AT-A-GLANCE ARTICLE

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 αβ 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 αI domain, including the collagen-binding integrins α1β1, α2β1, α10β1, and α11β1. 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.

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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 β1 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 β1 integrins, β2 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 β2 integrin subgroup of integrins, in the collagen-binding integrins belonging to the β1 subfamily (α1, α2, α10, and α11), and the αE integrin chain forming the αEβ7 heterodimer. The I domain assumes a Rossman 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

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α subunit - determines integrin ligand specificity.
αI domain - inserted domain of approx 200 amino acids, present in 9 integrin α subunits.
MIDAS - Metal **i**on **d**ependent **a**dhesion **s**ite, 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	αI	Prototypic ligands/ recognition sequences	Additional ligands
α1β1 (CD49a, VLA1)	1151 aa		X	collagens (collagen IV > collagen I (GFOGER); collagen IX)	semaphorin 7A
α2β1 (CD49b, VLA2)	1181 aa		X	collagens (collagen I >collagen IV (GFOGER); collagen IX)	E-cadherin, endorepellin
α3β1 (CD49c, VLA3)	1051 aa, splice variants α3 A and α3B	X		laminins (LN-511>LN-332>LN-211)	
α4β1 (CD49d, VLA4)	1038 aa			fibronectin VCAM-1	
α5β1 (CD49e, VLA5)	1049 aa	X		fibronectin (RGD)	endostatin
α6β1 (CD49f, VLA6)	1073 aa, splice variants α6A and α6B	X		laminins (LN-511>LN-332>LN-111>LN-411)	
α7β1	1137 aa, splice variants X1, X2, α7A, α7B	X		α7X1β1: laminins (LN-511>LN-211>LN-411>LN-111) α7X2β1: laminins (LN-111>LN-211>LN-511)	
α8β1	1025 aa	X		fibronectin, vitronectin, nephronectin (RGD)	
α9β1	1035 aa			tenascin-C, VEGF-C, VEGF-D	
α10β1	1167 aa		X	collagens (collagen IV> collagen VI >collagen II (GFOGER); collagen IX)	
α11β1	1188 aa, inserted domain 21 aa		X	collagens (collagen I>collagen IV (GFOGER); collagen IX)	
αLβ2 (CD11a)	1170 aa		X	ICAM-1, -2, -3, -5	
αMβ2 (CD11b)	1153 aa		X	iC3b, fibrinogen + more	
αXβ2 (CD11c)	1163 aa		X	iC3b, fibrinogen + more	
αDβ2 (CD11d)	1162 aa		X	ICAM-3, VCAM-1	
αIIBβ3 (CD41, GpIIb)	1039 aa	X		fibrinogen, fibronectin (RGD)	
α6β4		X		laminins (LN-332, LN-511)	
αvβ1 (CD51)	1048 aa	X		fibronectin, vitronectin (RGD)	
αvβ3		X		vitronectin, fibronectin, fibrinogen (RGD)	tumstatin
αvβ5		X		vitronectin (RGD)	
αvβ6		X		fibronectin, TGF-β-LAP (RGD)	
αvβ8		X		vitronectin, TGF-β-LAP (RGD)	
αEβ7 (CD103, HML-1)	1178 aa	X	X	E-cadherin	
α4β7				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
β1 (CD 29, Gp IIa)	798 aa, splice variants β1A, β1B, β1C, β1D	Splice variants β1B and β1C not present in mice, minor variants with unclear function
β2 (CD18)	769 aa	
β3 (CD 61, GP IIIa)	788 aa, splice variants β3A, β3B and β3C	β3A major form
β4 (CD104, TSP-180)	1875 aa, splice variants β4A-E	β4A and β4B major forms, similar function
β5	799 aa, splice variants β5A, β5B	Both splice variants have similar functions
β6	788 aa	
β7 (LPAM-1, βP)	798 aa	
β8	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
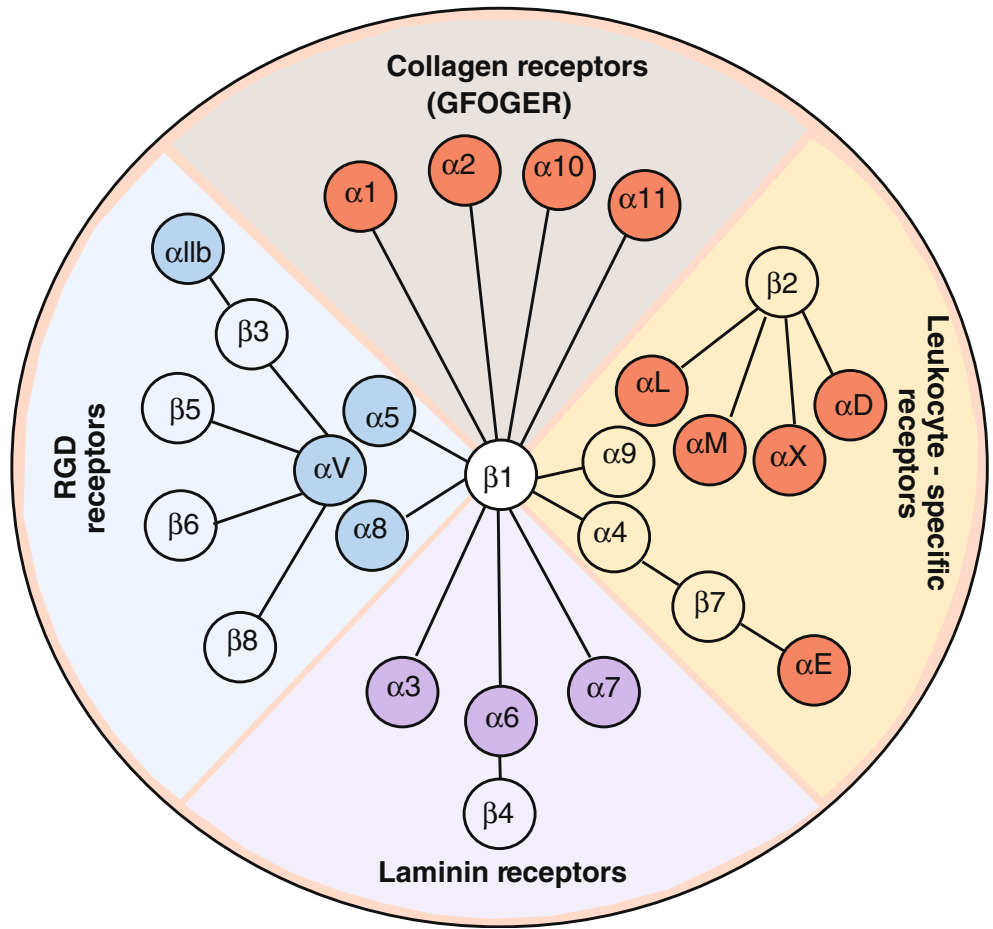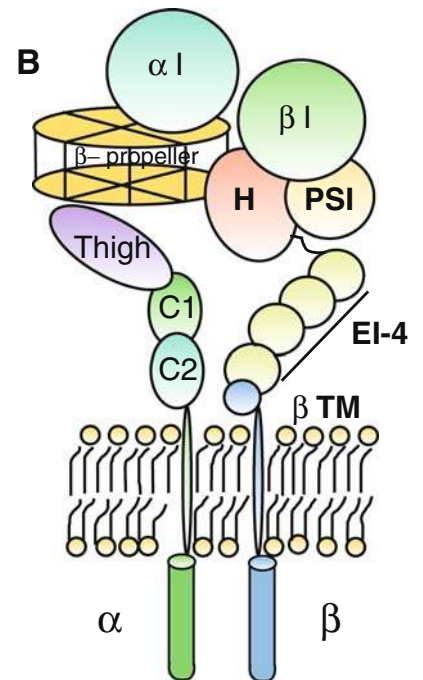

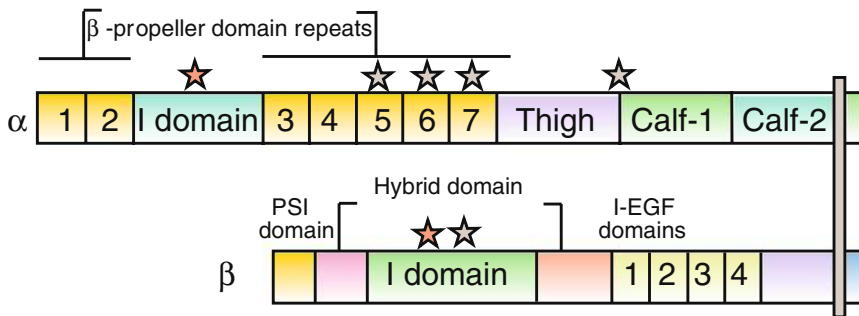**Fig. 3** Representation of a prototypical αI-domain-containing integrin heterodimer. Nine out of the 18 integrin α chains contains an αI domain, as shown, but all integrins contain a βI domain in the β subunit. **A** Representation of the domains in αI domain-containing integrin (*stars* divalent cation-binding sites). **B** Representation of arrangement of domains in αI-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-sempahorin-integrin (PSI) domain, a hybrid domain, a βI domain (Lee et al. 1995), and four cysteine-rich epidermal growth factor (EGF) repeats. The βI 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.
> **βI domain -** I domain-like region, takes part in ligand binding in non-αI containing integrins, metal ion binding.
> **ADMIDAS -** region adjacent to MIDAS in βI 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 αIIb and β3 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 heteodimer 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 α5β1, the mechanical tension induces α5β1 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 αIIβ3 and β2 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 βI domain, with the α chain being central in determining ligand specificity. Integrins with an αI domain bind ligands via the αI 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 αI domains, interactions with the β chain are even needed for the proper folding of the αI 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 αvβ6 and αvβ8, by binding RGD in LAP, are the major integrins that activate TGF-β in vivo either by allosteric changes in TGF-β-LAP (αvβ6) or by inducing matrix metalloproteinase-14 and causing proteolytic release of TGF-β (αvβ8; Aluwihare et al. 2009; Mu et al. 2002; Munger et al. 1999). More recently, a mechanical-strain-dependent contribution of myofibroblast β1 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 α5 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 αvβ1- and αvβ3-mediated binding to laminin-α5-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-specifc 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 α7 affects it 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 α11β1 integrin, if cartilaginous tissue is not dissected free of perichondrium, a signal from α11 will be derived from α11 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 α11β1-expressing cells over α2β1-expressing cells (Caswell et al. 2008).

Other integrin-binding motifs include the α4-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 β2 integrins and the α4β7 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 (Drosophila)	βPS3	(Tanentzapf et al. 2007)
Epidermal stem cells	β1 integrins	(Jensen et al. 1999, Jones et al. 1995)
Chondrogenic mesenchymal stem cells (human)	**α10**	(Varas et al. 2007)
Neural stem cells	β1 integrins	(Campos et al. 2004, Jacques et al. 1998)
Embryonic stem cells	α6B	(Hierck et al. 1993)
Satellite cells	**α7**	(Mayer 2003, Mayer et al. 1997, Sacco et al. 2008)
Epithelial cells	α6, α3	(Thorsteinsdottir et al. 1995)
Fibroblasts	**α11**, α2, α1, α5	(Gardner et al. 1996, Tiger et al. 2001, Zutter and Santoro 1990)
Endothelial cells	α1, α2, α6	(Gardner, Kreidberg, Koteliansky 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 α3 (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 α6β4 connects to the intermediate filament system (Nievers et al. 1999). Recently, the intermediate filament protein vimentin has been shown to be dependent on β3 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	α1	+	No phenotype. Cell adhesion defect to collagen IV.	Reduced tumor angiogenesis, increased glomeruloscleriosis, diminished callus size in bone fracture model, reduced atheroslcerosis in ApoE-/- mice, reduced psoriasis in xenograft model.
	α2	+	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 Listera infection, reduced thrombi formation increased embolization in thrombosis model.
	α10	+	Mild cartilage defect.	
	α11	+	Incisor eruption defect.	
Laminins	α3	+/-	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.
	α6	+/-	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.	
	α7	- 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.
RGD	α5	-	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.	
	α8	+/-	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.	
	α4	-	Embryonic lethality either due to failure of chorioalloantoic fusion or cardiac abnormalities including defects in epicardium formation.	
	α9	+/-	Bilaterlal chylothorax causing death within 14 days.	Altered cutaneous wound healing in wound model.
Leucocyte spesific	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.
	β1	-	Null mutants die soon after implantation due to inner cell mass defects in blastocysts.	
	β2	+	Leukocyte adhesion deficiency with immune, hematopoietic and skeleton defects.	Reduced listeriosis.
	β3	- 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.
	β4	+/-	Extensive detachment of epidermis and other squamous epithelia. Stratified tissues lack hemidesmosomes and simple epithelia are also defective in adherence.	
	β5	+	Age-related blindness due to defective retinal phagocytosis. Cell adhesion defect of keratinocytes to vitronectin.	Reduced lung injury in a ventilator-induced model.
	β6	+	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.
	β7	+	Hypoplasia of gut-associated lymph tissue due to defects in lymphocyte migration.	
	β8	+ 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 if often developmentally regulated.

Most cells in the body express β1 integrin, and the use of β1 as part of a stem cell signature should thus be used with some caution. However, β1 integrin expression levels have been successfully used as a marker for epidermal stem cells, which express high levels of β1 integrins (Jensen et al. 1999). In *Drosophila*, the finding that βPS3 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 α6β1 and αvβ1 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 α10/α11 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 β1 integrins in cartilage and skeletal muscle, respectively, and indicate important roles for β1 integrins during myogenesis and chondrogenesis (Aszodi et al. 2003; Schwander et al. 2003). The specific β1 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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