to a restricted number of joint antigens [4, 52]. Here they offer an obvious target for therapy. Interestingly, α1 has also been noted to be required for monocyte retention at sites of inflammation in skin [5], and a role for the receptor was similarly shown for T cells in a xenotransplantation model of psoriasis, where epidermal, but not dermal, T cells expressed α1 [26].

2.18 Therapeutics

In the early 2000s Biogen Idec developed a humanized function blocking anti-VLA1 antibody for immune diseases. This has now been taken through a phase 1 single dose escalation study by Santarus, as SAN-300, without remarkable side effects, and with anecdotal demonstration of efficacy in a single rheumatoid arthritis RA patient recruited to the study [63]. The potential for this molecule may be very high in diseases characterized by the persistence of localized pathological effector T cell memory, such as RA and psoriasis.

2.19 Summary and Prospects

Integrin α1 has major roles as a modulator of mesenchymal proliferation and differentiation, matrix turnover, and immune function. Its roles in the immune system make it a clear target for therapy. In its biochemical properties, α1 appears to have a unique role in binding basement membrane collagens, the significance of which in vivo is not yet entirely clear. Like the other collagen binding I domain containing integrins, α2, α10 and α11, its absence is not associated with major structural deficits in the mouse, illustrating the dense interweaving of redundant or partially redundant pathways in tissue morphogenesis.

References

1. Abair TD, Bulus N, Borza C, Sundaramoorthy M, Zent R, Pozzi A (2008) Functional analysis of the cytoplasmic domain of the integrin {alpha}1 subunit in endothelial cells. Blood 112:3242–3254
2. Aikio M, Alahuhta I, Nurmenniemi S, Suojanen J, Palovuori R, Teppo S, Sorsa T, López-Otín C, Pihlajaniemi T, Salo T et al (2012) Arresten, a collagen-derived angiogenesis inhibitor, suppresses invasion of squamous cell carcinoma. PLoS ONE 7:e51044
3. Balbin M, Fueyo A, Knauper V, Lopez JM, Alvarez J, Sanchez LM, Quesada V, Bordallo J, Murphy G, Lopez-Otin C (2001) Identification and enzymatic characterization of two diverging murine counterparts of human interstitial collagenase (MMP-1) expressed at sites of embryo implantation. J Biol Chem 276:10253–10262
4. Bank I, Koltakov A, Goldstein I, Chess L (2002) Lymphocytes expressing alpha1beta1 integrin (very late antigen-1) in peripheral blood of patients with arthritis are a subset of CD45RO(+) T-cells primed for rapid adhesion to collagen IV. Clin Immunol 105:247–258
5. Becker HM, Rullo J, Chen M, Ghazarian M, Bak S, Xiao H, Hay JB, Cybulsky MI (2013) α1β1 integrin-mediated adhesion inhibits macrophage exit from a peripheral inflammatory lesion. J Immunol 190:4305–4314
6. Belkin VM, Koteliansky VE, Belkin AM (1990) Human smooth muscle VLA-1 integrin: purification, substrate specificity, localization in aorta, and expression during development. J Cell Biol 111(5 Pt 1):2159–2170
7. Ben-Horin S, Bank I (2004) The role of very late antigen-1 in immune-mediated inflammation. Clin Immunol 113:119–129
8. Berditchevski F, Bazzoni G, Hemler ME (1995) Specific association of CD63 with the VLA-3 and VLA-6 integrins. J Biol Chem 270:17784–17790
9. Van Beurden HE, Snoek PaM, Von den Hoff JW, Torensma R, Kuijpers-Jagtman A-M (2003) Fibroblast subpopulations in intra-oral wound healing. Wound Repair Regen. 11:55–63
10. Bhat KP, Pezzuto JM (2001) Resveratrol exhibits cytostatic and antiestrogenic properties with human endometrial adenocarcinoma (Ishikawa) cells. Cancer Res 61(16):6137–6144
11. Borza CM, Chen X, Mathew S, Mont S, Sanders CR, Zent R, Pozzi A (2010) Integrin {alpha}1{beta}1 promotes caveolin-1 dephosphorylation by activating T cell protein-tyrosine phosphatase. J Biol Chem 285:40114–40124
12. Briesewitz R, Kern A, Marcantonio EE (1993) Ligand-dependent and -independent integrin focal contact localization: the role of the alpha chain cytoplasmic domain. Mol Biol Cell 4:593–604

13. Briesewitz R Marcantonio EE, Epstein MR (1993) Expression of native and truncated forms of the human integrin alpha 1 subunit. J Biol Chem 268(4):2989–2996
14. Broberg A, Heino J (1996) Integrin alpha2beta1-dependent contraction of floating collagen gels and induction of collagenase are inhibited by tyrosine kinase inhibitors. Exp Cell Res 228:29–35
15. Brown E, Hooper L, Ho T, Gresham H (1990) Integrin-associated protein: a 50-kD plasma membrane antigen physically and functionally associated with integrins. J Cell Biol 111:2785–2794
16. Burggraf D, Trinkl A, Burk J, Martens HK, Dichgans M, Hamann GF (2008) Vascular integrin immunoreactivity is selectively lost on capillaries during rat focal cerebral ischemia and reperfusion. Brain Res 1189:189–197
17. Calderwood DA, Eble J, Kuhn K, Humphries MJ, Tuckwell DS (1997) The integrin alpha1 A-domain is a ligand binding site for collagens and laminin. J Biol Chem 272(19):12311–12317
18. Camper L, Hellman U, Lundgren-Akerlund E (1998) Isolation, cloning, and sequence analysis of the integrin subunit alpha10, a beta1-associated collagen binding integrin expressed on chondrocytes. J Biol Chem 273:20383–20389
19. Carver W, Reaves TA, Borg TK, Terracio L, Molano I (1995) Role of the alpha 1 beta 1 integrin complex in collagen gel contraction in vitro by fibroblasts. J Cell Physiol 165(2):425–437
20. Cheli Y, Kanaji S, Jacquelin B, Chang M, Nugent DJ, Kunicki TJ (2007) Transcriptional and epigenetic regulation of the integrin collagen receptor locus ITGA1-PELO-ITGA2. Biochim Biophys Acta 1769:546–558
21. Chen X, Abair TD, Ibanez MR, Su Y, Frey MR, Dise RS, Polk DB, Singh AB, Harris RC, Zent R et al (2007) Integrin alpha1beta1 controls reactive oxygen species synthesis by negatively regulating epidermal growth factor receptor-mediated Rac activation. Mol Cell Biol 27:3313–3326
22. Chen X, Su Y, Fingleton B, Acuff H, Matrisian LM, Zent R, Pozzi A (2005) An orthotopic model of lung cancer to analyze primary and metastatic NSCLC growth in integrin alpha1-null mice. Clin Exp Metastasis 22:185–193
23. Chen X, Su Y, Fingleton B, Acuff H, Matrisian LM, Zent R, Pozzi A (2005) Increased plasma MMP9 in integrin alpha1-null mice enhances lung metastasis of colon carcinoma cells. Int J Cancer 116:52–61
24. Colognato-Pyke H, Yamada Y, Carbonetto S, Cheng YS, Yurchenco PD, O'Rear JJ (1995) Mapping of network-forming, heparin-binding, and alpha 1 beta 1 integrin-recognition sites within the alpha-chain short arm of laminin-1. J Biol Chem 270(16):9398–9406
25. Colorado PC, Torre A, Kamphaus G, Maeshima Y, Hopfer H, Takahashi K, Volk R, Zamborsky ED, Herman S, Sarkar PK et al (2000) Anti-angiogenic cues from vascular basement membrane collagen. Cancer Res 60:2520–2526
26. Conrad C, Boyman O, Tonel G, Tun-Kyi A, Laggner U, de Fougerolles A, Kotelianski V, Gardner H, Nestle FO (2007) Alpha1beta1 integrin is crucial for accumulation of epidermal T cells and the development of psoriasis. Nat Med 13:836–842
27. Cooke ME, Sakai T, Mosher DF (2000) Contraction of collagen matrices mediated by alpha2beta1A and alpha(v)beta3 integrins. J Cell Sci 113:2375–2383
28. Cosgrove D, Meehan DT, Delimont D, Pozzi A, Chen X, Rodgers KD, Tempero RM, Zallocchi M, Rao VH (2008) Integrin alpha1beta1 regulates matrix metalloproteinases via P38 mitogen-activated protein kinase in mesangial cells: implications for Alport syndrome. Am J Pathol 172:761–773
29. Cosgrove D, Meehan D, Miller C, Bovard K, Gilroy A, Gardner H, Kotelianski V, Gotwals P, Amatucci A, Kalluri R, Rodgers K (2000) Integrin alpha1beta1 and transforming growth factor-beta1 play distinct roles in alport glomerular pathogenesis and serve as dual targets for metabolic therapy. Am J Pathol 157(5):1649–1659
30. Cosio FG, Nahman NS Jr, Sedmak DD (1990) Cellular receptors for matrix proteins in normal human kidney and human mesangial cells. Kidney Int 38(5):886–895
31. Cárcamo C, Pardo E, Oyanadel C, Bravo-Zehnder M, Bull P, Cáceres M, Martínez J, Massardo L, Jacobelli S, González A et al (2006) Galectin-8 binds specific beta1 integrins and induces polarized spreading highlighted by asymmetric lamellipodia in Jurkat T cells. Exp Cell Res 312:374–386
32. Damsky CH, Lim KH, Fitzgerald ML, McMaster MT, Janatpour M, Zhou Y, Logan SK, Fisher SJ, Librach C (1994) Integrin switching regulates normal trophoblast invasion. Development 120(12):3657–3666
33. Defilippi P, Bertolotto A, Rossino P, Silengo L, Tarone G, van Hinsbergh V (1991) Differential distribution and modulation of expression of alpha 1/beta 1 integrin on human endothelial cells 1. J Cell Biol 114(4):855–863
34. Dennis J, Meehan DT, Delimont D, Zallocchi M, Ga Perry, O'Brien S, Tu H, Pihlajaniemi T, Cosgrove D (2010) Collagen XIII induced in vascular endothelium mediates alpha1beta1 integrin-dependent transmigration of monocytes in renal fibrosis. Am J Pathol 177:2527–2540
35. Desban N, Lissitzky JC, Rousselle P, Duband JL (2006) alpha1beta1-integrin engagement to distinct laminin-1 domains orchestrates spreading, migration and survival of neural crest cells through independent signaling pathways. J Cell Sci 119:3206–3218
36. Deschaseaux F, Charbord P (2000) Human marrow stromal precursors are alpha 1 integrin subunit-positive. J Cell Physiol 184(3):319–325

37. Duband JL, Belkin AM, Syfrig J, Thiery JP, Koteliansky VE (1992) Expression of alpha 1 integrin, a laminin-collagen receptor, during myogenesis and neurogenesis in the avian embryo. Development 116:585–600
38. Dustin ML, de Fougerolles AR (2001) Reprogramming T cells: the role of extracellular matrix in coordination of T cell activation and migration. Curr Opin Immunol 13:286–290
39. Eble JA, Golbik R, Mann K, Kuhn K (1993) The alpha 1 beta 1 integrin recognition site of the basement membrane collagen molecule [alpha 1(IV)]2 alpha 2(IV). Embo J 12:4795–4802
40. Eble JA, Kassner A, Niland S, Morgelin M, Grifka J, Grassel S (2006) Collagen XVI harbors an integrin alpha1 beta1 recognition site in its C-terminal domains. J Biol Chem 281:25745–25756
41. Ekholm E, Hankenson KD, Uusitalo H, Hiltunen A, Gardner H, Heino J, Penttinen R (2002) Diminished callus size and cartilage synthesis in alpha 1 beta 1 integrin-deficient mice during bone fracture healing. Am J Pathol 160:1779–1785
42. Emsley J, King SL, Bergelson JM, Liddington RC (1997) Crystal structure of the I domain from integrin alpha2beta1. J Biol Chem 272:28512–28517
43. Fiorucci S, Mencarelli A, Palazzetti B, Sprague AG, Distrutti E, Morelli A, Novobrantseva TI, Cirino G, Koteliansky VE, de Fougerolles AR (2002) Importance of innate immunity and collagen binding integrin alpha1beta1 in TNBS-induced colitis. Immunity 17:769–780
44. De Fougerolles AR, Nickerson-Nutter CL, Chi-Rosso G, Rennert PD, Gardner H, Gotwals PJ, Lobb RR, Koteliansky VE, S.A G (2000) Regulation of inflammation by collagen-binding integrins alpha 1beta1 and alpha2beta1 in models of hypersensitivity and arthritis. J Clin Invest 105(6):721–729
45. Frasca G, Carbonaro V, Merlo S, Copani A, Sortino MA (2008) Integrins mediate beta-amyloid-induced cell-cycle activation and neuronal death. J Neurosci Res 86:350–355
46. Fukuda K, Saikawa Y, Yagi H, Wada N, Takahashi T, Kitagawa Y (2012) Role of integrin alpha1 subunits in gastric cancer patients with peritoneal dissemination. Mol Med Rep 5:336–340
47. Gailit J, Bueller H, Clark RA, Xu J (1996) Platelet-derived growth factor and inflammatory cytokines have differential effects on the expression of integrins alpha 1 beta 1 and alpha 5 beta 1 by human dermal fibroblasts in vitro. J Cell Physiol 169(2):281–289
48. Gardner H, Koteliansky V, Jaenisch R, Kreidberg J (1996) Deletion of integrin alpha 1 by homologous recombination permits normal murine development but gives rise to a specific deficit in cell adhesion. Dev Biol 175(2):301–313
49. Gardner H, Pozzi A, Laato M, Heino J, Broberg A (1999) Absence of integrin alpha1beta1 in the mouse causes loss of feedback regulation of collagen synthesis in normal and wounded dermis. J Cell Sci 112(Pt 3):263–272
50. Gilhar A, Kalish RS, Berkutski T, Azizi E, Bank I, Ullmann Y (1997) Favourable melanoma prognosis associated with the expression of the tumour necrosis factor receptor and the alpha1beta1 integrin: a preliminary report. Melanoma Res 7(6):486–495
51. Goldstein I, Ben-Horin S, Koltakov A, Chermoshnuk H, Polevoy V, Berkun Y, Amariglio N, Bank I (2007) alpha1beta1 Integrin + and regulatory Foxp3 + T cells constitute two functionally distinct human CD4 + T cell subsets oppositely modulated by TNFalpha blockade. J Immunol 178:201–210
52. Goldstein I, Simon AJ, Ben Horin S, Matzri S, Koltakov A, Langevitz P, Rechavi G, Amariglio N, Bank I (2008) Synovial VLA-1 + T cells display an oligoclonal and partly distinct repertoire in rheumatoid and psoriatic arthritis. Clin Immunol 128:75–84
53. Gotwals PJ, Chi-Rosso G, Lindner V, Yang J, Ling L, Fawell SE, Koteliansky VE (1996) The alpha1beta1 integrin is expressed during neointima formation in rat arteries and mediates collagen matrix reorganization. J Clin Invest 97:2469–2477
54. Gronthos S, Graves SE, Robey PG, S.P J (2001) Integrin-mediated interactions between human bone marrow stromal precursor cells and the extracellular matrix. Bone 28(2):174–181
55. Gullberg D, Turner DC, Borg TK, Terracio L, Rubin K (1990) Different beta 1-integrin collagen receptors on rat hepatocytes and cardiac fibroblasts. Exp Cell Res 190:254–264
56. Heino J, Ignotz RA, Hemler ME, Crouse C, Massagué J (1989) 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(1):380–388
57. Hemler ME, Glass D, Coblyn JS, Jacobson JG (1986) Very late activation antigens on rheumatoid synovial fluid T lymphocytes. Association with stages of T cell activation. J Clin Invest 78:696–702
58. Hemler ME, Jacobson JG, Brenner MB, Mann D, Strominger JL (1985) VLA-1: a T cell surface antigen which defines a novel late stage of human T cell activation. Eur J Immunol 15:502–508
59. Hemler ME, Jacobson JG, Strominger JL (1985) Biochemical characterization of VLA-1 and VLA-2. Cell surface heterodimers on activated T cells. J Biol Chem 260:15246–15252
60. Hemler ME, Sanchez-Madrid F, Flotte TJ, Krensky AM, Burakoff SJ, Bhan AK, Springer TA, Strominger JL (1984) Glycoproteins of 210,000 and 130,000 m.w. on activated T cells: cell distribution and antigenic relation to components on resting cells and T cell lines. J Immunol 132:3011–3018
61. Hertle MD, Adams JC, Watt FM (1991) Integrin expression during human epidermal development in vivo and in vitro. Development 112:193–206

62. Ianaro A, Calignano A, Koteliansky V, Gotwals P, Bucci M, Gerli R, Santucci L, Fiorucci S, Cirino G, Cicala C (2000) Anti-very late antigen-1 monoclonal antibody modulates the development of secondary lesion and T-cell response in experimental arthritis. Lab Invest 80(1):73–80
63. Inderjeeth C, Redfern A, Huang M, Yun H, Grant T, Fritz L, Fuller D (2013) Safety, pharmacokinetics, and pharmacodynamics of SAN-300, a novel monoclonal antibody against very late antigen-1: results of a phase 1 study in healthy volunteers and patients with active rheumatoid arthritis. Arthritis Rheum 65:1439
64. Ivarsson M, McWhirter A, Black CM, Rubin K (1993) Impaired regulation of collagen pro-alpha 1(I) mRNA and change in pattern of collagen-binding integrins on scleroderma fibroblasts. J Invest Dermatol 101:216–221
65. Ivaska J, Reunanen H, Westermarck J, Koivisto L, Kähäri VM, Heino J (1999) Integrin alpha2beta1 mediates isoform-specific activation of p38 and upregulation of collagen gene transcription by a mechanism involving the alpha2 cytoplasmic tail. J Cell Biol 147(2):401–416
66. Jikko A, Chen D, Mendrick DL, Damsky CH, Harris SE (1999) Collagen integrin receptors regulate early osteoblast differentiation induced by BMP-2. J Bone Min. Res 14(7):1075–1083
67. Kagami S, Kondo S, Loster K, Reutter W, Tamaki T, Yoshizumi M, Kuroda Y, Urushihara M (2001) Requirement for tyrosine kinase-ERK1/2 signaling in alpha 1 beta 1 integrin-mediated collagen matrix remodeling by rat mesangial cells. Exp Cell Res 268(2):274–283
68. Kagami S, Loster K, Reutter W, Kuhara T, Yasutomo K, Kuroda Y, Kondo S (1999) Alpha1beta1 integrin-mediated collagen matrix remodeling by rat mesangial cells is differentially regulated by transforming growth factor-beta and platelet-derived growth factor-BB. J Am Soc Nephrol 10(4):779–789
69. Kagami S, Urushihara M, Kondo S, Hayashi T, Yamano H, Loster K, Vossmeyer D, Reutter W, Kuroda Y (2002) Effects of anti-alpha1 integrin subunit antibody on anti-Thy-1 glomerulonephritis. Lab Invest 82:1219–1227
70. Kagami S, Urushihara M, Loster K, Reutter W, Saijo T, Kitamura A, Kobayashi S, Kuroda Y, Kondo S (2000) Overexpression of alpha1beta1 integrin directly affects rat mesangial cell behavior. Kidney Int 58(3):1088–1097
71. Klekotka PA, Santoro SA, Ho A, Dowdy SF, Zutter MM (2001) Mammary epithelial cell-cycle progression via the alpha(2)beta(1) integrin: unique and synergistic roles of the alpha(2) cytoplasmic domain. Am J Pathol 159:983–992
72. Knight CG, Peachey AR, Tuckwell DS, Farndale RW, Barnes MJ, Morton LF (2000) The collagen-binding A-domains of integrins alpha(1)beta(1) and alpha(2)beta(1) recognize the same specific amino acid sequence, GFOGER, in native (triple-helical) collagens. J Biol Chem 275(1):35–40
73. Korhonen M, Ylanne J, Laitinen L, Virtanen I (1990) The alpha 1-alpha 6 subunits of integrins are characteristically expressed in distinct segments of developing and adult human nephron. J Cell Biol 111:1245–1254
74. Koukoulis GK, Virtanen I, Korhonen M, Laitinen L, Quaranta V, Gould VE (1991) Immunohistochemical localization of integrins in the normal, hyperplastic, and neoplastic breast. Correlations with their functions as receptors and cell adhesion molecules. Am J Pathol 139:787–799
75. Koukoulis GK, Virtanen I, Gould VE, Warren WH (1997) Immunolocalization of integrins in the normal lung and in pulmonary carcinomas. Hum Pathol 28(9):1018–1025 (Erratum in: Hum Pathol 1997 28(12):1442)
76. Käpylä J, Jäälinoja J, Tulla M, Ylöstalo J, Nissinen L, Viitasalo T, Vehviläinen P, Marjomäki V, Nykvist P, Säämänen A-M et al (2004) The fibril-associated collagen IX provides a novel mechanism for cell adhesion to cartilaginous matrix. J Biol Chem 279:51677–51687
77. Lahti M, Bligt E, Niskanen H, Parkash V, Brandt AM, Jokinen J, Patrikainen P, Kapyla J, Heino J, Salminen TA (2011) Structure of collagen receptor integrin alpha(1)I domain carrying the activating mutation E317A. J Biol Chem 286:43343–43351
78. Lallier, T., and Bronner-Fraser, M. (1993). Inhibition of neural crest cell attachment by integrin antisense oligonucleotides. *Science (80-.).* **259**, 692–695
79. Langholz O, Mauch C, Kozlowska E, Bank I, Krieg T, Eckes B, Rockel D (1995) Collagen and collagenase gene expression in three-dimensional collagen lattices are differentially regulated by alpha 1 beta 1 and alpha 2 beta 1 integrins. J Cell Biol 131(6 Pt 2):1903–1915
80. Lee HJ, Kim SY, Koh JM, Bok J, Kim KJ, Kim KS, Park MH, Shin HD, Park BL, Kim TH et al (2007) Polymorphisms and haplotypes of integrinalpha1 (ITGA1) are associated with bone mineral density and fracture risk in postmenopausal Koreans. Bone 41:979–986
81. Leikina E, Mertts MV, Kuznetsova N, Leikin S (2002) Type I collagen is thermally unstable at body temperature. Proc Natl Acad Sci USA 99:1314–1318
82. La Linn M, Eble JA, Lubken C, Slade RW, Heino J, Davies J, Suhrbier A (2005) An arthritogenic alphavirus uses the alpha1beta1 integrin collagen receptor. Virology 336:229–239
83. Liu X, Wu H, Byrne M, Jeffrey J, Krane S, Jaenisch R (1995) A targeted mutation at the known collagenase cleavage site in mouse type I collagen impairs tissue remodeling. J Cell Biol 130:227–237
84. Lochter A, Werb Z, Bissell MJ, Navre M (1999) alpha1 and alpha2 integrins mediate invasive activity of mouse mammary carcinoma cells

through regulation of stromelysin-1 expression. Mol Biol Cell 10(2):271–282
85. Loeser RF, Tan L, Goldring MB, Sadiev S (2000) Integrin expression by primary and immortalized human chondrocytes: evidence of a differential role for alpha1beta1 and alpha2beta1 integrins in mediating chondrocyte adhesion to types II and VI collagen. Osteoarthr Cartil 8(2):96–105
86. Loster K, Heidrich C, Hofmann W, Reutter W, Voigt S (1994) Cell-collagen adhesion is inhibited by monoclonal antibody 33.4 against the rat alpha 1-integrin subunit. Exp Cell Res 212(1):155–160
87. Loster K, Hofmann W, Reutter W, Danker K, Vossmeyer D (2001) alpha1 Integrin cytoplasmic domain is involved in focal adhesion formation via association with intracellular proteins. Biochem J 356(Pt 1):233–240
88. Louis H, Kakou A, Regnault V, Labat C, Bressenot A, Gao-Li J, Gardner H, Thornton SN, Challande P, Li Z et al (2007) Role of alpha1beta1-integrin in arterial stiffness and angiotensin-induced arterial wall hypertrophy in mice. Am J Physiol Hear. Circ Physiol 293:H2597–H2604
89. Ma Q, Shimaoka M, Lu C, Jing H, Carman CV, Springer TA (2002) Activation-induced conformational changes in the I domain region of lymphocyte function-associated antigen 1. J Biol Chem 277:10638–10641
90. Macias-Perez I, Borza C, Chen X, Yan X, Ibanez R, Mernaugh G, Matrisian LM, Zent R, Pozzi A (2008) Loss of integrin alpha1beta1 ameliorates Kras-induced lung cancer. Cancer Res 68:6127–6135
91. Makihira S, Ohno S, Kawamoto T, Fujimoto K, Okimura A, Yoshida E, Noshiro M, Hamada T, Kato Y, Yan W (1999) Enhancement of cell adhesion and spreading by a cartilage-specific noncollagenous protein, cartilage matrix protein (CMP/Matrilin-1), via integrin alpha1beta1. J Biol Chem 274(16):11417–11423
92. Marcinkiewicz C, Weinreb PH, Calvete JJ, Kisiel DG, Mousa SA, Tuszynski GP, Lobb RR (2003) Obtustatin: a potent selective inhibitor of α 1 β 1 integrin in vitro and angiogenesis in vivo advances in brief. 2020–2023
93. Mattila E, Pellinen T, Nevo J, Vuoriluoto K, Arjonen A, Ivaska J (2005) Negative regulation of EGFR signalling through integrin-alpha1beta1-mediated activation of protein tyrosine phosphatase TCPTP. Nat Cell Biol 7:78–85
94. Mechtersheimer G, Barth T, Quentmeier A, Moller P (1994) Differential expression of beta 1 integrins in nonneoplastic smooth and striated muscle cells and in tumors derived from these cells. Am J Pathol 144:1172–1182
95. Meharra EJ, Hassett D, Parker C, Havran W, Gardner H, Schon M (2000) Reduced gut intraepithelial lymphocytes in VLA1 null mice. Cell Immunol 201(1):1–5
96. Mendrick DL, duMont SS, Sandstrom DJ, Kelly DM (1995) Glomerular epithelial and mesangial cells differentially modulate the binding specificities of VLA-1 and VLA-2. Lab Invest 72(3):367–375
97. Moeckel GW, Zhang L, Chen X, Rossini M, Zent R, Pozzi A (2006) Role of integrin alpha1beta1 in the regulation of renal medullary osmolyte concentration. Am J Physiol Ren. Physiol 290:F223–F231
98. Moiseeva EP, Baron JH, de Bono DP, Spring EL (1999) Galectin 1 modulates attachment, spreading and migration of cultured vascular smooth muscle cells via interactions with cellular receptors and components of extracellular matrix. J Vasc Res 36(1):47–58
99. Morales SA, Mareninov S, Prasad P, Wadehra M, Braun J, Gordon LK (2007) Collagen gel contraction by ARPE-19 cells is mediated by a FAK-Src dependent pathway. Exp Eye Res 85:790–798
100. Moumen M, Chiche A, Cagnet S, Petit V, Raymond K, Faraldo MM, Deugnier M-A, Glukhova MA (2011) The mammary myoepithelial cell. Int J Dev Biol 55:763–771
101. Nishida W, Mori S, Takahashi M, Ohkawa Y, Tadokoro S, Yoshida K, Hiwada K, Hayashi K, Sobue K, Nakamura M (2002) A triad of serum response factor and the GATA and NK families governs the transcription of smooth and cardiac muscle genes. J Biol Chem 277(9):7308–7317
102. Nyberg P, Xie L, Sugimoto H, Colorado P, Sund M, Holthaus K, Sudhakar A, Salo T, Kalluri R (2008) Characterization of the anti-angiogenic properties of arresten, an alpha1beta1 integrin-dependent collagen-derived tumor suppressor. Exp Cell Res 314:3292–3305
103. Nykvist P, Ivaska J, Kapyla J, Pihlajaniemi T, Heino J, Tu H (2000) Distinct recognition of collagen subtypes by alpha(1)beta(1) and alpha(2)beta(1) integrins. Alpha(1)beta(1) mediates cell adhesion to type XIII collagen. J Biol Chem 275(11):8255–8261
104. Nymalm Y, Puranen JS, Nyholm TKM, Käpylä J, Kidron H, Pentikäinen OT, Airenne TT, Heino J, Slotte JP, Johnson MS et al (2004) Jararhagin-derived RKKH peptides induce structural changes in alpha1I domain of human integrin alpha1beta1. J Biol Chem 279:7962–7970
105. O'Reilly MS, Holmgren L, Shing Y, Chen C, Rosenthal RA, Moses M, Lane WS, Cao Y, Sage EH, Folkman J (1994) Angiostatin: a novel angiogenesis inhibitor that mediates the suppression of metastases by a Lewis lung carcinoma. Cell 79:315–328
106. Patterson BC, Sang QA (1997) Angiostatin-converting enzyme activities of human matrilysin (MMP-7) and gelatinase B/type IV collagenase (MMP-9). J Biol Chem 272:28823–28825

107. Peng YW, Zallocchi M, Meehan DT, Delimont D, Chang B, Hawes N, Wang W, Cosgrove D (2008) Progressive morphological and functional defects in retinas from alpha1 integrin-null mice. Invest Ophthalmol Vis Sci 49:4647–4654
108. Perris R, Syfrig J, Paulsson M, Bronner-Fraser M (1993) Molecular mechanisms of neural crest cell attachment and migration on types I and IV collagen. J Cell Sci 106:1357–1368
109. Pozzi A, Giancotti FG, Gardner HA, Wary KK (1998) Integrin alpha1beta1 mediates a unique collagen-dependent proliferation pathway in vivo. J Cell Biol 142:587–594
110. Pozzi A, LeVine WF, Gardner HA (2002) Low plasma levels of matrix metalloproteinase 9 permit increased tumor angiogenesis. Oncogene 21:272–281
111. Pozzi A, Miles LA, Wagner S, Soloway P, Gardner HA, Moberg PE (2000) Elevated matrix metalloprotease and angiostatin levels in integrin alpha 1 knockout mice cause reduced tumor vascularization. Proc Natl Acad Sci USA 97(5):2202–2207
112. Racine-Samson L, Bissell DM, Rockey DC (1997a) The role of alpha1beta1 integrin in wound contraction. A quantitative analysis of liver myofibroblasts in vivo and in primary culture. J Biol Chem 272:30911–30917
113. Racine-Samson L, Rockey DC, Bissell DM (1997b) The role of alpha1beta1 integrin in wound contraction. A quantitative analysis of liver myofibroblasts in vivo and in primary culture. J Biol Chem 272:30911–30917
114. Ratzinger S, Grassel S, Dowejko A, Reichert TE, Bauer RJ (2011) Induction of type XVI collagen expression facilitates proliferation of oral cancer cells. Matrix Biol 30:118–125
115. Ravanti L, Lopez-Otin C, Kahari VM, Heino J (1999) Induction of collagenase-3 (MMP-13) expression in human skin fibroblasts by three-dimensional collagen is mediated by p38 mitogen-activated protein kinase. J Biol Chem 274(4):2446–2455
116. Reunanen N, Foschi M, Han J, Kahari VM (2000) Activation of extracellular signal-regulated kinase 1/2 inhibits type I collagen expression by human skin fibroblasts. J Biol Chem 275:34634–34639
117. Rich RL, Owens RT, Carson M, Hook A, Moore D, Symersky J, Yang VW, Narayana SV, Hook M, Deivanayagam CC (1999) Trench-shaped binding sites promote multiple classes of interactions between collagen and the adherence receptors, alpha(1)beta(1) integrin and Staphylococcus aureus cna MSCRAMM. J Biol Chem 274(35):24906–24913
118. Richter M, Ray SJ, Chapman TJ, Austin SJ, Rebhahn J, Mosmann TR, Gardner H, Kotelianski V, deFougerolles AR, Topham DJ (2007) Collagen distribution and expression of collagen-binding alpha1beta1 (VLA-1) and alpha2beta1 (VLA-2) integrins on CD4 and CD8 T cells during influenza infection. J Immunol 178:4506–4516
119. Richter MV, Topham DJ (2007) The alpha1beta1 integrin and TNF receptor II protect airway CD8 + effector T cells from apoptosis during influenza infection. J Immunol 179:5054–5063
120. Rider DA, Nalathamby T, Nurcombe V, Cool SM (2007) Selection using the alpha-1 integrin (CD49a) enhances the multipotentiality of the mesenchymal stem cell population from heterogeneous bone marrow stromal cells. J Mol Histol 38:449–458
121. Ronzière M-C, Aubert-Foucher E, Gouttenoire J, Bernaud J, Herbage D, Mallein-Gerin F (2005) Integrin alpha1beta1 mediates collagen induction of MMP-13 expression in MC615 chondrocytes. Biochim Biophys Acta 1746:55–64
122. Sampson NS, Enke DA, Cosgrove D, Koteliansky V, Gotwals P, Ryan ST (2001) Global gene expression analysis reveals a role for the alpha 1 integrin in renal pathogenesis. J Biol Chem 276(36):34182–34188
123. Santala P, Heino J (1991) Regulation of integrin-type cell adhesion receptors by cytokines. J Biol Chem 266(34):23505–23509
124. Schadendorf D, Haney U, Ostmeier H, Suter L, Czarnetzki BM, Gawlik C (1993) Tumour progression and metastatic behaviour in vivo correlates with integrin expression on melanocytic tumours. J Pathol 170(4):429–434
125. Schadendorf D, Makki A, Alijagic S, Kupper M, Mrowietz U, Henz BM, Fichtner I (1996) Metastatic potential of human melanoma cells in nude mice–characterisation of phenotype, cytokine secretion and tumour-associated antigens. Br J Cancer 74(2):194–199
126. Schocklmann HO, Kralewski M, Hartner A, Ludke A, Sterzel RB, Lang S (2000) Distinct structural forms of type I collagen modulate cell cycle regulatory proteins in mesangial cells. Kidney Int 58(3):1108–1120
127. Schwartz MA, Ginsberg MH (2002) Networks and crosstalk: integrin signalling spreads. Nat Cell Biol 4:E65–E68
128. Senger DR, Benes JE, Perruzzi CA, Sergiou AP, Detmar M, Claffey KP (1997) Angiogenesis promoted by vascular endothelial growth factor: regulation through alpha1beta1 and alpha2beta1 integrins. Proc Natl Acad Sci USA 94(25):13612–13617
129. Senger DR, Perruzzi CA, Streit M, Koteliansky VE, de Fougerolles AR, Detmar M (2002) The alpha(1)beta(1) and alpha(2)beta(1) integrins provide critical support for vascular endothelial growth factor signaling, endothelial cell migration, and tumor angiogenesis. Am J Pathol 160:195–204
130. Seo N, Russell BH, Rivera JJ, Liang X, Xu X, Afshar-Kharghan V, Hook M (2010) An engineered alpha1 integrin-binding collagenous sequence. J Biol Chem 285:31046–31054
131. Seo NS, Zeng CQ, Hyser JM, Utama B, Crawford SE, Kim KJ, Hook M, Estes MK (2008) Integrins alpha1beta1 and alpha2beta1 are receptors for the

rotavirus enterotoxin. Proc Natl Acad Sci USA 105:8811–8818
132. Shi M, Pedchenko V, Greer BH, Van Horn WD, Santoro Sa, Sanders CR, Hudson BG, Eichman BF, Zent R, Pozzi A (2012) Enhancing integrin α1 inserted (I) domain affinity to ligand potentiates integrin α1β1-mediated down-regulation of collagen synthesis. J Biol Chem 287:35139–35152
133. Shimaoka M, Takagi J, Springer TA (2002) Conformational regulation of integrin structure and function. Annu Rev Biophys Biomol Struct 31:485–516
134. Skinner MP, Raines EW, Ross R (1994) Dynamic expression of alpha 1 beta 1 and alpha 2 beta 1 integrin receptors by human vascular smooth muscle cells. Alpha 2 beta 1 integrin is required for chemotaxis across type I collagen-coated membranes. Am J Pathol 145:1070–1081
135. Sobel RA, Maeda A, Chen M, Hinojoza JR (1998) Endothelial cell integrin laminin receptor expression in multiple sclerosis lesions. Am J Pathol 153(2):405–415
136. Soligo D, Luksch R, Manara G, Quirici N, Parravicini C, Lambertenghi Deliliers G, Schiró R (1990) Expression of integrins in human bone marrow. Br J Haematol 76(3):323–332
137. Stamatoglou SC, Johansson S, Forsberg E, Hughes RC, Bawumia S (1991) Affinity of integrin alpha 1 beta 1 from liver sinusoidal membranes for type IV collagen. *1*. FEBS Lett 288(1–2):241–243
138. Sterry W, Konter U, Kellner I, Boehncke WH, Mielke U (1992) Role of beta 1-integrins in epidermotropism of malignant T cells. Am J Pathol 141(4):855–860
139. Stewart HJ, Jessen KR, Mirsky R, Turner D (1997) Expression and regulation of alpha1beta1 integrin in Schwann cells. J Neurobiol 33(7):914–928
140. Sutherland AE, Calarco PG, Damsky CH (1993) Developmental regulation of integrin expression at the time of implantation in the mouse embryo. Development 119:1175–1186
141. Suzuki K, Okuno T, Yamamoto M, Pasterkamp RJ, Takegahara N, Takamatsu H, Kitao et al (2007) Semaphorin 7A initiates T-cell-mediated inflammatory responses through alpha1beta1 integrin. Nature 446(7136):680–684
142. Szulgit G, Wandel A, Tenenhaus M, Panos R, Gardner H, Rudolph R (2002) Alterations in fibroblast alpha1beta1 integrin collagen receptor expression in keloids and hypertrophic scars. J Invest Dermatol 118(3):409–415
143. Tawil NJ, Blacher R, Esch F, Reichardt LF, Turner DC, Carbonetto S, Houde M (1990) Alpha 1 beta 1 integrin heterodimer functions as a dual laminin/collagen receptor in neural cells. Biochem 29(27):6540–6544
144. Terracio L, Rubin K, Gullberg D, Balog E, Carver W, Jyring R, Borg TK (1991) Expression of collagen binding integrins during cardiac development and hypertrophy. Circ Res 68:734–744
145. Tomaselli KJ, Doherty P, Emmett CJ, Damsky CH, Walsh FS, Reichardt LF (1993) Expression of beta 1 integrins in sensory neurons of the dorsal root ganglion and their functions in neurite outgrowth on two laminin isoforms. J Neurosci 13:4880–4888
146. Tulla M, Lahti M, Puranen JS, Brandt AM, Kapyla J, Domogatskaya A, Salminen TA, Tryggvason K, Johnson MS, Heino J (2008) Effects of conformational activation of integrin alpha 1I and alpha 2I domains on selective recognition of laminin and collagen subtypes. Exp Cell Res 314:1734–1743
147. Tulla M, Pentikäinen OT, Viitasalo T, Käpylä J, Impola U, Nykvist P, Nissinen L, Johnson MS, Heino J (2001) Selective binding of collagen subtypes by integrin alpha 1I, alpha 2I, and alpha 10I domains. J Biol Chem 276:48206–48212
148. Vaalamo M, Mattila L, Johansson N, Kariniemi AL, Karjalainen-Lindsberg ML, Kahari VM, Saarialho-Kere U (1997) Distinct populations of stromal cells express collagenase-3 (MMP-13) and collagenase-1 (MMP-1) in chronic ulcers but not in normally healing wounds. J Invest Dermatol 109:96–101
149. Vossmeyer D, Loster K, Reutter W, Danker K, Hofmann W (2002) Phospholipase Cgamma binds alpha1beta1 integrin and modulates alpha1beta1 integrin-specific adhesion. J Biol Chem 277(7):4636–4643
150. Wary KK, Mainiero F, Isakoff SJ, Marcantonio EE, Giancotti FG (1996) The adaptor protein Shc couples a class of integrins to the control of cell cycle progression. Cell 87:733–743
151. Wary KK, Mariotti A, Zurzolo C, Giancotti FG (1998) A requirement for caveolin-1 and associated kinase Fyn in integrin signaling and anchorage-dependent cell growth. Cell 94:625–634
152. Wu JE, Santoro SA (1994) Complex patterns of expression suggest extensive roles for the alpha 2 beta 1 integrin in murine development. Dev Dyn 199:292–314
153. Xu Y, Gurusiddappa S, Rich RL, Owens RT, Keene DR, Mayne R, Höök a, Höök M (2000) Multiple binding sites in collagen type I for the integrins alpha1beta1 and alpha2beta1. J Biol Chem 275:38981–38989
154. Yu L, Su Y, Paueksakon P, Cheng H, Chen X, Wang H, Harris RC, Zent R, Pozzi A (2012) Integrin alpha1/Akita double-knockout mice on a Balb/c background develop advanced features of human diabetic nephropathy. Kidney Int 81:1086–1097
155. Zallocchi M, Johnson BM, Meehan DT, Delimont D, Cosgrove D (2013) alpha1beta1 Integrin/Rac1-Dependent Mesangial Invasion of Glomerular Capillaries in Alport Syndrome. Am J Pathol 183:1269–1280
156. Zemmyo M, Meharra EJ, Kuhn K, Creighton-Achermann L, Lotz M (2003) Accelerated, aging-dependent development of osteoarthritis in alpha1 integrin-deficient mice. Arthritis Rheum 48: 2873–2880

157. Zent R, Yan X, Su Y, Hudson BG, Borza DB, Moeckel GW, Qi Z, Sado Y, Breyer MD, Voziyan P et al (2006) Glomerular injury is exacerbated in diabetic integrin alpha1-null mice. Kidney Int 70:460–470
158. Zhang WM, Kapyla J, Puranen JS, Knight CG, Tiger CF, Pentikainen OT et al (2003) alpha11beta1 integrin recognizes the GFOGER sequence in interstitial collagens. J Biol Chem 278:7270–7277
159. Zhang Z, Turner DC, Tarone G (1993) 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 1. J Biol Chem 268(8):5557–5565

http://www.springer.com/978-94-017-9152-6

I Domain Integrins
Gullberg, D. (Ed.)
2014, XIV, 179 p. 50 illus., 32 illus. in color., Hardcover
ISBN: 978-94-017-9152-6