

Integrins

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Abstract Integrins are cell adhesion receptors that are evolutionary old and that play important roles during developmental and pathological processes. The integrin family is composed of 24 $\alpha\beta$ heterodimeric members that mediate the attachment of cells to the extracellular matrix (ECM) but that also take part in specialized cell-cell interactions. Only a subset of integrins (8 out of 24) recognizes the RGD sequence in the native ligands. In some ECM molecules, such as collagen and certain laminin isoforms, the RGD sequences are exposed upon denaturation or proteolytic cleavage, allowing cells to bind these ligands by using RGD-binding receptors. Proteolytic cleavage of ECM proteins might also generate fragments with novel biological activity such as endostatin, tumstatin, and endorepellin. Nine integrin chains contain an α I domain, including the collagen-binding integrins $\alpha1\beta1$, $\alpha2\beta1$, $\alpha10\beta1$, and $\alpha11\beta1$. The collagen-binding integrins recognize the triple-helical GFOGER sequence in the major collagens, but their ability to recognize these sequences *in vivo* is dependent on the fibrillar status and accessibility of the interactive domains in the fibrillar collagens. The current review summarizes some basic facts about the integrin family including a historical perspective, their structure, and their ligand-binding properties.

Keywords Integrins · History · Ligands · α and β subunits · RGD · GFOGER · Collagen

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History

Integrins are cell adhesion receptors that are evolutionary old (Johnson et al. 2009). Despite their long history, they have only been characterized at the molecular level for approximately 25 years. During this period, a large number of articles on the ever-increasing intricacies of integrin action has been published. To summarize this large amount of data on integrins “at a glance” is thus almost an impossible task. In the current review, we have however attempted to provide some of the basic facts about integrins. Recent excellent reviews on various aspects of integrins structure and function will be referred to in the text.

One reason for the difficulties encountered when trying to characterize the integrin family is that many of their ligands are large multi-adhesive extracellular matrix (ECM) molecules that, in addition to binding integrins, bind other proteins including ECM molecules, growth factors, cytokines, and matrix-degrading proteases. One successful approach that was instrumental in the identification of integrins took advantage of antibodies that blocked cell adhesion (Horwitz et al. 1985; Knudsen et al. 1985). In another approach, the mapping of the minimal cell adhesion site in fibronectin to the RGDS sequence gave rise to affinity chromatography protocols with increased specificity (Pierschbacher et al. 1983; Ruoslahti and Pierschbacher 1986). In these affinity protocols, the optimization of ion composition in the purification buffers was essential and resulted in the empirical finding that manganese ions (Mn^{2+}) increased integrin affinity (Gailit and Ruoslahti 1988). In 1986, the antibody approach led to the expression cloning of cDNA encoding the chick integrin $\beta1$ subunit (Tamkun et al. 1986). The name “integrin” was given to denote the importance of these receptors for maintaining the integrity of the cytoskeletal-ECM linkage (Hynes 2004, Tamkun et

al. 1986). In the 1980s, several groups were working on seemingly disparate cell surface proteins, which at the time were named position specific (PS) antigens in *Drosophila* (Leptin et al. 1987; Wilcox et al. 1984), very late antigens of activation (VLA) on immune cells (Hemler et al. 1985), cell surface receptors on lymphoid and myeloid cells (Springer et al. 1986), and platelet glycoproteins (Parise and Phillips 1985, 1986). With the cloning of the cDNAs encoding these proteins, it became clear that they were related to the fibronectin receptors isolated by using RGD peptides or cell adhesion blocking antibodies, and that they all belonged to what was to be called the integrin family of cell adhesion receptors (Hynes 2004; Fig. 1, see also [Electronic Supplementary Material](#)).

Structure

When integrins were being identified with antibodies to integrin β subunits, several proteins were co-immunoprecipitated, and the number of subunits that composed the functional receptors was by no means obvious. However, with antibodies to integrin α subunits, and with protocols using RGDS peptides enabling the affinity purification of pure receptors, it became clear that the functional receptors were heterodimers. Integrin heterodimers are composed of non-covalently associated α and β subunits (Hynes 2002). In vertebrates, the family is composed of 18 α subunits and 8 β subunits that can assemble into 24 different heterodimers (Takada et al. 2007). The integrins can be grouped into subgroups based on ligand-binding properties or based on their subunit composition (see Table 1, 2).

The $\beta 1$ integrins, $\beta 2$ integrins, and αv -containing integrins are the three largest groups in this kind of classification (Fig. 2, see also [Electronic Supplementary Material](#)). The α and β subunits show no homology to each

other, but different α subunits have similarities among themselves, just as there are conserved regions in the different integrin β subunits.

Integrin α subunits

The α subunit is composed of a seven-bladed β -propeller, which is connected to a thigh, a calf-1, and a calf-2 domain, together forming the leg structure that supports the integrin head (Fig. 3, see also [Electronic Supplementary Material](#)). The last three or four blades of the β -propeller contain EF-hand domains that bind Ca^{2+} on the lower side of the blades facing away from the ligand-binding surface. Ca^{2+} binding to these sites allosterically affects ligand binding (Humphries et al. 2003; Oxvig and Springer 1998).

Nine of the integrin α chains contain an I domain, also called the A domain, which is a domain of approximately 200 amino acids, inserted between blades 2 and 3 in the β -propeller (Larson et al. 1989). The αI first appeared in chordate integrins, and is thus absent in invertebrates but is present in vertebrates (Johnson et al. 2009). The αI domain is present in the $\beta 2$ integrin subgroup of integrins, in the collagen-binding integrins belonging to the $\beta 1$ subfamily ($\alpha 1$, $\alpha 2$, $\alpha 10$, and $\alpha 11$), and the αE integrin chain forming the $\alpha E\beta 7$ heterodimer. The I domain assumes a Rossmann fold with five β -sheets surrounded by seven α helices. Ligand binding occurs via a coordinating Mg^{2+} ion in the so-called metal-ion-dependent adhesion site (MIDAS) motif (Lee et al. 1995). The αI domains with the capacity to interact with collagens, in addition, contains a so-called αC helix (Emsley et al. 1997), which has been suggested to play a role in collagen binding.

The αI -domain-containing integrins show fairly high homology in their αI domains, but the α chain cytoplasmic domains are highly divergent, only sharing the GFFKR sequence or even the core GFFXR sequence in the membrane proximal region.



Fig. 1 Integrin founding fathers. Erkki Ruoslahti (left) and Richard O. Hynes (right) contributed seminal data in the early days of cell adhesion research leading to the characterization of the integrin family

α subunit - determines integrin ligand specificity.

αI domain - inserted domain of approx 200 amino acids, present in 9 integrin α subunits.

MIDAS - Metal ion dependent adhesion site, crucial Mg^{2+} -binding site in the I domain, bridges ligand binding.

Relatively little is known about proteins interacting with the α -chain cytoplasmic tails.

An area between the hybrid domain in the β subunit and a surface in the β -propeller of the α subunit seems to be crucial

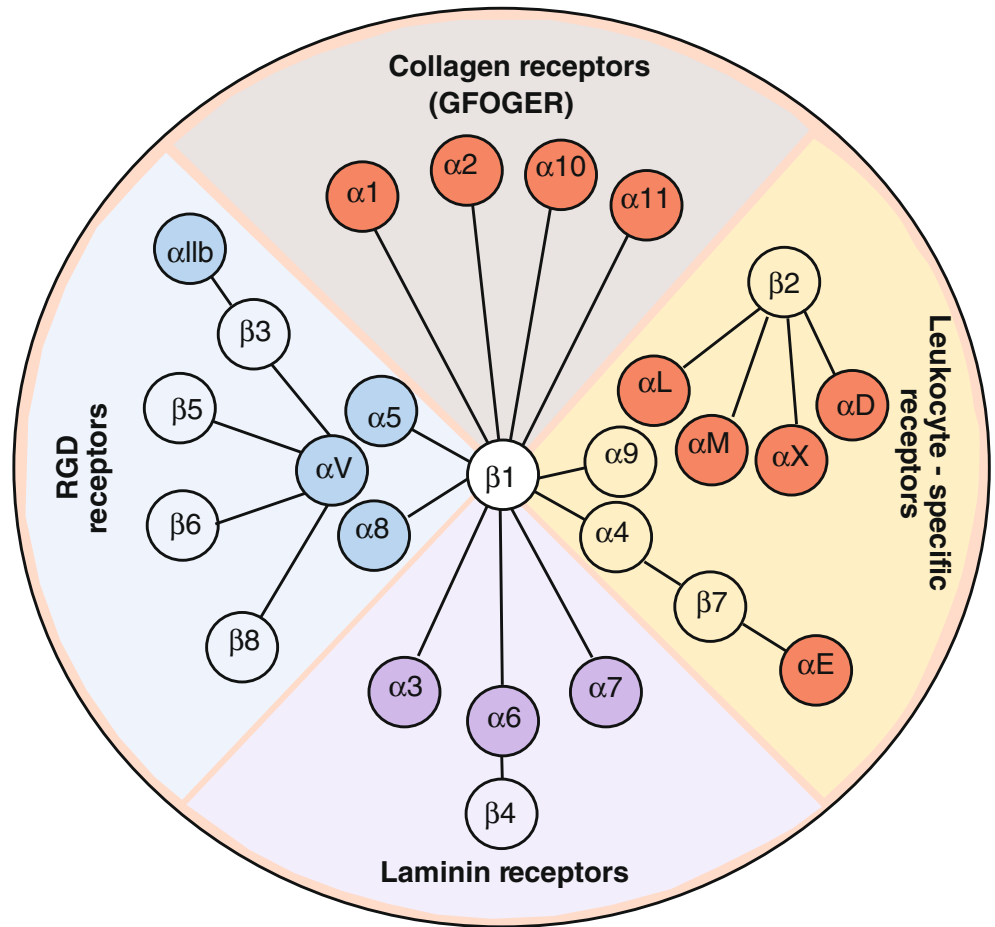
Table 1 Characteristics of human integrin α subunits. Data are presented for the human integrin α chains and have been retrieved from original data submitted to the NCBI database (<http://www.ncbi.nlm.nih.gov/sites/>**entrez**) and original publications. For ligand specificity, see references in text (*ICAM* intercellular adhesion molecule, *VCAM* vascular cell adhesion molecule, *VEGF* vascular endothelial growth factor)

Integrin	Human α chain characteristics	Cleavage	α I	Prototypic ligands/ recognition sequences	Additional ligands
$\alpha 1\beta 1$ (CD49a, VLA1)	1151 aa		X	collagens (collagen IV > collagen I (GFOGER); collagen IX)	semaphorin 7A
$\alpha 2\beta 1$ (CD49b, VLA2)	1181 aa		X	collagens (collagen I > collagen IV (GFOGER); collagen IX)	E-cadherin, endorepellin
$\alpha 3\beta 1$ (CD49c, VLA3)	1051 aa, splice variants $\alpha 3A$ and $\alpha 3B$	X		laminins (LN-511>LN-332>LN-211)	
$\alpha 4\beta 1$ (CD49d, VLA4)	1038 aa			fibronectin VCAM-1	
$\alpha 5\beta 1$ (CD49e, VLA5)	1049 aa	X		fibronectin (RGD)	endostatin
$\alpha 6\beta 1$ (CD49f, VLA6)	1073 aa, splice variants $\alpha 6A$ and $\alpha 6B$	X		laminins (LN-511>LN-332>LN-111>LN-411)	
$\alpha 7\beta 1$	1137 aa, splice variants X1, X2, $\alpha 7A$, $\alpha 7B$	X		$\alpha 7X1\beta 1$: laminins (LN-511>LN-211>LN-411>LN-111) $\alpha 7X2\beta 1$: laminins (LN-111>LN-211>LN-511)	
$\alpha 8\beta 1$	1025 aa	X		fibronectin, vitronectin, nephronectin (RGD)	
$\alpha 9\beta 1$	1035 aa			tenascin-C, VEGF-C, VEGF-D	
$\alpha 10\beta 1$	1167 aa		X	collagens (collagen IV> collagen VI>collagen II (GFOGER); collagen IX)	
$\alpha 11\beta 1$	1188 aa, inserted domain 21 aa		X	collagens (collagen I>collagen IV (GFOGER); collagen IX)	
$\alpha L\beta 2$ (CD11a)	1170 aa		X	ICAM-1, -2, -3, -5	
$\alpha M\beta 2$ (CD11b)	1153 aa		X	iC3b, fibrinogen + more	
$\alpha X\beta 2$ (CD11c)	1163 aa		X	iC3b, fibrinogen + more	
$\alpha D\beta 2$ (CD11d)	1162 aa		X	ICAM-3, VCAM-1	
$\alpha IIB\beta 3$ (CD41, GpIIb)	1039 aa	X		fibrinogen, fibronectin (RGD)	
$\alpha 6\beta 4$		X		laminins (LN-332, LN-511)	
$\alpha v\beta 1$ (CD51)	1048 aa	X		fibronectin, vitronectin (RGD)	
$\alpha v\beta 3$		X		vitronectin, fibronectin, fibrinogen (RGD)	tumstatin
$\alpha v\beta 5$		X		vitronectin (RGD)	
$\alpha v\beta 6$		X		fibronectin, TGF- β -LAP (RGD)	
$\alpha v\beta 8$		X		vitronectin, TGF- β -LAP (RGD)	
$\alpha E\beta 7$ (CD103, HML-1)	1178 aa	X	X	E-cadherin	
$\alpha 4\beta 7$				MadCAM-1, fibronectin, VCAM-1	

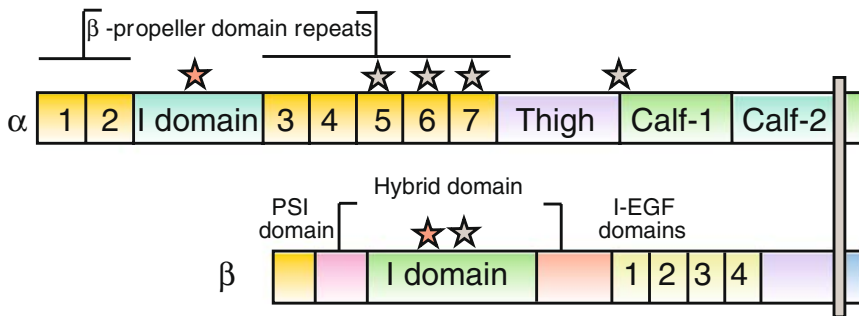
Table 2 Characteristic of human integrin β subunits. Data are presented for the human integrin β chains and have been retrieved from original data submitted to NCBI database (<http://www.ncbi.nlm.nih.gov/sites/entrez>) and original publications (see text)

Integrin β chain	Characteristics	Notes
$\beta 1$ (CD 29, Gp IIa)	798 aa, splice variants $\beta 1A$, $\beta 1B$, $\beta 1C$, $\beta 1D$	Splice variants $\beta 1B$ and $\beta 1C$ not present in mice, minor variants with unclear function
$\beta 2$ (CD18)	769 aa	
$\beta 3$ (CD 61, GP IIIa)	788 aa, splice variants $\beta 3A$, $\beta 3B$ and $\beta 3C$	$\beta 3A$ major form
$\beta 4$ (CD104, TSP-180)	1875 aa, splice variants $\beta 4A-E$	$\beta 4A$ and $\beta 4B$ major forms, similar function
$\beta 5$	799 aa, splice variants $\beta 5A$, $\beta 5B$	Both splice variants have similar functions
$\beta 6$	788 aa	
$\beta 7$ (LPAM-1, βP)	798 aa	
$\beta 8$	769 aa	

Fig. 2 Representation of the integrin family. In vertebrates, the integrin family contains 24 heterodimers. Isolated species that have undergone genome duplication (e.g., *Danio rerio*) have more integrin family members. In higher vertebrates, the integrin family has 24 prototypical members



A



B

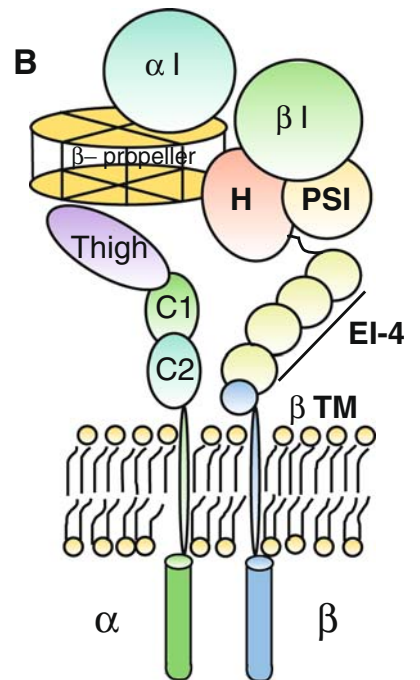


Fig. 3 Representation of a prototypical α I-domain-containing integrin heterodimer. Nine out of the 18 integrin α chains contains an α I domain, as shown, but all integrins contain a β I domain in the β

subunit. **A** Representation of the domains in α I domain-containing integrin (stars divalent cation-binding sites). **B** Representation of arrangement of domains in α I-domain-containing integrin

for the integrin heterodimerization that occurs intracellularly prior to transport to the cell surface (Humphries 2000). Presumably, the specificity of chain selection lies in those sequences adjacent to these interacting surfaces. Generally, an excess of β subunits exists in the cell, and the amount of α subunit determines the amount of receptor that will go to the cell surface (Santala and Heino 1991). Free α and β subunits do thus not exist at the cell surface.

Integrin β subunit

The β subunit contains a plexin-semaphorin-integrin (PSI) domain, a hybrid domain, a β I domain (Lee et al. 1995), and four cysteine-rich epidermal growth factor (EGF) repeats. The β I domain contains an Mg^{2+} coordinating MIDAS and a site adjacent to MIDAS (ADMIDAS) binding an inhibitory Ca^{2+} ion. This ADMIDAS site binds the Mn^{2+} ion leading to a conformational change resulting in an active form of the integrin (Humphries et al. 2003).

The β integrin chains share homology in the cytoplasmic tail, with NPX/Y motifs able to bind proteins containing PTB domains. In recent years, several proteins have been found to interact with the β subunit (Legate and Fassler 2009).

β subunit - connected to cytoskeleton, affects multiple signalling pathways.

β I domain - I domain-like region, takes part in ligand binding in non- α I containing integrins, metal ion binding.

ADMIDAS - region adjacent to MIDAS in β I domain, contains metal ion binding site that is inhibitory.

Some key proteins seem to be essential for binding and, in doing so, break salt bridges formed with the α subunit that keeps the integrin in the inactive conformation. A detailed study has recently clarified the interacting regions in the α IIb and β 3 subunit transmembrane domains, suggesting a model for conformation-mediated changes over the membrane (Lau et al. 2009). Talin 1–2 and kindlins 1–3 seem to act synergistically to activate integrins by binding to integrin β subunit tails (Larjava et al. 2008; Senetar et al. 2007; Tadokoro et al. 2003), whereas filamin A negatively regulates activation (Kiema et al. 2006). Migfilin is another molecular switch that, by blocking the integrin-binding region of filamins (Ithychanda et al. 2009), can regulate integrin activation. More recently, the integrin-linked kinases (ILK) (Honda et al. 2009) and focal adhesion kinase (FAK) (Michael et al. 2009) enzymes taking part in

outside-in signaling have also been shown to affect integrin activation via inside-out signaling.

Conformational changes in integrins

The crystallization of a soluble integrin heterodimer has made clear that integrins can exist in a compact bent conformation (Xiong et al. 2002). Later research has shown that this conformation represents an inactive conformation (Nishida et al. 2006). Some data suggest that integrins “breathe” and change between different conformations with individual variations as to their degree of bending. Furthermore, the bent conformation does not always seem to be inactive, especially with regard to small ligands (Askari et al. 2009). More recently, mechanical tension has been demonstrated to consolidate integrin contact points by further stretching the conformation to stabilize the active conformation, thereby increasing affinity (Askari et al. 2009; Astrof et al. 2006; Friedland et al. 2009). For integrin α 5 β 1, the mechanical tension induces α 5 β 1 engagement with the synergy site in fibronectin, in turn leading to FAK phosphorylation (Friedland et al. 2009). A recent synergy site in nephronectin has been suggested mainly to exert its action by bringing the RGD site into a best-fit conformation with regard to high-affinity integrin binding (Sato et al. 2009).

In addition to the affinity modulation that occurs in various activation states, integrin clustering by multivalent ligands, and possibly also changes in membrane fluidity, cause avidity changes of integrin contacts (Carman and Springer 2003).

For integrins that require a tight control of activity, such as platelet integrin α IIb β 3 and β 2 integrins, precise activating mechanisms must exist (Luo et al. 2007). When kindlin-3 is mutated, integrin activation in leukocytes and platelets fails (Moser et al. 2008; Svensson et al. 2009), demonstrating the central role of kindlin-3 for integrin activation on these cell types.

Ligand recognition

The ligand-binding site forms in a region at the intersection of the integrin α -chain β -propeller and the β I domain, with the α chain being central in determining ligand specificity. Integrins with an α I domain bind ligands via the α I domain, but since this ligand-binding causes distinct conformational changes in the I domain, this in turn affects the conformation of the β subunit (Luo et al. 2007). For some α I domains, interactions with the β chain are even needed for the proper folding of the α I domain (Valdramidou et al. 2008). The list of integrin ligands is long (Humphries et al. 2006; Johnson et al. 2009) and includes the major constituents of the ECM.

Prototypic integrin ligands and recognition sequences

The prototypic integrin ligand, fibronectin, contains the amino acid sequence RGDS at the apex of a flexible loop connecting two β -strands in the 10th fibronectin type III repeat (Dickinson et al. 1994). The RGD sequence is also present in vitronectin, fibrinogen, and the LAP complex part of inactive transforming growth factor- β (TGF- β) and many other ECM proteins (Humphries et al. 2006). Elegant studies have shown that the epithelial $\alpha\beta6$ and $\alpha\beta8$, by binding RGD in LAP, are the major integrins that activate TGF- β in vivo either by allosteric changes in TGF- β -LAP ($\alpha\beta6$) or by inducing matrix metalloproteinase-14 and causing proteolytic release of TGF- β ($\alpha\beta8$; Aluwihare et al. 2009; Mu et al. 2002; Munger et al. 1999). More recently, a mechanical-strain-dependent contribution of myofibroblast $\beta1$ integrins to TGF- β activation has been demonstrated (Wipff et al. 2007).

RGD- minimal integrin recognition sequence in ligands like fibronectin, vitronectin and fibrinogen.

GFOGER - minimal integrin recognition sequence in collagens when present as triple helical conformation (O= hydroxyproline).

LDV - minimal integrin recognition sequence in alternatively spliced region of fibronectin.

In many biochemistry and cell biology books, the RGD sequence is presented as the major integrin-binding sequence, but only a third of the integrins are known to bind this sequence (Table 1). RGD peptides can be used to assess the involvement of RGD-binding integrins in a certain event, but lack of effect of RGD peptides does not exclude integrin involvement in a process since two-thirds of integrins bind ligands RGD-independently.

Some isoforms of the basement membrane protein laminin contain an RGD sequence, but the sequence is not evolutionary conserved in these isoforms and is not recognized by the laminin-binding integrins. In laminin-111, the RGD site is masked in the native molecule (Aumailley et al. 1990; Schulze et al. 1996), whereas in laminin isoforms containing the $\alpha5$ chain, it is exposed in the native molecule (Domogatskaya et al. 2008; Forsberg et al. 1994; Genersch et al. 2003; Sasaki and Timpl 2001). The full physiological importance of the $\alpha\beta1$ - and $\alpha\beta3$ -mediated binding to laminin- $\alpha5$ -containing laminins however remains unclear. As pointed out, the EHS-produced laminin-111 is a poor ligand for the laminin-binding

integrins. Accumulating data suggest that a major integrin-binding site is present in laminin LG1-3 domains in the C-terminal part of the laminin heterotrimer (Ido et al. 2004; Kunneken et al. 2004). In addition to laminin α -chain-specific sequences, C-terminal residues of both β - and γ -chains contribute/facilitate integrin binding (Ido et al. 2004; Kunneken et al. 2004). Splicing in the extracellular domain of integrin $\alpha7$ affects its preference for certain laminin isoforms (Nishiuchi et al. 2003; Taniguchi et al. 2009; von der Mark et al. 2002; Table 1).

RGD sequences present in triple helical fibrillar collagen sequences are normally not available for fibronectin receptors in native fibrillar collagen (Davis 1992; Gullberg et al. 1990), only becoming available in denatured collagen I. Instead, the collagen-binding integrins recognize the triple-helical GFOGER sequence (Knight et al. 1998), or variants thereof, in native collagens. An assembled database on collagen-I-binding sites and mutations has enabled the construction of a model in which the GFOGER site is present in a cell-interactive domain that is suggested to be exposed once per microfibril unit (each microfibrillar unit is composed of five collagen triple helix monomers), allowing the clustering of integrins (Sweeney et al. 2008). However, a number of components in the fibrillar matrix might influence the availability of these sites. Interestingly, collagen IX, which is present in cartilage, has been shown to be a good ligand for all of the collagen-binding integrins (Kapyla et al. 2004), but in vivo, not all of the collagen-binding integrins are expressed in chondrocytes. In the case of $\alpha11\beta1$ integrin, if cartilaginous tissue is not dissected free of perichondrium, a signal from $\alpha11$ will be derived from $\alpha11$ expression in the perichondrium (Tiger et al. 2001), which lacks collagen IX. The identity of the integrins that might physiologically be relevant as collagen IX receptors in various regions of cartilage thus remains to be defined.

Collagen IX lacks the prototypic collagen-binding integrin recognition sequence GFOGER, and the exact sequence awaits mapping. Certain variants of the GFOGER sequence might show specificity for the different collagen-binding integrins, as indicated by a recent finding showing that the bacterial collagen-like peptide, sscl, with the active binding site GLPGER, is preferred by $\alpha11\beta1$ -expressing cells over $\alpha2\beta1$ -expressing cells (Caswell et al. 2008).

Other integrin-binding motifs include the $\alpha4$ -integrin-binding sequence LDV (Clements et al. 1994; Komoriya et al. 1991), variants of which are also present in the adhesion molecules ICAMs and MadCAM recognized by $\beta2$ integrins and the $\alpha4\beta7$ heterodimer, respectively (Wang and Springer 1998).

In addition to physiological ligands, integrin ligands generated by proteolysis are receiving increasing recognition. Endostatin (derived from collagen XVIII), endorepel-

Table 3 Integrin signatures of some selected cell types. Each cell in an organism contains a specific integrin signature under certain conditions. The integrin repertoire is dynamic, changes with developmental age, and

is strongly responsive to microenvironmental conditions. Sometimes, a specific integrin isoform is indicative of the cell type or the differentiation status (integrins given in *bold* are the predominating integrins present)

Cell type	Integrin Expression	Selected References
Hub cells in germline stem cell niche (<i>Drosophila</i>)	β PS3	(Tanentzapf et al. 2007)
Epidermal stem cells	β 1 integrins	(Jensen et al. 1999, Jones et al. 1995)
Chondrogenic mesenchymal stem cells (human)	α10	(Varas et al. 2007)
Neural stem cells	β 1 integrins	(Campos et al. 2004, Jacques et al. 1998)
Embryonic stem cells	α 6B	(Hierck et al. 1993)
Satellite cells	α7	(Mayer 2003, Mayer et al. 1997, Sacco et al. 2008)
Epithelial cells	α 6, α 3	(Thorsteinsdottir et al. 1995)
Fibroblasts	α11 , α 2, α 1, α 5	(Gardner et al. 1996, Tiger et al. 2001, Zutter and Santoro 1990)
Endothelial cells	α 1, α 2, α 6	(Gardner, Kreidberg, Kotliansky and Jaenisch 1996, Thorsteinsdottir et al. 1995, Zutter and Santoro 1990)
Chondrocytes	α10	(Camper et al. 1998, Camper et al. 2001)
Skeletal myofibers	β1D , α7A and α7B	(Baudoin et al. 1998, Martin et al. 1996, Velling et al. 1996)
Cardiac myocytes	α7B	(Velling et al. 1996)

lin (derived from perlecan), and tumstatin derived from collagen α 3 (IV) are the best-known examples (Bix and Iozzo 2005; Suhr et al. 2009; Table 1). In addition, integrins can bind snake toxins called disintegrins (Calvete et al. 2005; Swenson et al. 2007) and certain viruses (Stewart and Nemerow 2007) and bacteria (Hauck et al. 2006; Palumbo and Wang 2006). Some of these interactions occur outside the regular ligand-binding sites in the integrins and display distinct binding characteristics compared with the binding of physiological ligands.

Integrins as mechanical links

The first function established for integrins was their function as links between the ECM and the cytoskeleton. For a majority of integrins, the linkage is to the actin cytoskeleton (Geiger et al. 2009), whereas α 6 β 4 connects to the intermediate filament system (Nievers et al. 1999). Recently, the intermediate filament protein vimentin has been shown to be dependent on β 3 integrins for its recruitment to the cell surface (Bhattacharya et al. 2009), indicating that an intimate relationship exists between the various cytoskeletal networks and integrins.

Some of the components in this mechanical linkage, such as talin, play a dual role and also take part in activating integrins in an inside-out signaling mechanism (Tadokoro et al. 2003). A new dimension of integrins as mechanical links has come to the fore with the realization that integrins can act as mechanosensors and generate signals that affect cell physiology via complex intracellular

signaling mechanisms including autocrine and paracrine mechanisms (Chen and O'Connor 2005; Linton et al. 2007; Millward-Sadler and Salter 2004; Millward-Sadler et al. 1999; Zhu et al. 2007). As mentioned above, mechanical tension can also increase integrin affinity.

Integrins as signaling receptors

Integrins are bi-directional signaling receptors involved in outside-in and inside-out signaling. The inside-out signaling mainly acts to bring the integrin into the active conformation. As previously mentioned, talins, kindlins, filamins, migfilin, FAK, but also ILK (Honda et al. 2009) can regulate integrin activation.

Upon ligand binding, integrins undergo conformation changes leading to outside-in signaling. This activates signaling events that are complex and cell-specific, depending on what other signaling receptors and signaling systems are available in the cell. The scope of this review does not include these events, but readers are referred to recent excellent reviews on this subject (Askari et al. 2009; Gahmberg et al. 2009; Larjava et al. 2008; Legate et al. 2009; Luo and Springer 2006).

Integrin expression

Integrins are widely expressed, and every nucleated cell in the body possesses a specific integrin signature. Importantly, the regulation of integrins is dynamic and quickly

	Integrin	Viability	Unchallenged mutant phenotype	Challenged mutant phenotype
Collagen	$\alpha 1$	+	No phenotype. Cell adhesion defect to collagen IV.	Reduced tumor angiogenesis, increased glomerulosclerosis, diminished callus size in bone fracture model, reduced atherosclerosis in ApoE ^{-/-} mice, reduced psoriasis in xenograft model.
	$\alpha 2$	+	Mild mammary gland branching morphogenesis phenotype. Platelet, fibroblast, and keratinocyte adhesion defect to collagen I.	Reduced angiogenesis in tumor and wound healing models, reduced innate immune response to peritoneal <i>Listeria</i> infection, reduced thrombi formation increased embolization in thrombosis model.
	$\alpha 10$	+	Mild cartilage defect.	
	$\alpha 11$	+	Incisor eruption defect.	
Laminins	$\alpha 3$	+/-	Defects of kidney and submandibular gland, decreased bronchial branching of the lungs, skin blisters, abnormal layering of the cerebral cortex.	Faster wound healing in a Cre-model.
	$\alpha 6$	+/-	Severe blistering of the skin and other epithelia, absence of hemidesmosomes, altered laminin deposition in the brain, and ectopic neuroblastic outgrowths on the brain and in the eye. Mutants die at birth.	
	$\alpha 7$	- or +	Embryonic vasculature defect, cerebral hemorrhage, and placenta defects. Muscular dystrophy in adult mice.	Fibrotic muscle tissue when crossed with mdx mice. Protective role in exercise-induced muscle injury.
	$\alpha 5$	-	Severe defects in posterior trunk and yolk sac mesodermal structures, lack of epithelialization of somites, reduced numbers of Schwann cells and embryonic lethality at E10-E11.	
RGD	$\alpha 8$	+/-	Absent or reduced kidneys and abnormal steriosilia in the inner ear.	
	αv	- or +/-	Placental defects and intracerebral, intestinal hemorrhages and cleft palate. Death varies from midgestation to perinatal.	
	αIIB	+	Bleeding disorder, lack of platelet binding to fibrinogen, absence of fibrinogen in platelet alpha granules, and increased numbers of hematopoietic progenitors in yolk sac, fetal liver, and bone marrow.	
	$\alpha 4$	-	Embryonic lethality either due to failure of chorioalloantoic fusion or cardiac abnormalities including defects in epicardium formation.	
Leucocyte specific	$\alpha 9$	+/-	Bilateral chylothorax causing death within 14 days.	Altered cutaneous wound healing in wound model.
	αL	+	Reduced immune response, defects in neutrophil adhesion to endothelium, and in osteoclast adhesion.	Reduced leukocyte adhesion in TNF- α induced inflammation.
	αM	+	Reduced immune response, reduced neutrophil adhesion to fibrinogen and reduced degranulation of neutrophils.	Reduced T-cell proliferative response to Staphylococcal enterotoxin, reduced wound healing, reduced cerebral ischemia, reduced encephomyelitis, reduced melanoma rejection.
	αX	+	Reduced immune response.	
	αD	+	Reduced immune response.	
	αE	+	Reduced number of intestinal and vaginal interepithelial lymphocytes, skin inflammation.	Reduced experimental colitis.
	$\beta 1$	-	Null mutants die soon after implantation due to inner cell mass defects in blastocysts.	
	$\beta 2$	+	Leukocyte adhesion deficiency with immune, hematopoietic and skeleton defects.	Reduced listeriosis.
	$\beta 3$	- or +	Platelet defects, extended bleeding times, cutaneous and gastrointestinal bleeding, anemia, increased bone mass, hypocalcemia, reduced survival, and placental defects associated with some fetal loss.	Enhanced wound healing.
	$\beta 4$	+/-	Extensive detachment of epidermis and other squamous epithelia. Stratified tissues lack hemidesmosomes and simple epithelia are also defective in adherence.	
	$\beta 5$	+	Age-related blindness due to defective retinal phagocytosis. Cell adhesion defect of keratinocytes to vitronectin.	Reduced lung injury in a ventilator-induced model.
	$\beta 6$	+	Baldness associated with macrophage infiltration of skin and exaggerated pulmonary inflammation.	Reduced fibrosis in a bleomycin-induced lung model, impaired mucosal mast cell response to nematode infection, reduced wound healing, increased periodontal infection.
$\beta 7$	+	Hypoplasia of gut-associated lymph tissue due to defects in lymphocyte migration.		
$\beta 8$	+ or +/-	Death either at midgestation (E11.5) as a result of circulatory abnormalities in the placenta, or the days around birth due to intracerebral hemorrhaging.		

◀ **Table 4** Phenotypes of unchallenged and challenged integrin mutant mice. The knockout data were collected from the Mouse Genome Informatics (MGI) database (<http://www.informatics.jax.org/>) and, whenever needed, updated with relevant Pubmed (<http://www.ncbi.nlm.nih.gov/pubmed/>) retrieved original references

changes once cells are taken out of their normal environment. A few integrins are more restricted than others to certain cell lineages, but the expression is often developmentally regulated.

Most cells in the body express $\beta 1$ integrin, and the use of $\beta 1$ as part of a stem cell signature should thus be used with some caution. However, $\beta 1$ integrin expression levels have been successfully used as a marker for epidermal stem cells, which express high levels of $\beta 1$ integrins (Jensen et al. 1999). In *Drosophila*, the finding that $\beta PS3$ is needed to maintain the germ-line stem cell niche has shown the importance of integrin-mediated events for early stem cell function (Tanentzapf et al. 2007). In vitro studies have revealed that cell adhesive interactions can provide signals that keep stem cells undifferentiated on certain ECM molecules. The signals emanating from cell adhesion mediated via $\alpha 6\beta 1$ and $\alpha v\beta 1$ integrins to specific laminin isoforms can influence intracellular signaling to maintain the undifferentiated state (Domogatskaya et al. 2008). As stem cells differentiate, they change their integrin expression. In chondrogenic mesenchymal stem, the $\alpha 10/\alpha 11$ ratio reflects chondrogenic differentiation (Varas et al. 2007). Table 3 lists some integrins expressed on various characteristic cell types. The list is not complete and does not consider the dynamic changes in integrin expression that take place during growth and regeneration phases.

Integrin function

Integrins are essential cell adhesion receptors, and individual integrins have become specialized for certain functions. Although knockout animal models have provided essential information about integrin function (Table 4), several integrin functions remain to be clarified. Two examples come from the conditional deletion of $\beta 1$ integrins in cartilage and skeletal muscle, respectively, and indicate important roles for $\beta 1$ integrins during myogenesis and chondrogenesis (Aszodi et al. 2003; Schwander et al. 2003). The specific $\beta 1$ integrin heterodimers involved in skeletal muscle and cartilage have not as yet been characterized. A combination of conditional deletions of multiple integrin α -chains might be needed to resolve these issues.

We have just started to comprehend the way that integrins work in complex biological systems. A new age with more refined assays, methods, and tools is likely to meet the challenge of understanding the integrated role of integrins in these biological systems.

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References

- Aluwihare P, Mu Z, Zhao Z, Yu D, Weinreb PH, Horan GS, Violette SM, Munger JS (2009) Mice that lack activity of $\{\alpha\}v\{\beta\}6$ - and $\{\alpha\}v\{\beta\}8$ -integrins reproduce the abnormalities of Tgfb1- and Tgfb3-null mice. *J Cell Sci* 122:227–232
- Askari JA, Buckley PA, Mould AP, Humphries MJ (2009) Linking integrin conformation to function. *J Cell Sci* 122:165–170
- Astrof NS, Salas A, Shimaoka M, Chen J, Springer TA (2006) Importance of force linkage in mechanochemistry of adhesion receptors. *Biochemistry* 45:15020–15028
- Aszodi A, Hunziker EB, Brakebusch C, Fassler R (2003) $\beta 1$ integrins regulate chondrocyte rotation, G1 progression, and cytokinesis. *Genes Dev* 17:2465–2479
- Aumailley M, Gerl M, Sonnenberg A, Deutzmann R, Timpl R (1990) Identification of the Arg-Gly-Asp sequence in laminin α chain as a latent cell-binding site being exposed in fragment P1. *FEBS Lett* 262:82–86
- Baudoin C, Goumans M-J, Mummery C, Sonnenberg A (1998) Knockout and knockin of the $\beta 1$ exon D define distinct roles for integrin splice variants in heart function and embryonic development. *Genes Dev* 12:1202–1216
- Bhattacharya R, Gonzalez AM, Debiase PJ, Trejo HE, Goldman RD, Flitney FW, Jones JC (2009) Recruitment of vimentin to the cell surface by $\beta 3$ integrin and plectin mediates adhesion strength. *J Cell Sci* 122:1390–1400
- Bix G, Iozzo RV (2005) Matrix revolutions: “tails” of basement-membrane components with angiostatic functions. *Trends Cell Biol* 15:52–60
- Calvete JJ, Marcinkiewicz C, Monleon D, Esteve V, Celda B, Juarez P, Sanz L (2005) Snake venom disintegrins: evolution of structure and function. *Toxicon* 45:1063–1074
- Camper L, Hellman U, Lundgren-Akerlund E (1998) Isolation, cloning, and sequence analysis of the integrin subunit $\alpha 10$, a $\beta 1$ -associated collagen binding integrin expressed on chondrocytes. *J Biol Chem* 273:20383–20389
- Camper L, Holmval K, Wangnerud C, Aszodi A, Lundgren-Akerlund E (2001) Distribution of the collagen-binding integrin $\alpha 10\beta 1$ during mouse development. *Cell Tissue Res* 306:107–116
- Campos LS, Leone DP, Relvas JB, Brakebusch C, Fassler R, Suter U, French-Constant C (2004) $\beta 1$ integrins activate a MAPK signalling pathway in neural stem cells that contributes to their maintenance. *Development* 131:3433–3444
- Carman CV, Springer TA (2003) Integrin avidity regulation: are changes in affinity and conformation underemphasized? *Curr Opin Cell Biol* 15:547–556
- Caswell CC, Barczyk M, Keene DR, Lukomska E, Gullberg DE, Lukomski S (2008) Identification of the first prokaryotic collagen-sequence motif that mediates binding to human collagen receptors, integrins $\alpha 2\beta 1$ and $\alpha 11\beta 1$. *J Biol Chem* 283:36168–36175
- Chen M, O’Connor KL (2005) Integrin $\alpha 6\beta 4$ promotes expression of autotaxin/ENPP2 autocrine motility factor in breast carcinoma cells. *Oncogene* 24:5125–5130
- Clements JM, Newham P, Shepherd M, Gilbert R, Dudgeon TJ, Needham LA, Edwards RM, Berry L, Brass A, Humphries MJ (1994) Identification of a key integrin-binding sequence in

- VCAM-1 homologous to the LDV active site in fibronectin. *J Cell Sci* 107:2127–2135
- Davis GE (1992) Affinity of integrins for damaged extracellular matrix: alpha v beta 3 binds to denatured collagen type I through RGD sites. *Biochem Biophys Res Commun* 182:1025–1031
- Dickinson CD, Veerapandian B, Dai XP, Hamlin RC, Xuong NH, Ruoslahti E, Ely KR (1994) Crystal structure of the tenth type III cell adhesion module of human fibronectin. *J Mol Biol* 236:1079–1092
- Domogatskaya A, Rodin S, Boutaud A, Tryggvason K (2008) Laminin-511 but not -332, -111, or -411 enables mouse embryonic stem cell self-renewal in vitro. *Stem Cells* 26:2800–2809
- Emsley J, King SL, Bergelson JM, Liddington RC (1997) Crystal structure of the I domain from integrin $\alpha 2\beta 1$. *J Biol Chem* 272:28512–28517
- Forsberg E, Lindblom A, Paulsson M, Johansson S (1994) Laminin isoforms promote attachment of hepatocytes via different integrins. *Exp Cell Res* 215:33–39
- Friedland JC, Lee MH, Boettiger D (2009) Mechanically activated integrin switch controls $\alpha 5\beta 1$ function. *Science* 323:642–644
- Gahmberg CG, Fagerholm SC, Nurmi SM, Chavakis T, Marchesan S, Grönholm M (2009) Regulation of integrin activity and signaling. *Biochim Biophys Acta* 1790:431–444
- Gailit J, Ruoslahti E (1988) Regulation of the fibronectin receptor affinity by divalent cations. *J Biol Chem* 263:12927–12932
- Gardner H, Kreidberg J, Koteliensky V, Jaenisch R (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* 175:301–313
- Geiger B, Spatz JP, Bershadsky AD (2009) Environmental sensing through focal adhesions. *Nat Rev Mol Cell Biol* 10:21–33
- Genersch E, Ferletta M, Virtanen I, Haller H, Ekblom P (2003) Integrin $\alpha v\beta 3$ binding to human $\alpha 5$ -laminins facilitates FGF-2- and VEGF-induced proliferation of human ECV304 carcinoma cells. *Eur J Cell Biol* 82:105–117
- 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
- Hauck CR, Agerer F, Muenzner P, Schmitter T (2006) Cellular adhesion molecules as targets for bacterial infection. *Eur J Cell Biol* 85:235–242
- 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
- Hierck BP, Thorsteinsdottir S, Niessen CM, Freund E, Iperen LV, Feyen A, Hogervorst F, Poelmann RE, Mummery CL, Sonnenberg A (1993) 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. *Cell Adhes Commun* 1:33–53
- Honda S, Shirota-Ikejima H, Tadokoro S, Maeda Y, Kinoshita T, Tomiyama Y, Miyata T (2009) Integrin-linked kinase associated with integrin activation. *Blood* 113:5304–5313
- Horwitz A, Duggan K, Greggs R, Decker C, Buck C (1985) The cell substrate attachment (CSAT) antigen has properties of a receptor for laminin and fibronectin. *J Cell Biol* 101:2134–2144
- Humphries MJ (2000) Integrin structure. *Biochem Soc Trans* 28:311–339
- Humphries MJ, Symonds EJ, Mould AP (2003) Mapping functional residues onto integrin crystal structures. *Curr Opin Struct Biol* 13:236–243
- Humphries JD, Byron A, Humphries MJ (2006) Integrin ligands at a glance. *J Cell Sci* 119:3901–3903
- Hynes RO (2002) Integrins: bidirectional, allosteric signaling machines. *Cell* 110:673–687
- Hynes RO (2004) The emergence of integrins: a personal and historical perspective. *Matrix Biol* 23:333–340
- Ido H, Harada K, Futaki S, Hayashi Y, Nishiuchi R, Natsuka Y, Li S, Wada Y, Combs AC, Ervasti JM, Sekiguchi K (2004) Molecular dissection of the alpha-dystroglycan- and integrin-binding sites within the globular domain of human laminin-10. *J Biol Chem* 279:10946–10954
- Ithychanda SS, Das M, Ma YQ, Ding K, Wang X, Gupta S, Wu C, Plow EF, Qin J (2009) Migfilin, a molecular switch in regulation of integrin activation. *J Biol Chem* 284:4713–4722
- Jacques TS, Relvas JB, Nishimura S, Pytela R, Edwards GM, Streuli CH, French-Constant C (1998) Neural precursor cell chain migration and division are regulated through different beta1 integrins. *Development* 125:3167–3177
- Jensen UB, Lowell S, Watt FM (1999) The spatial relationship between stem cells and their progeny in the basal layer of human epidermis: a new view based on whole-mount labelling and lineage analysis. *Development* 126:2409–2418
- Johnson MS, Lu N, Denessiouk K, Heino J, Gullberg D (2009) Integrins during evolution: evolutionary trees and model organisms. *Biochim Biophys Acta* 1788:779–789
- Jones PH, Harper S, Watt FM (1995) Stem cell patterning and fate in human epidermis. *Cell* 80:83–93
- Kapyla J, Jaalinoja J, Tulla M, Ylostalo J, Nissinen L, Viitasalo T, Vehvilainen P, Marjomaki V, Nykvist P, Saamanen AM, Farndale RW, Birk DE, Ala-Kokko L, Heino J (2004) The fibril-associated collagen IX provides a novel mechanism for cell adhesion to cartilaginous matrix. *J Biol Chem* 279:51677–51687
- Kiema T, Lad Y, Jiang P, Oxley CL, Baldassarre M, Wegener KL, Campbell ID, Ylanne J, Calderwood DA (2006) The molecular basis of filamin binding to integrins and competition with talin. *Mol Cell* 21:337–347
- Knight CG, Morton LF, Onley DJ, Peachey AR, Messent AJ, Smethurst PA, Tuckwell DS, Farndale RW, Barnes MJ (1998) Identification in collagen type I of an integrin $\alpha 2\beta 1$ -binding site containing an essential GER sequence. *J Biol Chem* 273:33287–33294
- Knudsen KA, Horwitz AF, Buck CA (1985) A monoclonal antibody identifies a glycoprotein complex involved in cell-substratum adhesion. *Exp Cell Res* 157:218–226
- Komoriya A, Green LJ, Mervic M, Yamada SS, Yamada KM, Humphries MJ (1991) The minimal essential sequence for a major cell type-specific adhesion site (CS1) within the alternatively spliced type III connecting segment domain of fibronectin is leucine-aspartic acid-valine. *J Biol Chem* 266:15075–15079
- Kunneken K, Pohlentz G, Schmidt-Hederich A, Odenthal U, Smyth N, Peter-Katalinic J, Bruckner P, Eble JA (2004) Recombinant human laminin-5 domains. Effects of heterotrimerization, proteolytic processing, and N-glycosylation on $\alpha 3\beta 1$ integrin binding. *J Biol Chem* 279:5184–5193
- Larjava H, Plow EF, Wu C (2008) Kindlins: essential regulators of integrin signalling and cell-matrix adhesion. *EMBO Rep* 9:1203–1208
- Larson RS, Corbi AL, Berman L, Springer T (1989) Primary structure of the leukocyte function-associated molecule-1 alpha subunit: an integrin with an embedded domain defining a protein superfamily. *J Cell Biol* 108:703–712
- Lau TL, Kim C, Ginsberg MH, Ulmer TS (2009) The structure of the integrin $\alpha IIb\beta 3$ transmembrane complex explains integrin transmembrane signalling. *EMBO J* 28:1351–1361
- Lee JO, Bankston LA, Arnaout MA, Liddington RC (1995) Two conformations of the integrin A-domain (I-domain): a pathway for activation? *Structure* 3:1333–1340
- Legate KR, Fassler R (2009) Mechanisms that regulate adaptor binding to beta-integrin cytoplasmic tails. *J Cell Sci* 122:187–198
- Legate KR, Wickstrom SA, Fassler R (2009) Genetic and cell biological analysis of integrin outside-in signaling. *Genes Dev* 23:397–418

- Leptin M, Aebersold R, Wilcox M (1987) *Drosophila* position-specific antigens resemble the vertebrate fibronectin-receptor family. *EMBO J* 6:1037–1043
- Linton JM, Martin GR, Reichardt LF (2007) The ECM protein nephronectin promotes kidney development via integrin $\alpha 8$ - $\beta 1$ -mediated stimulation of Gdnf expression. *Development* 134:2501–2509
- Luo BH, Springer TA (2006) Integrin structures and conformational signaling. *Curr Opin Cell Biol* 18:579–586
- Luo BH, Carman CV, Springer TA (2007) Structural basis of integrin regulation and signaling. *Annu Rev Immunol* 25:619–647
- Mark H von der, Williams I, Wendler O, Sorokin L, Mark K von der, Poschl E (2002) Alternative splice variants of $\alpha 7 \beta 1$ integrin selectively recognize different laminin isoforms. *J Biol Chem* 277:6012–6016
- Martin PT, Kaufman SJ, Kramer RH, Sanes JR (1996) Synaptic integrins in developing, adult, and mutant muscle: selective association of $\alpha 1$, $\alpha 7A$ and $\alpha 7B$ integrins with the neuromuscular junction. *Dev Biol* 174:125–139
- Mayer U (2003) Integrins: redundant or important players in skeletal muscle? *J Biol Chem* 278:14587–14590
- Mayer U, Saher G, Fassler R, Bornemann A, Echtermeyer F, Mark H von der, Miosge N, Poschl E, Mark K von der (1997) Absence of integrin $\alpha 7$ causes a novel form of muscular dystrophy. *Nat Genet* 17:318–323
- Michael KE, Dumbauld DW, Burns KL, Hanks SK, Garcia AJ (2009) FAK modulates cell adhesion strengthening via integrin activation. *Mol Biol Cell* 20:2508–2519
- Millward-Sadler SJ, Salter DM (2004) Integrin-dependent signal cascades in chondrocyte mechanotransduction. *Ann Biomed Eng* 32:435–446
- Millward-Sadler SJ, Wright MO, Lee H, Nishida K, Caldwell H, Nuki G, Salter DM (1999) Integrin-regulated secretion of interleukin 4: a novel pathway of mechanotransduction in human articular chondrocytes. *J Cell Biol* 145:183–189
- Moser M, Nieswandt B, Ussar S, Pozgajova M, Fassler R (2008) Kindlin-3 is essential for integrin activation and platelet aggregation. *Nat Med* 14:325–330
- Mu D, Cambier S, Fjellbirkeland L, Baron JL, Munger JS, Kawakatsu H, Sheppard D, Broaddus VC, Nishimura SL (2002) The integrin $\alpha (v)\beta 8$ mediates epithelial homeostasis through MT1-MMP-dependent activation of TGF- $\beta 1$. *J Cell Biol* 157:493–507
- Munger JS, Huang X, Kawakatsu H, Griffiths MJ, Dalton SL, Wu J, Pittet JF, Kaminski N, Garat C, Matthay MA, Rifkin DB, Sheppard D (1999) The integrin $\alpha v\beta 6$ binds and activates latent TGF $\beta 1$: a mechanism for regulating pulmonary inflammation and fibrosis. *Cell* 96:319–328
- Nievers MG, Schaapveld RQ, Sonnenberg A (1999) Biology and function of hemidesmosomes. *Matrix Biol* 18:5–17
- Nishida N, Xie C, Shimaoka M, Cheng Y, Walz T, Springer TA (2006) Activation of leukocyte $\beta 2$ integrins by conversion from bent to extended conformations. *Immunity* 25:583–594
- Nishiuchi R, Murayama O, Fujiwara H, Gu J, Kawakami T, Aimoto S, Wada Y, Sekiguchi K (2003) Characterization of the ligand-binding specificities of integrin $\alpha 3\beta 1$ and $\alpha 6\beta 1$ using a panel of purified laminin isoforms containing distinct α chains. *J Biochem* 134:497–504
- Oxvig C, Springer TA (1998) Experimental support for a b-propeller domain in integrin α -subunits and a calcium binding site on its lower surface. *Proc Natl Acad Sci USA* 95:4870–4875
- Palumbo RN, Wang C (2006) Bacterial invasin: structure, function, and implication for targeted oral gene delivery. *Current Drug Deliv* 3:47–53
- Parise LV, Phillips DR (1985) Reconstitution of the purified platelet fibrinogen receptor. Fibrinogen binding properties of the glycoprotein IIb-IIIa complex. *J Biol Chem* 260:10698–10707
- Parise LV, Phillips DR (1986) Fibronectin-binding properties of the purified platelet glycoprotein IIb-IIIa complex. *J Biol Chem* 261:14011–14017
- Pierschbacher M, Hayman EG, Ruoslahti E (1983) Synthetic peptide with cell attachment activity of fibronectin. *Proc Natl Acad Sci USA* 80:1224–1227
- Ruoslahti E, Pierschbacher MD (1986) Arg-Gly-Asp: a versatile cell recognition signal. *Cell* 44:517–518
- Sacco A, Doyonnas R, Kraft P, Vitorovic S, Blau HM (2008) Self-renewal and expansion of single transplanted muscle stem cells. *Nature* 456:502–506
- Santala P, Heino J (1991) Regulation of integrin-type cell adhesion receptors by cytokines. *J Biol Chem* 266:23505–23509
- Sasaki T, Timpl R (2001) Domain IVa of laminin $\alpha 5$ chain is cell-adhesive and binds $\beta 1$ and $\alpha v\beta 3$ integrins through Arg-Gly-Asp. *FEBS Lett* 509:181–185
- Sato Y, Uemura T, Morimitsu K, Sato-Nishiuchi R, Manabe RI, Takagi J, Yamada M, Sekiguchi K (2009) Molecular basis of the recognition of nephronectin by integrin $\alpha 8\beta 1$. *J Biol Chem* (in press)
- Schulze B, Mann K, Poschl E, Yamada Y, Timpl R (1996) Structural and functional analysis of the globular domain IVa of the laminin $\alpha 1$ chain and its impact on an adjacent RGD site. *Biochem J* 314:847–851
- Schwander M, Leu M, Stumm M, Dorchie OM, Ruegg UT, Schittny J, Muller U (2003) $\beta 1$ integrins regulate myoblast fusion and sarcomere assembly. *Dev Cell* 4:673–685
- Senetar MA, Moncman CL, McCann RO (2007) Talin2 is induced during striated muscle differentiation and is targeted to stable adhesion complexes in mature muscle. *Cell Motil Cytoskeleton* 64:157–173
- Springer TA, Miller LJ, Anderson DC (1986) p150, 95, the third member of the Mac-1, LFA-1 human leukocyte adhesion glycoprotein family. *J Immunol* 136:240–245
- Stewart PL, Nemerow GR (2007) Cell integrins: commonly used receptors for diverse viral pathogens. *Trends Microbiol* 15:500–507
- Suhr F, Brixius K, Bloch W (2009) Angiogenic and vascular modulation by extracellular matrix cleavage products. *Curr Pharma Des* 15:389–410
- Svensson L, Howarth K, McDowall A, Patzak I, Evans R, Ussar S, Moser M, Metin A, Fried M, Tomlinson I, Hogg N (2009) Leukocyte adhesion deficiency-III is caused by mutations in KINDLIN3 affecting integrin activation. *Nat Med* 15:306–312
- Sweeney SM, Orgel JP, Fertala A, McAuliffe JD, Turner KR, Di Lullo GA, Chen S, Antipova O, Perumal S, Ala-Kokko L, Forlino A, Cabral WA, Barnes AM, Marini JC, San Antonio JD (2008) Candidate cell and matrix interaction domains on the collagen fibril, the predominant protein of vertebrates. *J Biol Chem* 283:21187–21197
- Swenson S, Ramu S, Markland FS (2007) Anti-angiogenesis and RGD-containing snake venom disintegrins. *Curr Pharma Des* 13:2860–2871
- Tadokoro S, Shattil SJ, Eto K, Tai V, Liddington RC, Pereda JM de, Ginsberg MH, Calderwood DA (2003) Talin binding to integrin β tails: a final common step in integrin activation. *Science* 302:103–106
- Takada Y, Ye X, Simon S (2007) The integrins. *Genome Biol* 8:215
- Tamkun JW, DeSimone DW, Fonda D, Patel RS, Buck C, Horwitz AF, Hynes RO (1986) Structure of integrin, a glycoprotein involved in the transmembrane linkage between fibronectin and actin. *Cell* 46:271–282
- Tanentzapf G, Devenport D, Godt D, Brown NH (2007) Integrin-dependent anchoring of a stem-cell niche. *Nat Cell Biol* 9:1413–1418

- Taniguchi Y, Ido H, Sanzen N, Hayashi M, Sato-Nishiuchi R, Futaki S, Sekiguchi K (2009) The C-terminal region of laminin beta chains modulates the integrin binding affinities of laminins. *J Biol Chem* 284:7820–7831
- Thorsteinsdottir S, Roelen BA, Freund E, Gaspar AC, Sonnenberg A, Mummery CL (1995) Expression patterns of laminin receptor splice variants $\alpha 6\text{Ab}1$ and $\alpha 6\text{Bb}1$ suggest different roles in mouse development. *Dev Dyn* 204:240–258
- Tiger CF, Fougerousse F, Grundstrom G, Velling T, Gullberg D (2001) $\alpha 11\beta 1$ integrin is a receptor for interstitial collagens involved in cell migration and collagen reorganization on mesenchymal nonmuscle cells. *Dev Biol* 237:116–129
- Valdramidou D, Humphries MJ, Mould AP (2008) Distinct roles of beta 1 MIDAS, ADMIDAS and LIMBS cation-binding sites in ligand recognition by integrin $\alpha 2\beta 1$. *J Biol Chem* 283:32704–32714
- Varas L, Ohlsson LB, Honeth G, Olsson A, Bengtsson T, Wiberg C, Bockermann R, Jarnum S, Richter J, Pennington D, Johnstone B, Lundgren-Akerlund E, Kjellman C (2007) $\alpha 10$ integrin expression is up-regulated on fibroblast growth factor-2-treated mesenchymal stem cells with improved chondrogenic differentiation potential. *Stem Cells Dev* 16:965–978
- Velling T, Collo G, Sorokin L, Durbeej M, Zhang H, Gullberg D (1996) Distinct $\alpha 7\text{A}$ $\beta 1$ and $\alpha 7\text{B}$ $\beta 1$ integrin expression patterns during mouse development: $\alpha 7\text{A}$ is restricted to skeletal muscle but $\alpha 7\text{B}$ is expressed in striated muscle, vasculature, and nervous system. *Dev Dyn* 207:355–371
- Wang J, Springer TA (1998) Structural specializations of immunoglobulin superfamily members for adhesion to integrins and viruses. *Immunol Rev* 163:197–215
- Wilcox M, Brown N, Piovant M, Smith RJ, White RA (1984) The *Drosophila* position-specific antigens are a family of cell surface glycoprotein complexes. *EMBO J* 3:2307–2313
- Wipff PJ, Rifkin DB, Meister JJ, Hinz B (2007) Myofibroblast contraction activates latent TGF- $\beta 1$ from the extracellular matrix. *J Cell Biol* 179:1311–1323
- Xiong JP, Stehle T, Zhang R, Joachimiak A, Frech M, Goodman SL, Arnaout MA (2002) Crystal structure of the extracellular segment of integrin $\alpha \text{V}\beta 3$ in complex with an Arg-Gly-Asp ligand. *Science* 296:151–155
- Zhu CQ, Popova SN, Brown ER, Barsyte-Lovejoy D, Navab R, Shih W, Li M, Lu M, Jurisica I, Penn LZ, Gullberg D, Tsao MS (2007) Integrin $\alpha 11$ regulates IGF2 expression in fibroblasts to enhance tumorigenicity of human non-small-cell lung cancer cells. *Proc Natl Acad Sci USA* 104:11754–11759
- Zutter MM, Santoro SA (1990) Widespread histologic distribution of the $\alpha 2\beta 1$ integrin cell-surface collagen receptor. *Am J Pathol* 137:113–120