Integrins and Actin Filaments: Reciprocal Regulation of Cell Adhesion and Signaling

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Integrin adhesion receptors link the extracellular matrix (ECM) to the actin cytoskeleton and transmit biochemical signals and mechanical force across the plasma membrane. This enables cells to generate traction during migration and exert tension during matrix remodeling (1). Cytoskeletal linkages also enable integrins to mediate cell adhesion and regulate cell shape and gene expression (1). Here we will summarize the evidence for direct interactions between integrin cytoplasmic tails and specific actin-binding proteins and discuss how these interactions influence cell adhesion. We will also discuss how some of these same interactions may promote dynamic changes in the actin cytoskeleton to promote cell spreading and migration.

**Role of integrin cytoplasmic tails in integrin-cytoskeletal linkages.** Integrin α and β subunits are type I transmembrane proteins expressed in surface membranes as heterodimers. Each consists of a large extracellular domain, a single transmembrane segment and a relatively short cytoplasmic tail. The latter contain anywhere from 20 to 70 amino acid residues, with the notable exception of the much larger β4 tail, which is linked primarily to intermediate filaments instead of actin filaments (2). β-cytoplasmic tails are necessary and sufficient to link integrins to the actin cytoskeleton (2). In contrast, there is little evidence to date that α tails are directly linked to the cytoskeleton; indeed the removal of the α1, α4 or αIIb cytoplasmic tail appears to increase β tail-mediated interactions with the cytoskeleton (2). Direct binding of the signaling adapter protein paxillin to α4 cytoplasmic tails has recently been demonstrated and this binding regulates α4β1 mediated cell spreading, migration and stress fiber formation (3). There is direct biochemical support for the interaction of α and β tails with each other (4,5), and for the modulation of this interaction by the binding of ligands to the extracellular domain (6). Consequently, regulated changes in the interactions between the α and β tails may affect integrin-cytoskeletal linkages.
In addition to mediating integrin linkages with the actin cytoskeleton, β cytoplasmic tails are important for adhesion, spreading and migration of cells on ECM, processes dependent on an intact actin cytoskeleton. Integrins typically cluster within “matrix adhesions”, sites of close apposition of the cell membrane to the ECM. Matrix adhesions are extremely dynamic and heterogeneous structures with respect to size, composition and orientation to actin filaments (7). Relatively small ones within filopodia and lamellipodia are sometimes called focal complexes, and the largest ones are usually referred to as focal adhesions (FA), which are aligned at the ends of actin stress fibers (2,8,9). As such, FA represent a morphologically prominent association between integrins and the cytoskeleton, and investigation of integrin targeting to FA has shed light on the mechanisms of integrin-cytoskeletal association.

Mutational analysis of the 47 amino acid β1 cytoplasmic tail has identified 3 clusters of amino acids important for integrin localization to FA, a membrane-proximal region and two conserved NPXY (single letter amino acid code) motifs (10). Deletion analysis and tyrosine-to-alanine (Y/A) mutagenesis have shown that similar motifs in the β3 cytoplasmic tail are important for localization of β3 integrins to FA (11). An additional Thr-containing motif between the two NPXY sites has also been implicated in β2 integrin-cytoskeletal linkages (12).

Specific integrin-cytoskeletal linkages. Integrins are linked to actin filaments by specific actin-binding proteins, and there is now an emerging consensus concerning which proteins are involved (Fig 1).

Talin-mediated linkages. Talin is composed of two ~270 kDa subunits arranged as an antiparallel homodimer (8), and it co-localizes with integrins at certain sites of cell-substratum contact. Talin is a major structural component of FA along with actin and vinculin. It consists of an N-terminal ~50 kDa globular head domain, which includes an ~200 amino acid region with homology to the ezrin radixin and moesin (ERM) family of proteins, and an ~220 kDa, C-
terminal rod domain containing a conserved ILWEQ actin-binding domain (8,13). Talin contains binding sites for actin, vinculin, focal adhesion kinase, phospholipids and the transmembrane protein laylin (8,14). Talin was the first actin-binding protein shown to directly bind integrins, and was proposed to mediate the link to the actin cytoskeleton (2). Talin binds to β1, β2, and β3 and more weakly to β7 integrin cytoplasmic tails (15-18). Talin accumulation is an early step in FA formation and requires integrins but not vinculin (19). Microinjection of antibodies to talin, or talin antisense RNA, disrupts stress fibers and inhibits adhesion, spreading and migration of fibroblasts and HeLa cells (8,20).

The significance of talin for integrin function has been underscored by studies of talin-null ES cells, which exhibit extensive membrane blebbing, defects in cell adhesion and spreading, and a failure to assemble FA or stress fibers (21). These results suggest that talin is required for the integrin-cytoskeletal associations needed for FA and stress fiber formation. However, undifferentiated talin-null ES cells also express reduced levels of β1 integrin, vinculin, and α-actinin, which may contribute to the phenotype. Following differentiation of talin-null ES cells, only two morphologically distinct cell types emerged and no organized tissues were formed (21). The differentiated cells expressed normal levels of β1 integrin and vinculin and were capable of spreading and forming actin filaments and FA-like structures, indicating that in a subset of differentiated cell types, talin is dispensable for maintenance of β1 integrin expression and FA assembly.

Integrin-binding sites have been localized to both the talin-head and rod domains (17,18), suggesting that binding of two or more integrin β tails to the talin dimer may facilitate integrin clustering (Fig.1). Binding of both the head and rod domains are inhibited by Y/A mutations in the membrane proximal NPXY motif of β1 and β3 integrins (15,17,22), consistent with the failure of integrins expressing this mutation to localize to FA (10,11). In v-Src-transformed cells, which exhibit reduced cell adhesion and a disorganized cytoskeleton, the NPXY motif in the β1
tail is phosphorylated on tyrosine, and talin binding is inhibited (23). Furthermore, synthetic peptides spanning the NPXY motif bind purified talin and inhibit talin binding to β1 (22,23). Thus, the talin-binding site in the β1 tail includes this sequence.

However, other regions of the β tail are likely to contribute to the interaction with talin since the NPXY motif is highly conserved between integrin β subunits but talin displays differential binding to various integrin β tails (15). Indeed, deletion of the C-terminal 13 amino acids of the β1 cytoplasmic tail, which leaves the membrane proximal NPXY site intact, inhibits both talin binding in vitro and co-localization of talin and actin with clustered β1 integrins in vivo (22,24). In contrast, deletion of only the 4 most C-terminal amino acids from β1 has no effect on talin binding or recruitment of talin and actin to sites of clustered integrins (22,24). Furthermore, a recent report concluded that talin could bind specifically to peptides corresponding to the membrane-proximal sequence of the β3 tail (18). Thus, further work is required to determine the precise mode of interaction between integrin β tails and talin.

Filamin-mediated linkages. Three distinct filamin genes have been reported and alternative splicing allows for additional isoforms (25). Filamins are actin filament crosslinking proteins composed of two parallel 280 kDa subunits. Each subunit contains an N-terminal actin-binding domain, composed of two calponin homology (CH) domains, followed by 23 repeating domains (8,13). Depending on the filamin:F-actin ratio, filamin reinforces loose microfilament nets, such as those found in the cell cortex (Fig.1), or tightly packed bundles as found in stress fibers (8). Filamin also binds to the cytoplasmic domains of transmembrane proteins (e.g. GP Ibα) and to intracellular signaling molecules (e.g. RalA) (25,26). Filamin localizes to the cortical actin cytoskeleton and along the length of stress fibers but is also found in some FA (8).

β1A, β2, β3, β7, and to a lesser extent β1D integrin tails can bind filamin, and Y/A point mutations in the membrane proximal β1, β3 and β7 NPXY motif inhibit binding ((15,27);
Calderwood and Ginsberg unpublished results). Both filamin and F-actin are recruited to β1-containing FA in response to mechanical stress, but F-actin recruitment does not take place in melanoma cells lacking filamin (28). The gene encoding human filamin-1 is located on the X-chromosome, and mutations of this gene are associated with periventricular heterotopia in humans, indicating a requirement for filamin-1 in neuronal migration during brain development (26). Loss of filamin-1 expression in neuronal or melanocytic cells results in impaired migration and altered morphology (26,29). However, filamin-1 null melanocytic cells also have reduced levels of many cell surface receptors, including β integrins (30), which may account for some of these phenotypes. Filamin-1-deficient cells, produced due to X-inactivation in females heterozygous for filamin-1 null alleles (26), should facilitate further investigation of the requirement for filamin-1 in cell migration and actin assembly.

**α-actinin-mediated linkages.** α-actinin is another homodimeric actin-binding protein localized to FA (8). Non-muscle α-actinin monomers are ~100 kDa rod-like proteins containing 3 functional domains; an N-terminal actin-binding domain, composed of two CH domains, a central region of 4 spectrin-like repeats and a C-terminal domain containing 2 EF hands. At least 2 α-actinin genes and alternative splicing allow for production of a number of α-actinin isoforms. In addition to binding F-actin, α-actinin binds the FA proteins vinculin, zyxin, and β1, β2 and β3 integrins (2,8) (Fig.1,2). α-actinin targets to FA in microinjected cells and in a cell free system, apparently by interaction with β cytoplasmic tails (31,32). The binding sites for α-actinin have been localized to the membrane-proximal half of the β1 or β2 integrin tail and binding to β2 is negatively-regulated by sequences in the C-terminal region of the tail (16). The membrane-proximal location of the α-actinin binding site within β tails is consistent with the observation that antibody-mediated clustering of β1 integrins lacking the C-terminal 13 amino acids also induces clustering of α-actinin (24). However, α-actinin binding to clustered integrins is not sufficient to recruit F-actin (24,32). Overexpression of α-actinin in fibroblasts leads to more
stable attachment sites while isolated integrin-binding fragments of α-actinin disrupt stress fibers, FA and shear induced mechanical signaling in fibroblasts and osteoblasts (8,31).

Other integrin-binding cytoskeletal proteins. Recent reports suggest that additional proteins may serve as direct links between integrin tails and the cytoskeleton. In platelets, the two tyrosines in the β3 cytoplasmic tail become phosphorylated during agonist-induced cell aggregation (33). Synthetic peptides corresponding to the tyrosine-phosphorylated β3 tail bind to the actin-binding protein, myosin, and the adapter molecules, Grb2 and Shc (34). These interactions may be physiologically relevant because conversion of the two β3 tail tyrosines to phenylalanine is associated with a mild bleeding phenotype in mice (33). Skelemin, a cytoskeletal M-band protein thought to bind myosin, can bind β1 and β3, but not β2 tails expressed in vitro (35). In CHO cells, skelemin co-localizes with stably-expressed αIIbβ3 under some conditions and microinjection of the integrin-binding domain of skelemin causes myoblasts to round up (35). Whether these interactions represent widespread or specialized cases of integrin-cytoskeletal linkages remains to be determined.

Vinculin-mediated interactions. Vinculin, an ~120 kDa molecule, is one of the most abundant FA proteins and interacts with F-actin, talin, α-actinin, paxillin and VASP (8,36). Vinculin does not bind directly to integrins but may be recruited by integrin-bound talin or α-actinin (Fig.3). Artificial clustering of vinculin at cell membranes results in accumulation of F-actin (36) suggesting that vinculin may contribute to integrin-cytoskeletal linkages. However, while reduced levels of vinculin expression result in a reduction in the mechanical stiffness of the integrin-cytoskeletal linkage and increased cell motility, vinculin-null ES cells can differentiate in vitro into a variety of cell types, including rhythmically beating cardiomyocytes (37), and they can spread and form talin-rich FA and stress fibers (21). Thus, despite ubiquitous expression, vinculin is not absolutely required for some integrin-F-actin linkages, and is likely to function as a molecular bridge to stabilize pre-existing linkages.
Inside-out integrin signaling: the role of cytoskeletal proteins. Integrins are subject to rapid regulation of their ligand-binding activity by intracellular signals, and this has been termed inside-out signaling or integrin activation (38). Inside-out signaling may act by 1) inducing conformational changes in and altering the affinity of integrin heterodimers, and 2) clustering heterodimers into multimers within the plane of the plasma membrane, leading to changes in effective valency or avidity (38).

Affinity and avidity modulation are not mutually exclusive and they may operate in a complementary manner to control both ligand binding and post-ligand binding events. This combinatorial view of integrin activation is supported by recent studies of $\alpha_{\text{IIb}}\beta_3$ in a CHO cell model (39). In this system, affinity modulation was found to be the major factor responsible for the initial, reversible phase of ligand binding to $\alpha_{\text{IIb}}\beta_3$, but integrin clustering promoted irreversible binding and was necessary for outside-in signaling, as manifested by induction of tyrosine phosphorylation signals (39). While the relative contributions of affinity and avidity modulation appear to vary by integrin and cell type, recent evidence suggests that integrin-cytoskeletal linkages and signaling molecules associated with the actin cytoskeleton may play key roles in both processes.

Inside-out signals to integrins originate from diverse plasma membrane receptors. As with signal propagation to other parts of the cell, these excitatory receptors presumably regulate integrins by triggering post-translational changes, such as phosphorylation/dephosphorylation, that affect the activity and/or subcellular localization of key enzymes and substrates in integrin-regulatory pathways (40). Thus, cytoskeletal proteins could modulate inside-out signaling by promoting the activity of integrin-regulatory molecules and/or by controlling their proximity to integrin cytoplasmic tails (38). Alternatively, or in addition, certain cytoskeletal proteins might able to modulate integrin activation state directly as the result of regulated changes in integrin-
cytoskeletal linkages. Furthermore, in cases where integrins bind to counter-receptors on other cells instead of ECM, integrin avidity may be influenced by cytoskeleton-driven alignment of the membranes on the opposing cells (41).

As a possible example of regulation of integrin affinity or avidity by cytoskeletal linkages, β2 integrins from unstimulated neutrophils do not engage β2 ligands, and they co-immunoprecipitate with talin but not α-actinin (16). However, cell activation by f-Met-Leu-Phe, induces ligand binding to the β2 integrins and stimulates talin proteolysis and dissociation from β2 in a manner dependent on the calcium-dependent protease, calpain. During a later phase of cell activation, β2 now co-precipitates with α-actinin and not talin, an association hypothesized to result from a change in conformation of the β2 cytoplasmic tail (16). In this scheme, integrin activation would be initiated by calpain-dependent release of one integrin-cytoskeletal linkage and later reinforced by another. This overall model may also apply to activation of other integrins, but the precise details may differ. For example, calpain activation in platelets is a relatively late event, occurring after the initial phase of αIibβ3 activation, and it is responsible for cleavage of numerous cytoskeletal and signaling proteins, including the β3 cytoplasmic tail itself (42).

Regulated interactions between cytoskeletal proteins and integrin cytoplasmic tails might also explain why αLβ2 in phorbol ester-stimulated EBV-transformed B lymphocytes exhibits a 10-fold increase in random diffusion rate, a change that correlates with increased cell adhesion to ICAM-1 (41). Treatment of these cells with low concentrations of cytochalasin D, which caps actin filaments preventing further polymerization, has the same effect, while higher concentrations of cytochalasin D inhibit cell adhesion. Similarly, exposure of peripheral blood lymphocytes to cytochalasins induces clustering of αLβ2 and adhesion of the cells to ICAM-1 (43), and the same is observed in peripheral blood-derived T lymphoblasts after cross-linking of the T cell receptor (44). In leukocytes, it has been proposed that L-plastin, an actin-bundling
protein, may modulate the avidity of $\alpha M\beta 2$ in a manner dependent on L-plastin phosphorylation by PKC. (45).

Cytoskeletal linkages may also be involved in the activation of $\alpha IIb\beta 3$ in platelets. For example, in unstimulated platelets a subpopulation of $\alpha IIb\beta 3$ is associated with the membrane cytoskeleton, and relatively low concentrations of cytochalasin D or latrunculin A, which blocks polymerization of actin monomers, induces ligand binding to $\alpha IIb\beta 3$ (46). This effect requires a stimulus, such as ADP released from the washed platelets, which the authors suggest might increase actin turnover by binding to purinergic receptors and stimulating the actin filament-severing activity of gelsolin and the filament-disassembly activity of ADF-cofilin.

Rho family GTPases play a prominent role in actin polymerization and reorganization during cell migration (9), and it is logical to consider whether they are directly involved in promoting integrin activation. In fibroblasts, activation of cdc42 and Rac is associated with the formation of focal complexes (9), but their effects on ligand binding to integrins has not been studied. Inhibition of Rho with C3 exoenzyme decreases $\beta 2$ and $\beta 3$ integrin-dependent aggregation of leukocytes and platelets, respectively (2). However, in adherent platelets inhibition of Rho with C3 exoenzyme blocks certain post-ligand binding events, such as the formation of vinculin patches and actin cables, but it has no effect on agonist-induced activation and ligand binding to $\alpha IIb\beta 3$ (47). Similarly, C3 exoenzyme blocks the formation of FA and stress fibers in fibroblasts, but it has no significant effect on the activation state of $\alpha 5\beta 1$ (48). In these cases, therefore, Rho may function to regulate cell adhesion through effects on post-ligand binding events (9).

Integrin-associated proteins regulate actin filament assembly. The studies pointing to a role for actin and actin-binding proteins in regulating integrin function have coincided with remarkable recent advances in understanding the regulation of actin filament assembly. Integrins may provide the appropriate subcellular locale for actin filament assembly and organization in adherent and
migratory cells by virtue of integrin-cytoskeletal linkages and integrin-triggered outside-in signals. In this context, several proteins implicated in the regulation of actin assembly are either components of FA or interact with cytoskeletal proteins that are linked to integrin β cytoplasmic tails.

The Mena/VASP family. Members of this protein family, which include VASP (vasodilator-stimulated phosphoprotein), the Drosophila protein Enabled (Ena), its mammalian orthologue Mena, and Evl (Ena-VASP like), contain conserved N- and C-terminal domains (EVH1 and EVH2) separated by a proline rich domain that binds profilin and SH3 domains (49,50)(Fig.2). The VASP EVH2 domain mediates tetramerization of the molecule, F-actin binding and bundle formation (51). The EVH1 domain mediates targeting to FA by binding to proline-rich motifs in zyxin and vinculin (Fig.2), and binding to the ActA movement protein of the intracellular bacteria Listeria monocytogenes (49,50). Mena/VASP proteins are localized to sites of actin assembly, such as FA and membrane ruffles, and are concentrated at the tips of rapidly moving lamellipodia and at the focal contacts at their base (52). This localization of VASP is consistent with its proposed role in linking membrane proteins, which presumably include integrins, to polymerizing actin.

VASP is also a substrate for cyclic AMP-dependent protein kinase A and cyclic GMP-dependent protein kinase G. In platelets, cyclic AMP and cyclic GMP are potent inhibitors of agonist-induced activation of αIIbβ3, and phosphorylation of VASP by protein kinase A or protein kinase G correlates with inhibition of fibrinogen binding to activated platelets (53). There may be a causal relationship between VASP phosphorylation and inhibition of αIIbβ3 activation since VASP-deficient murine platelets show enhanced agonist-induced fibrinogen binding to αIIbβ3 and the inhibitory effects of cyclic nucleotides on fibrinogen binding are reduced (49,53). However, the molecular basis for the effects of VASP deletion on αIIbβ3 function remain to be determined.
Investigation of ActA has provided insight into eukaryotic mechanisms for regulating actin filament assembly (54). This has led to a model in which Mena/VASP proteins are targeted to FA by binding to zyxin or vinculin, which in turn bind α-actinin or talin. This would allow Mena/VASP to bind to actin filaments via their EVH2 domains or though profilin that is bound to oligomerized Mena/VASP (Fig.2). Microinjection of peptides that inhibit EVH-1 binding to vinculin and zyxin displace Mena/VASP from FA and cause retraction of membrane protrusions. Furthermore, a recessive lethal Ena allele contains a point mutation which impairs zyxin binding in vitro. Consequently, Mena/VASP function probably requires its targeting to FA via interactions with α-actinin (54). Surprisingly, mice deficient in VASP or Mena are viable, fertile and display relatively mild phenotypes, which may reflect functional compensation by related family members (49,50,53). Mena-deficient mice that are also heterozygous for a profilin-1 deletion die perinatally. Thus, a 50% reduction in profilin-1 sensitizes animals to loss of Mena, consistent with their cooperation in regulating the actin cytoskeleton (50).

In summary, Mena/VASP proteins appear to contribute to F-actin binding at FA but are not required for FA assembly or maintenance. Mena/VASP proteins play important roles in regulating actin filament assembly, particularly at the leading edge of migrating cells, and Mena/VASP associations with integrins, although indirect, may target actin polymerization to fresh sites of integrin-ECM contact.

**Arp2/3 and WASP.** The studies on Listeria which highlighted the role of Mena/VASP also revealed a requirement for the Arp2/3 complex for actin polymerization (54,55). This complex consists of seven proteins, including actin-related proteins (Arp) 2 and 3, and co-localizes with Mena/VASP proteins at the leading edges of cells to promote the assembly of actin filament networks (55). Hence, recruitment of Arp2/3 to focal contacts containing integrin-associated Mena/VASP may contribute to actin assembly at sites of ECM contact (54). Machesky and
Insall (55) describe a model for the activation of Arp2/3 by extracellular signals, leading to regulated assembly of actin filaments allowing production of force for cell motility and shape changes. A critical question in this model is how the Arp2/3 complex becomes localized at sites where actin polymerization is required, such as lamellipodia at the leading edge of cells.

Identification of members of the WASP (Wiskott-Aldrich syndrome protein) family as Arp2/3-binding proteins (55) suggests a complex multimolecular assembly which may bring Arp2/3 into contact with integrin-associated Mena/VASP (Fig.2). Expression of WASP appears to be limited to cells of hematopoietic lineage, however two family members N-WASP and WAVE have more widespread distributions (56). WASP proteins are proline-rich scaffolding molecules and effectors of the small GTPases, cdc42 and Rac1 (56). WASP family members bind to actin, either through a direct interaction, or via profilin or Arp2/3, and so may mediate some of the effects of cdc42 or Rac on the cytoskeleton (57). Overexpression of WASP or N-WASP in mammalian cells leads to co-localization of F-actin with the overexpressed protein, and WASP-coated beads accumulate F-actin and exhibit motility within cells (56).

A model for Shigella motility suggests that co-localization of vinculin, VASP, profilin and N-WASP may drive actin polymerization (58). Although speculative, such co-localization may also occur in vivo via associations of Nck, PINCH, and ILK (integrin linked kinase) with integrins (Fig.2). ILK was identified as a binding protein of the integrin β1 and β3 tails (59), and ankyrin repeats within ILK appear to mediate binding to the LIM domain-only protein PINCH and recruit it to integrin complexes in spreading cells (59). PINCH also interacts with Nck-2 an SH2/SH3-containing protein, and so mediates an association between Nck-2 and ILK (59). The C-terminal SH-3 domain of the closely related adapter protein Nck-1 binds to WASP (56). This domain is 75% identical to the corresponding Nck-2 SH-3 domain suggesting that a protein complex containing integrin, ILK, PINCH, Nck-2, WASP, and Arp2/3 might localize actin polymerization to sites of integrin-ECM contact in the lamellipodia of migrating cells. Some
support for this hypothesis comes from unc-97 mutants in C. elegans. The UNC-97 protein belongs to the PINCH family of LIM domain proteins and is co-localized with β integrin at dense-bodies (60), where it is required for the assembly and stability of these FA-like structures (60).

In conclusion, integrins associate with the actin cytoskeleton through a number of molecular linkages. In most cells, binding of the β integrin cytoplasmic tail to talin is an early and important step and probably provides a preliminary connection which is reinforced by subsequent binding of α-actinin and vinculin. In turn, these proteins probably function to bring additional F-actin to the adhesion site, and they may also recruit zyxin, Mena/VASP and profilin. Recruitment of WASP and Arp2/3 to this growing membrane-tethered assemblage may lead to further actin polymerization and reorganization. The large number of actin-binding proteins within matrix adhesions and their numerous structural and functional interactions with integrins provide an important basis for the control of cellular functions by integrins.

**Figure 1.** Models of the physical links between integrins and F-actin. When known, the modular architecture of the linking proteins is shown based on domain assignments by the SMART program (13). Three potential structural links between integrins and F-actin, mediated by talin, α-actinin and filamin, are shown. Vinculin is also shown reinforcing both the talin- and α-actinin-mediated linkages. The β integrin tail is depicted binding to ERM domains within the talin head domain, however integrin-binding sites have also been identified in the rod domain raising the possibility that binding of a talin dimer may induce integrin tetramers. The spectrin repeats within the α-actinin rod domain also mediate binding to the integrin β tail, however it is not known which of the three repeats contains the binding site. Filamin binds integrins via C-terminal filamin repeats however the exact binding site has not yet been determined.
Figure 2. Models for integrin localization of actin nucleation and polymerization. As discussed in the text VASP, profilin, Arp2/3 and WASP may regulate actin filament assembly at sites of integrin-ECM contact. Profilin binds to VASP which may be recruited to these sites by binding zyxin which in turn binds integrin-bound α-actinin. Arp2/3 and WASP may also be localized with integrins via Nck-2, PINCH, ILK interactions. Nck-2-WASP interactions have not been demonstrated but are hypothesized on the basis of Nck-1 binding to WASP.

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Integrin

vinculin

F-actin

filamin

α-actinin

α β

CH domain
Spectrin repeat
ERM domain
ILWEQ domain
vinculin head domain
filamin repeat
EF hand
- CH domain
- Proline rich sequence
- EVH-1
- EVH-2
- Ankyrin repeat
- WASP homology 1
- WASP homology 2
- PBD
- SH3 domain
- SH2 domain
- LIM domain
- Spectrin repeat
- EF hand
Integrins and Actin Filaments: Reciprocal Regulation of Cell Adhesion and Signaling
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