Preface

What Has Been

The integrin family is composed of 24 members [5]. Ten years ago we published a book devoted to the nine αI domain integrin subunits [24]. These are shown in Fig. 1. I am pleased that most of the original authors have been able to contribute to the updated version.

In 2003, the knockout mouse phenotypes for all of the αI domain integrins had not yet been published. They are now. The phenotypes of mouse strain deficient in individual αI integrins are summarized in Table 1.

During the last decade we have learned more about the role of β2 integrins in leukocytes and in leukocyte adhesion deficiencies [29, 27], and the role of β7 integrins in different subsets of immune cells [20]. Much of this knowledge would not have been possible without the use of animal models and have generated results which could not have been predicted from in vitro analyses. Separate from the interesting results in disease models, analyses of αE knockout mice indicate that there is a missing ligand that has not yet been identified for this integrin [20]. Indeed, in human skin and oral mucosa, there is evidence of a ligand for αEβ7 other than E-cadherin [30].

Regarding the role of collagen-binding integrins the knockout phenotypes of mice deficient in integrin α10 and α11, respectively, have now been published [6, 45] and interestingly the enigmatic DDR collagen receptors have recently been shown to affect the function of collagen-binding integrins [1, 53, 62]. In coming years we are likely to learn more about the cross-talk of collagen-binding integrins with other receptor groups. Maybe most surprising in the field of collagen receptors are the relatively mild phenotypes seen in individual knockout strains and the limited role collagen-binding integrins appear to play in classical connective tissue diseases like fibrosis. This is in contrast to the phenotypes observed for different members of the collagen family, where mutants are characterized by major structural defects impacting tissue structure during development and tissue integrity in adult animals [63]. This discrepancy between collagen and collagen receptor-knockout mouse phenotypes is summarized in Table 2. Interestingly, a recent α10 integrin mutation in dogs have indicated that collagen-binding integrins in the muscoskeletal system might have much more severe phenotypes in larger animals/humans compared to the mild integrin phenotypes observed in collagen-binding integrin deficient mice [33].

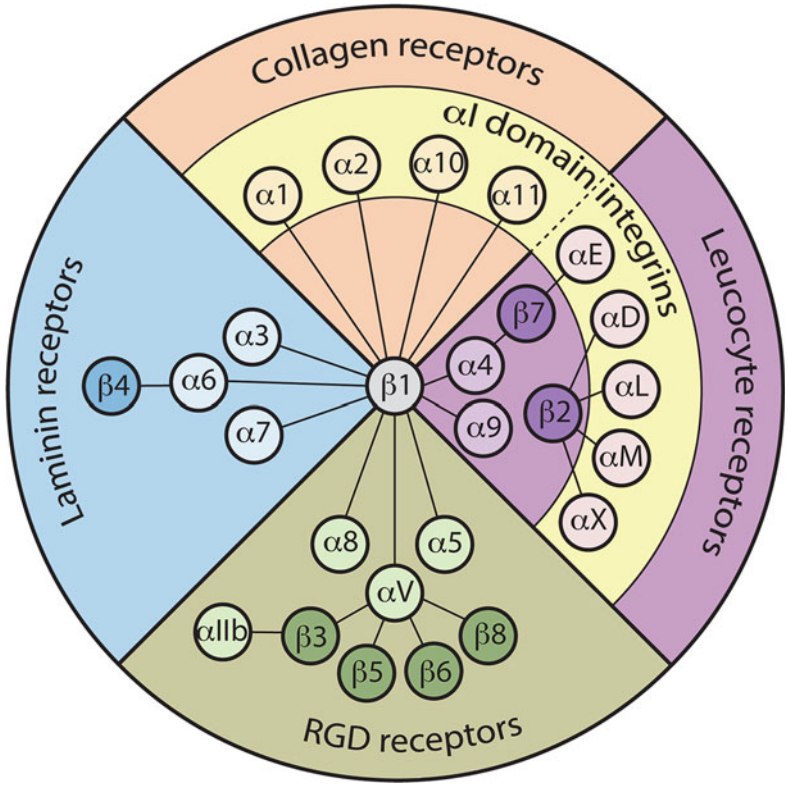

Fig. 1 The integrin family

Table 1 αI integrin knockout phenotypes

Integrin subunit	Distribution	Ligands	Knockout viability	Knockout phenotype
Collagen receptors				
α1	Endothelial cells, smooth muscle cells, fibroblasts, and more cell types [19]	Collagens	+	Normal development [19], hypocellular dermis [18, 47], isolated cells display defect in collagen IV cell attachment
α2	Platelets, epithelial cells, endothelial cells [65], mesenchymal stem cells [44], fibroblasts, and more cell types	Collagens	+	Mild mammary gland phenotype, otherwise normal development [13, 28], cell attachment defect to collagen I of isolated platelets [49], needed for thrombus stabilization [32]
α10	Chondrocytes and subsets of junctional fibroblasts [9, 10]	Collagens	+	Mild cartilage phenotype [6]
α11	Subsets of fibroblasts [46, 55, 57], cancer associated fibroblasts [64], increased levels on myofibroblasts [11], developmental expression in odontoblasts, mesenchymal stem cells [44], induced in cultures of mesenchymally derived cells including myoblasts (do not express α11 in vivo) [25]	Collagens	+	Defective incisor eruption [45], dwarfism [8], increased mortality
Leucocyte receptors				
αD	Macrophages and eosinophils [23, 56]	ICAM-3, VCAM-1	+	Fertile, no gross abnormalities, mild T-cell phenotypic changes [61]
αE	Intraepithelial lymphocytes, some circulating lymphocytes, lamina propria lymphocytes, subsets of CD4+ T-cells, CD8+ T-cells, dendritic cells, mast cells [12, 31, 35]	E-cadherin, uncharacterized ligand	+	Impaired development of gut associated lymphoid tissue [51]
αL	All leucocytes [54]	ICAM-1,-2,-3,-4,-5, JAM-1	+	Splenomegaly and reduced lymph node size [50], increased white blood cells counts [15], reduced lymphocyte homing [7], reduced neutrophil adhesion [15], Treg and NKT cell development affected [42, 59] reduced T-cell proliferation and co-stimulation [21, 50, 52]
αM	Monocytes, macrophages, NK cells, neutrophils, and subsets of T-cells [22, 34, 41]	iC3b, fibrinogen, and more ligands	+	Neutrophil phagocytosis and degranulation reduced [14, 40], impaired mast cell development and function [48], excessive macrophage and dendritic cell toll-like receptor signaling [26, 4], excessive Th17 differentiation [17]
αX	Monocytes, macrophages, dendritic cells, NK cells [41]	iC3b, fibrinogen and more ligands	+	Fertile, no gross abnormalities, affects monocyte firm adhesion [60]

Table 2 Phenotypes of mice deficient in fibrillar collagens and integrin collagen receptors

Ligand			Receptor		
Fibrillar collagen	KO phenotype in mouse	KO phenotype in human	Putative collagen receptor in vivo	Correlation KO phenotypes collagen/ receptor in mouse	KO phenotype in human/dog
I	Mov13 mice [39]: embryonic lethality E12-14, major blood vessel rupture	EDS[a] VIIA, EDS VIIB, OI[b], osteoporosis, joint hypermobility	$\alpha2\beta1$ $\alpha11\beta1$	Not in single integrin mutant strains	?
II	Perinatal lethality [2, 36] short long bones, rudimentary vertebral arches, lack of inter-vertebral discs, notochord defect	Lethal achondrogenesis II, osteochondrodysplasia, osteoarthrosis	$\alpha1\beta1$ $\alpha2\beta1$ $\alpha10\beta1$	$\alpha10$ integrin mutation [6], mild cartilage defect $\beta1$ integrin [3], severe cartilage defect	Chondrodysplasia in dogs, integrin $\alpha10$ mutation [33], severe cartilage phenotype
III	Neonatal lethality [38], 5 % survival with shorter lifespan, intestinal defect, skin lesions, arterial rupture	EDS IV, arterial aneurysms	$\alpha2\beta1$ $\alpha11\beta1$	?	?
V	Embryonic lethality E10-11 [58], cardiovascular insufficiency, lack of collagen fibrillogenesis	EDS I, EDS II	$\alpha2\beta1$ $\alpha11\beta1$	?	?
XI	Cho mice: perinatal lethality by asphyxia [37], weak tracheal cartilage, short snout and mandible, cleft palate, short limbs, externally rotated distal portion of hindlimbs	Schmid chondrodysplasia, non-syndromic hearing loss, osteoarthrosis	$\alpha2\beta1$ $\alpha10\beta1$ $\alpha11\beta1$	$\alpha10$ integrin mutation [6], mild cartilage defect $\beta1$ integrin [3], severe cartilage defect	Chondrodysplasia in dogs, integrin $\alpha10$ mutation [33], severe cartilage phenotype
XXIV	?	?		?	?
XXVII	Mutant transgene [43]: perinatal lethality, lung defect, chondrodysplasia	?	$\alpha2\beta1$ $\alpha11\beta1$	?	?

a Ehlers–Danlos syndrome
b Osteogenesis imperfecta

What Will Come

As in all biological fields, techniques are moving the fields forward as methods become more refined. We now have access to new tools, enabling studies at the nano-scale, and reagents designed to block integrin function can thus be applied to nanoparticles.

In the cancer field, the microenvironment is taking center stage, and here integrins on fibroblasts are predicted to play important roles in paracrine signaling, in regulating tissue stiffness [16] and matrix remodeling.

With exome sequencing of rare genetic diseases becoming more widely used, this will enable new human integrin mutations to be tested in disease models. The development of new molecular techniques to more easily generate mutations in vivo might also contribute to more animal disease models being established.

New technologies, new mouse models in combination with analyses of αI integrins in larger animals/humans are thus predicted to increase our knowledge about this group of receptors. With these things in mind we look forward to another 10 years of research with αI domain integrins.

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Bergen, March 2014 Donald Gullberg

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