INTEGRINS: ATTACHMENT STRUCTURES AND MATRIX RECEPTORS

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Mainiero et al. Signal transduction by the α6β4 integrin: distinct β4 subunit sites mediate recruitment of Shc/Grb2 and association with the cytoskeleton of hemidesmosomes. EMBO J. 14:4470-4481, 1995.

Mainiero et al. The coupling of α6β4 integrin to Ras-MAP kinase pathways mediated by Shc controls keratinocyte proliferation. EMBO J. 16, 2365-2375, 1997.

These two paper provide evidence for a role of α6β4 as a signaling molecule that regulates proliferation in response to the interaction of cells with laminin. One of these signals is mediated by Shc which, after ligation of α6β4, binds to tyrosine phosphorylated β4 and thereby couples the integrin to the Ras-MAP kinase pathways.

Margia et al. Cell cycle and adhesion defects in mice carrying a targeted deletion of the integrin β4 cytoplasmic domain. EMBO J. 17: 3940-3951, 1998.

This paper documents the targeted deletion of the β4 cytoplasmic domain in a mouse model and demonstrates that the interactions mediated by the β4 tail are crucial for the assembly of hemidesmosomes and the stable adhesion of basal keratinocytes to the underlying basement membrane. Furthermore, it is shown that the β4 tail is essential for proper cell cycle control in basal keratinocytes and intestinal epithelial cells. The phenotype of these mice is very similar to that of mice carrying a null mutation at the α6 or β4 locus (Dowling et al., J. Cell Biol. 134: 559-572, 1996; George-Labouesse et al., Nature Genet. 13: 370-373, 1996; van der Neut et al., Nature Genet. 13: 366-369, 1996).

Hopkinson et al. Interaction of BP 180 (Type XVII collagen) and α6 integrin is necessary for stabilization of hemidesmosome structure J. Invest. Dermatol. 111: 1015-1022, 1998.

This paper extends previous work by the same group (Hopkinson et al., J. Cell Biol. 130: 117-126, 1995) and provides further support for an interaction of the bullous pemphigoïd antigen 180 (BP 180) with the integrin α6 subunit in a region of its extracellular domain, the NC16A domain. The interaction between BP180 and the β4 subunit of the α6β4 integrin that has been identified by Borradori et al. (J. Cell Biol. 136: 1333-1347, 1997) and Schaapveld et al. (J. Cell Biol. 142: 271-284, 1998) is dependent on sequences within the cytoplasmic domain of BP180. Transfection studies have shown that this interaction is crucial for the incorporation of BP180 into hemidesmosomes. The interaction between BP180 and α6, on the contrary, may be more important for the stabilization of hemidesmosomes (see also Borradori and Sonnenberg, J. Invest Dermatol. 112: 411-418, 1999 and Nievers et al., Matrix Biol. 18: 5-17, 1999).

Rezniczek et al. Linking integrin α6β4-based cell adhesion to the intermediate filament cytoskeleton: Direct interaction between the β4 subunit and plectin at multiple molecular sites. J Cell Biol. 141: 209-225, 1998.

Blot overlay assays and transfection experiments were used to show that plectin and β4 interact with each other at multiple sites. A major binding site for the integrin β4 was found to be contained

within the carboxy terminus of plectin and an additional site in the amino-terminal globular domain of plectin. Two separate plectin binding sites were identified in the cytoplasmic domain of β4 and were localized within the segment connecting the two pairs of fibronectin repeats, the other in the ultimate domain of the β4 tail. These results are essentially different from those reported by Geerts et al. (J. Cell Biol., in press).

Schaapveld et al. Hemidesmosome formation is initiated by the β4 integrin subunit, requires complex formation of β4 and HD1/plectin, and involves a direct interaction between β4 and the Bullous Pemphigoid Antigen 180. J. Cell Biol. 142: 271-284, 1998.

This paper together with a previous paper (Borradori et al., J. Cell Biol. 136: 1333-1347, 1997) by the same group provide evidence that the β4 cytoplasmic domain is involved in the localization of BP180 into hemidesmosomes. Evidence is presented that BP180 can directly interact with β4 and that the binding site of BP180 on β4 is distinct from the region of the β4 cytoplasmic domain that is required for the localization of plectin into hemidesmosomes. Furthermore, it is shown that the β4 cytoplasmic domain is folded back upon itself.

Geerts et al. Binding of integrin α6β4 to plectin prevents plectin association with F-actin but does not interfere with intermediate filament binding. J. Cell Biol. (in press).

In this paper the authors demonstrate that plectin interacts through its actin binding domain with the integrin β4 tail and that binding of β4 to plectin prevents the latter from interacting with actin. This ability of β4 to prevent binding of F-actin to plectin explains why F-actin has never been found in association with hemidesmosomes and provides a molecular mechanism for a switch in plectin localization, from actin filaments to basal intermediate filament-anchoring hemidesmosomes, when α6β4 is expressed.

Nievers et al. Ligand-independent role of the β4 integrin subunit in the formation of hemidesmosomes. J. Cell Sci. 111: 1659-1672, 1998.

Homan et al. Endothelial cells assemble two distinct α6β4-containing vimentin-associated structures: roles for ligand binding and the β4 cytoplasmic tail. J. Cell Sci. 111: 2717-2728, 1998.

These two papers provide evidence that in the absence of an extracellular ligand, the integrin α6β4 can still become clustered at the basal surface of cells and initiate the formation of hemidesmosome-ike structures. Furthermore, it is shown that the essential information for clustering is localized in the region which contains the first pair of type III fibronectin repeats and 27 amino acids of the connecting segement. This region also happens to be the minimal binding site for plectin. In endothelial cells, the integrin α6β4 is concentrated in fibrillar structures, which in addition to plectin also contain vimentin.

De Pereda et al. Crystal structure of a tandem pair of fibronectin type III domains from the cytoplasmic tail of integrin α6β4**.** EMBO J. 18: 4087-4095, 1999.

In this study, the authors present the crystal structure of the first tandem fibronectin repeats in the cytoplasmic domain of the integrin β4 subunit. The structure reveals two candidate protein binding motifs: a large acidic cleft formed form the surfaces of the two fibronectin type III repeats and a prominent loop composed of five amino acids (NDDNR) that protrudes from the body of the second fibronectin repeat in a manner reminiscent of the integrin-binding RGD loop of the tenth fibronectin type III repeat.

Andrä et al. Not just scaffolding: plectin regulates actin dynamics in cultured cells. Genes & Dev. 12: 3442-3451, 1998.

This paper provides data showing that plectin not only provides cells with mechanical strength by scaffolding the actin cytoskeleton, but is also a regulator of cellular processes involving actin filament dynamics. It is shown that plectin deficient fibroblasts respond differently to stimuli activating the small GTP binding proteins Rho/Rac/Cdc42. They displayed an increase in the number of actin stress fibers and focal contacts, and associated changes in adhesion and migration.

Yang et al. Integrators of the cytoskeleton that stabilizes microtubules. Cell 98: 229-238, 1999.

This paper documents the characterization of a new sensory neural isoform of the BPAG1 gene (BPAG3n), and demonstrates that this isoform which lacks the amino-terminal half of the actin binding domain, is preferentially associated with microtubules and contains a microtubule binding domain. This domain is also a feature of BPAG1n and BPAG2n, two differentially expressed isoforms of BPAG1 which are associated exclusively with actin and intermediate filament cytoskeletons and of the epidermal specific isoform of BPAG1 (BPAG1e or BP230), which is associated with hemidesmosomes in basal keratinocytes. Ablation of BPAG1e in keratinoytes has previously been shown to severs keratin intermediate filaments from hemidesmosomes, resulting in intracellular fragility at the base of the epithelium (Guo et al., Cell 81: 233-243, 1995).

Rabinovitz et al. Protein kinase C-dependent mobilization of the α6β4 integrin from hemidesmosomes and its association with actin-rich cell protrusions drive the chemotactic migration of carcinoma cells. J. Cell Biol. 146: 1147-1159, 1999.

In previous studies by the same group, it has been shown that α6β4 participates in the chemotactic migration of carcinoma cells by interacting with the actin cytoskeleton at their leading edge (Rabinovitz et al,. J. Cell Biol. 139:1873-1884, 1997) and activating distinct signaling pathways including PI3K (Shaw et al., Cell 91:949-960, 1997) and cAMP-specific phosphodiesterase (O'Conner et al., J. Cell Biol. 143:1749-1760, 1998). In this study, the authors demonstrate that the EGF stimulated chemotaxis of the squamous carcinoma derived A431 cells is associated with the redistribution of α6β4 from hemidesmosomes to cell protrusion and that this redistribution occurs by a mechanism that involves the activation of protein kinase Ca and the phosphorylation of the β4 integrin subunit on serine residues.

Goldfinger et al. The α3 laminin subunit, α6β4 and α3β1 integrin coordinately regulate wound healing in cultured epithelial cells and in the skin. J. Cell Sci. 112: 2615-2629, 1999.

This paper extends previous work by the same group that proteolytic processing within the globular domain of the α3 subunit of laminin-5 converts laminin-5 from a matrix protein, which supports cell motility to one that triggers the formation of hemidesmosomes (Goldfinger et al. J. Cell Biol. 141: 255-265, 1998). Using a newly generated monoclonal antibody against the globular domain of the α3 subunit, the authors show that the unprocessed laminin α3 chain is expressed in skin wound in vivo and at the leading edge of the migrating sheet of epithelial cells repopulating scrape wounds in vitro, where it is colocalized with the integrin α3β1. The processed laminin α3 form is found in the more distal regions of the migrating sheet where it may play a role in stabilizing cell-substrate interactions via the integrin α6β4.

Jones, J.C. et al. Structure and assembly of hemidesmosomes. Bioessays 20, 488-494, 1998.

Borradori and Sonnenberg, Structure and function of hemidesmosomes: more than simple adhesion

complexes. J. Invest. Dermatol. 112: 411-418, 1999.

Nievers et al. Biology and function of hemidesmosomes 18: 5-17, 1999.

Three recent reviews on the structural biology of hemidesmosomes. The authors discuss the different protein-protein interactions that are involved in the assembly of hemidesmosomes and describe results that indicate an important role of α6β4 as a signaling molecule, controlling proliferation, migration, differentiation and apoptosis.