Composition and function of integrin adhesions

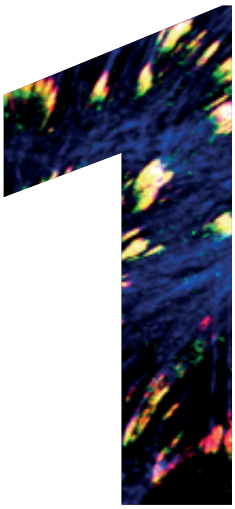
Zuidema, A.C.

Crosstalk between cell adhesion complexes in regulation of mechanotransduction

Published in BioEssays, Volume 42, Issue 11 (2020).

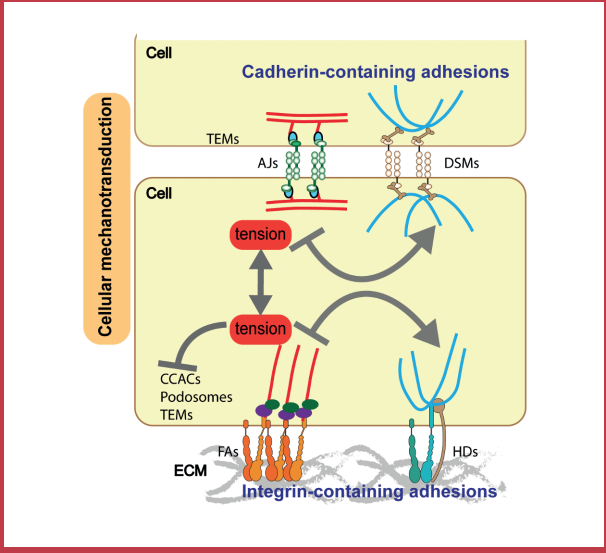
Alba Zuidema, Wei Wang, and Arnoud Sonnenberg.

Division of Cell Biology, The Netherlands Cancer Institute, Amsterdam, The Netherlands.



ABSTRACT

Physical forces regulate numerous biological processes during development, physiology and pathology. Forces between the external environment and intracellular actin cytoskeleton are primarily transmitted through integrin-containing focal adhesions and cadherin-containing adherens junctions. Crosstalk between these complexes is well established and modulates the mechanical landscape of the cell. However, integrins and cadherins constitute large families of adhesion receptors and form multiple complexes by interacting with different ligands, adaptor proteins and cytoskeletal filaments. Recent findings indicate that integrin-containing hemidesmosomes oppose force transduction and traction force generation by focal adhesions. The cytolinker plectin mediates this crosstalk by coupling intermediate filaments to the actin cytoskeleton. Similarly, cadherins in desmosomes might modulate force generation by adherens junctions. Moreover, mechanotransduction can be influenced by podosomes, clathrin lattices, and tetraspanin-enriched microdomains. This review discusses mechanotransduction by multiple integrin- and cadherin-based cell adhesion complexes, which together with the associated cytoskeleton form an integrated network that allows cells to sense, process, and respond to their physical environment.

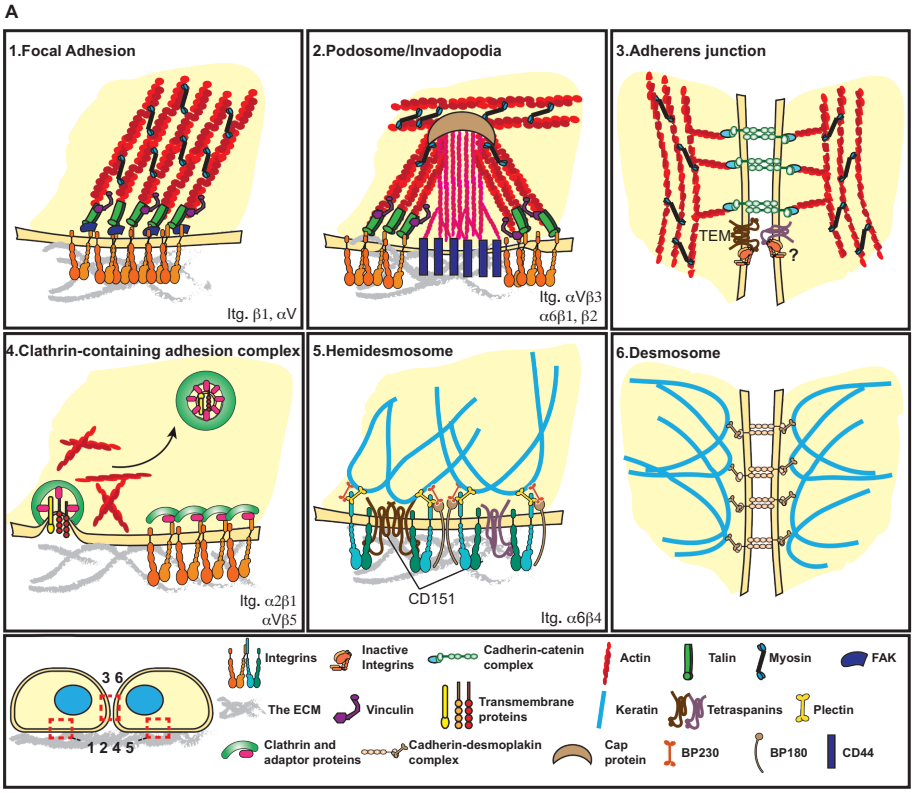


INTRODUCTION

Cells do not exist in isolation and must interact with their local environment, which means that they need to sense, process, and respond to chemical and physical stimuli. Cells can sense their physical environment and translate information about the extracellular matrix (ECM), neighbouring cells, and physical stress into biochemical and biological responses. This process, called mechanotransduction, regulates multiple and wide-ranging cellular processes, such as proliferation, migration, differentiation, and apoptosis. Ultimately, mechanotransduction is crucial for organ development and tissue homeostasis. Molecular defects that perturb mechanical sensing and/or the subsequent biochemical signalling events can lead to diverse diseases such as muscular dystrophy, hearing loss, cardiovascular diseases, and cancer [1, 2].

Mechanical stimuli can be sensed by cells through a diverse group of membrane-anchored receptors, including stretch-activated ion channels, cell membrane-spanning G-protein-coupled receptors, integrins and cadherins [2]. Integrin- and cadherin-based adhesion complexes assemble at cell-ECM and cell-cell contact sites, respectively. They both contain proteins that are sensitive to changes in tensile forces and adapt their composition and dynamics in response to these forces, resulting in biochemical signaling events that transduce the mechanical input [3, 4].

Many integrins assemble in adhesion complexes called focal adhesions (FAs), which transmit mechanical forces bidirectionally between the ECM and the intracellular actomyosin cytoskeleton [5, 6]. The contribution of integrins (especially integrin α5β1) in FAs to mechanotransduction has been well established [6-8]. Yet integrins are not uniform but consist of a family of 24 different heterodimeric receptors consisting of one α and β subunit [9]. Depending on the combination of α and β subunits, integrin subtypes bind to specific ligands in the ECM and can interact with a range of intracellular adaptor proteins. While most studies have focused on mechanotransduction by specific integrin subtypes in FAs, there is now growing evidence that the contribution of different integrins to this process can greatly vary and might depend on the specific subtype and ligand interaction [10]. Other types of integrin-based adhesions include podosomes [5, 11], hemidesmosomes (HDs) [12-14] and clathrin lattices [15-17]. Additionally, integrins in association with tetraspanins can be recruited into discrete plasma membrane domains called tetraspanin-enriched microdomains (TEMs) (Figure 1) [18, 19]. Notably, while podosomes, like FAs, are connected to actin, HDs are associated with the intermediate filament (IF) network. Adhesive structures containing clathrin or tetraspanins are not obviously linked to the cytoskeleton network.


A
1.Focal Adhesion
Itg. β1, αV
2.Podosome/Invadopodia
Itg. αVβ3
α6β1, β2
3.Adherens junction
TEM
?
4.Clathrin-containing adhesion complex
Itg. α2β1
αVβ5
5.Hemidesmosome
CD151
Itg. α6β4
6.Desmosome
3 6
1 2 4 5
Integrins
Inactive Integrins
Cadherin-catenin complex
Actin
Talin
Myosin
FAK
The ECM
Vinculin
Transmembrane proteins
Keratin
Tetraspanins
Plectin
Clathrin and adaptor proteins
Cadherin-desmoplakin complex
Cap protein
BP230
BP180
CD44

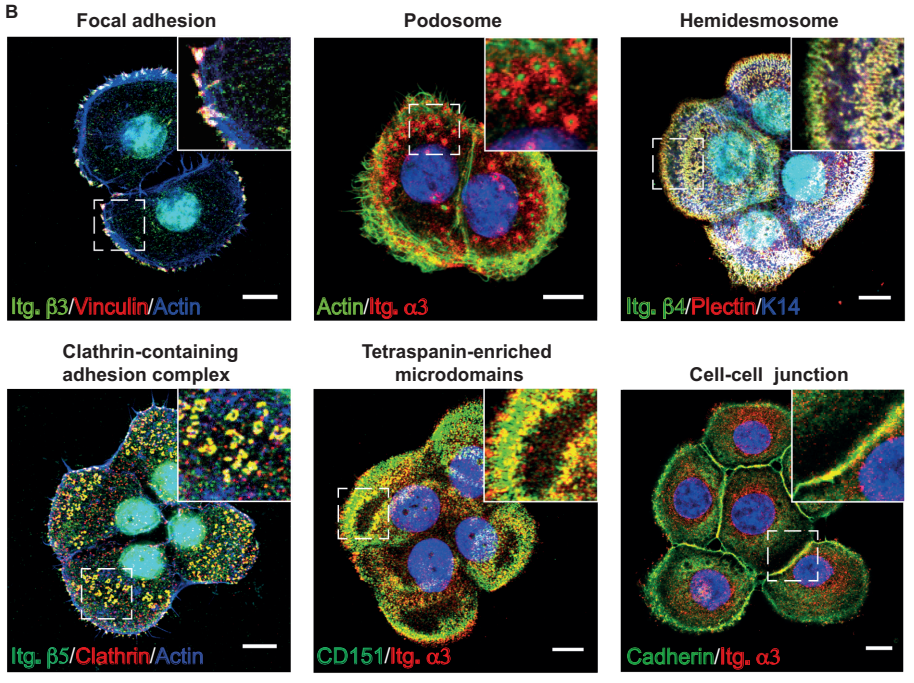

B
Focal adhesion
Podosome
Hemidesmosome
Itg. β3/Vinculin/Actin
Actin/Itg. α3
Itg. β4/Plectin/K14
Clathrin-containing adhesion complex
Tetraspanin-enriched microdomains
Cell-cell junction
Itg. β5/Clathrin/Actin
CD151/Itg. α3
Cadherin/Itg. α3

Figure 1 Different types of cell-ECM and cell-cell adhesion complexes. A) Schematic representation of distinct integrin- and cadherin-containing adhesion complexes. Focal adhesions (panel 1), invadopodia/podosome (panel 2) and adherens junctions (panel 3) are actin cytoskeleton-associated adhesion complexes. Hemidesmosomes (panel 5) and desmosomes (panel 6) are IFs-associated adhesion complexes. Panel 4 shows F-actin around a developing clathrin-coated pit and clathrin-containing adhesion complexes (CCACs). CCACs are not associated with F-actin. The different integrins localized in the various adhesion complexes are presented in each panel. **B)** Confocal microscopy images showing the presence of six different adhesion complexes in keratinocytes. In focal adhesions, integrin β3 (green; exogenous expression after cDNA transfection) is co-localized with vinculin (red). In podosomes, integrin α3β1 (red) is present in the adhesion rings that form around the actin cores (green). Hemidesmosomes contain integrin β4 (green) and plectin (red), and are linked to keratin 14 intermediate filaments (K14; blue). Integrin β5 (green) co-localizes with clathrin (red) in clathrin-containing adhesion structures. The tetraspanin CD151 (green) together with integrin α3β1 (red) is present in tetraspanin-enriched microdomains. Integrin α3β1 (red) can also be found in cell-cell junctions, where it co-localizes with cadherins (green; pan-cadherin). Nuclei were counterstained with DAPI (cyan or blue). Actin fibers are visualized by Phalloidin-ifluor647 (blue or green). Scale bar: 10 μm.

The organization and function of FAs shows some resemblance to adherens junctions (AJs). These junctions are cadherin-based cell-cell adhesions that transmit forces at the cell-cell interface by coupling the force-generating actomyosin cytoskeleton of neighboring cells [3, 20]. Crosstalk between AJs and FAs integrates mechanotransduction at cell-cell and cell-ECM adhesions and regulates cellular behavior, including collective cell migration and tissue development [21]. A second type of cadherin-based junctions are desmosomes (DSMs), which contain a distinct class of cadherins and mediate firm cell-cell adhesion. Like HDs, DSMs are associated with IFs (Figure 1) [20, 22].
Even though mechanotransduction by and crosstalk between integrin-containing FAs and cadherin-based AJs has been well established, the contribution of other integrin/cadherin-containing adhesions to mechanotransduction is largely unexplored. Earlier studies discussed by Seetharaman and Etienne-Manneville provide insights into the different roles of integrins in mechanotransduction [10]. This review highlights the intricate interplay between different integrin and cadherin-based cell adhesions in mechanosensing and force generation.

Mechanotransduction at focal adhesions

FAs are the best studied integrin-containing adhesion complexes with regard to their role in mechanotransduction [6-8, 23]. They originate from smaller adhesive structures, called nascent adhesions and focal complexes (FXs). Nascent adhesions are short-lived adhesions formed during early cell spreading. They contain only few (3-6) integrin dimers bound to their ECM ligands [7]. Some of these nascent adhesions are stabilized and recruit more integrins, which then associate with intracellular adaptor proteins to

form FXs [10, 23]. These FXs mature into larger and more stable FAs once they are coupled to the actomyosin force machinery. In FAs, mechanosensitive proteins are stretched by tensile forces to expose cryptic binding sites and recruit proteins that strengthen the connection with actomyosin fibers [6, 7]. The maturation of nascent adhesions into FAs requires tensile forces but is also affected by the physical properties of the ECM, as cells only form small, short-lived FAs on soft substrates [23]. On a rigid substratum, tension mediated by activity of the small GTPase RhoA promotes FA growth and recruitment of multiple proteins to these structures, which are then able to generate more tension in a positive feedback loop [23]. Finally, FAs also serve as sites where traction forces generated by the contractility of the actin cytoskeleton are transmitted onto the ECM. This can lead to the movement of integrin α5β1 along with its ligand fibronectin out of FAs into centrally located fibrillar adhesions and promote fibronectin fibrillogenesis [5] Most of the early work on FAs concentrated on the assembly of FAs after ligation of the integrin α5β1 to fibronectin [23, 24]. However, recent studies indicate that the contribution of FAs to mechanotransduction can greatly vary, depending on the presence of specific integrin dimers. These differences can be attributed to multiple factors, including differences in integrin-ligand binding affinities, association of integrins with the actin cytoskeleton, and regulation of integrin trafficking [10]. Comparison of integrins α5β1 and αVβ3 in force generation showed that α5β1, but not αVβ3, supports RhoA-mediated actomyosin contractility [25, 26]. In line with these findings, deletion of α5β1 decreases traction force generation, while forces are increased in αVβ3-deficient cells [27]. Notably, both α5β1 and αVβ3 can bind the RGD site in fibronectin, but only α5β1 can engage with the synergy site, which strengthens the bond between α5β1 and fibronectin upon force application [23, 28]. Accordingly, α5β1 can tolerate higher RhoA-mediated tensile forces than αVβ3, needed for this integrin to promote traction force generation [10]. While α5β1 interacts specifically with fibronectin, αVβ3 can bind multiple RGD-containing ligands. Remarkably, αVβ3 binds preferentially to fibronectin in response to mechanical force [29] and resides longer in cell-ECM adhesions if tension is increased [30]. Thus, although αVβ3 cannot generate (high) traction forces, it may play a role in mechanosensing by integrating information about the composition of the ECM in response to changes in cellular actomyosin contractility [29].

Integrins interact with the cytoskeleton indirectly via (mechanosensitive) adaptor proteins that associate with actin. The best characterized protein that links integrins to actin is talin, a mechanosensitive protein that can be stretched by tensile forces to reveal cryptic binding sites for vinculin, thereby re-enforcing the connection of the integrin with actin [31, 32]. There are two different isoforms of talin, of which talin-1 is ubiquitously expressed. Talin-2 exhibits a more restricted distribution, with high protein levels in the heart, brain, and skeletal muscle. Talin isoform-specific differences in integrin force transduction have been measured using FRET-based sensors, which revealed that talin-

2 bears higher forces than talin-1. Cells expressing talin-2 spread more efficiently on soft substrates with rigidities that resembles that of brain tissue [33]. Talin-2 also has a higher binding affinity for the β1D splice variant, which is primarily expressed in cardiac and skeletal muscle cells, than for the β1A or β3 subunits. These findings indicate a tissue-specific fine-tuning of the interaction between integrins and talin isoforms [34]. Additionally, talin and α-actinin compete for binding to the β3-cytoplasmic domain, while these two proteins cooperate to activate integrin α5β1, resulting in a differential regulation of force transmission via β1 or β3 containing adhesions [35, 36]. Similar mechanisms may apply to other integrin binding proteins that compete with talin, e.g. filamins and tensins [37].

Integrins can also connect to the actin cytoskeleton via kindlin and the integrin-linked kinase (ILK), PINCH, and parvin (IPP) complex [38]. The role of kindlin in mechanotransduction has been less explored, but molecular dynamics simulations suggest that kindlin-2 might function as a mechanosensitive protein and strengthen integrin-mediated FAs under force [39]. Similar to talin, different isoforms of kindlin exist that may have different affinities for integrin β subunits and hence influence the mechanical properties of cells in an integrin-specific manner [40]. Additionally, the antagonistic relation between integrin α5β1 and αVβ3 in regulating activities of Rho and Rac GTPases, cell adhesion, and spreading, was shown to be mediated by kindlin-2 [41].

Notably, FAs contain a multitude of other proteins, collectively referred to as the integrin adhesome. Many proteomic studies have provided insight into the molecular composition of FAs and revealed that the FA composition can vary extensively between cell types and experimental conditions [24]. Furthermore, alterations in adhesome composition in response to changes in applied forces have been identified [42, 43]. The most notable changes are the force-dependent recruitment of LIM domain-containing proteins into cell-matrix adhesions and the contractility-independent recruitment of Rac1 activators and effectors to nascent adhesions.

Finally, the contribution of integrins in mechanotransduction depends on their availability at the plasma membrane. The regulation of integrin cell surface expression is regulated by endocytosis and recycling back to the surface. This process is regulated in multiple context-dependent ways and also shows specific routes of integrin trafficking for the different integrin heterodimers, as recently discussed by Moreno-Layseca et al. [44]. Taken together, integrins in FAs can play specific roles in mechanotransduction, depending on their ligand-binding affinities and interactions with cytoskeletal and/or endocytic adaptor proteins.

Mechanosensory function of podosomes/invadopodia

Like FAs, podosomes and invadopodia are actin-based structures that contain integrins and mediate adhesion of cells to the ECM. These structures were first identified in fibro-

blasts in which actin stress fibers are disrupted and cell spreading is compromised by transformation with Rous sarcoma virus [45]. In these cells, the oncogene Src promoted the relocation of the cytoskeletal proteins vinculin and α-actinin from FAs into circular "rosettes" [45, 46]. Since then, multiple studies reported similar circular structures, called podosomes or invadopodia, that were involved in cell-ECM adhesion and degradation. Besides fibroblasts, these structures are found in invasive cancer cells, epithelial and endothelial cells, osteoclasts, myoblasts, neural crest cells, and immune cells [47]. Although the same type of structure is studied, the nomenclature differs depending on the cell type. The term podosome originated from the association of these structures with "cellular feet" and is used to describe actin-rich ventral protrusions in normal cells. Invadopodia is used to refer to these structures in cancer cells and this term highlights their adhesive and degradative capacity. If no distinction is made between the cell type and cell-specific function, these structures are called invadosomes [46].

Invadosomes consist of an actin-rich core, surrounded by a ring of actin-associated and signalling proteins. Key players in these structures are the actin regulators cortactin, Arp2/3 and (N-) WASP, adaptor proteins Tks4 and Tks5, and metalloprotease MT1-MMP. Podosomes in dendritic cells and macrophages contain β2 integrins, while those in osteoclasts and transformed cells contain β1 and β3 integrins [10]. Invadosome formation is regulated by β1, but not by β3 integrins [48]. Strikingly, invadosome disassembly by inactivation of β1 resulted in the formation of β3-containing FAs [48]. In endothelial cells, VEGF stimulation induces the assembly of podosome rosettes by upregulating the laminin-binding integrin α6β1. This assembly is inhibited when the cells are cultured on high concentrations of laminin and α6β1 is tightly bound to its ligand in FAs [49]. Moreover, other studies correlated invadosome formation with reduced cellular tension and decreased FAs, as discussed by Kedziora et al. [50]. These findings indicate an inverse relationship between FAs and invadosomes. But how is crosstalk between similar actin-containing adhesion complexes regulated?

In contrast to elongated FAs, invadosomes form a ring of adhesive proteins centred around an actin column that protrudes from the cell body and applies compressive forces onto the underlying substrate. Similar to FAs, podosomes are mechanosensitive and apply higher protrusive forces if the stiffness of the substratum increases [51]. While tensile forces are required for FA maturation and function, invadosome formation and growth is promoted by a decrease in local cellular contractility and is dependent on actin polymerization [52]. Recent work by Glazier et al. showed that integrins residing in the podosomal ring surrounding its actin core apply tensile forces on RGD ligands needed for podosome stability and maturation [53]. However, these tensile forces are controlled by the polymerization of the actin core but not by actomyosin contractions in the podosomal ring [53] and seem to be the result of local forces needed to stabilize actin protrusion into the ECM. Indeed, the integrity of the podosomal ring is needed to

support actin polymerization and protrusion at the core, as depletion of talin and vinculin decreases protrusion force [54]. How the different protrusive and tensile forces are balanced in podosomes is still poorly understood. Super-resolution microscopy analysis of the podosome architecture shows that both vinculin and myosin II are linked to actin filaments in the podosomal ring and that these proteins and their associated actin filaments form two separate modules surrounding the actin core [55]. This organization of integrins, mechanosensitive proteins, actin and myosin in podosomes thus differs from FAs, in which talin/vinculin directly connect integrins to actomyosin cytoskeleton. Invadosomes can form under low cellular tension, since they are driven by actin polymerization, and might act as mechanosensors by integrins that pull on the ECM adjacent to the protrusive actin core. More insights into the architecture and force generation of podosomes have been recently discussed by Van den Dries et al. [56].

Integrin α6β1 in endothelial podosome rosettes is believed to originate from FAs, as inhibition of integrin recycling and microtubules, but not *de novo* protein synthesis, impaired podosomes rosette formation [49]. Recent studies suggest that the crosstalk between FAs and podosomes is regulated by microtubules, which are captured by the cortical microtubule stabilizing complex (CMSC) [57]. This complex consists of KANK, liprins, ELKS, and LL5α/β and associates with integrin adhesions through an interaction between talin in FAs and KANK in CMSCs [57-60]. Podosome formation depends on the presence of microtubules, while FAs are increased after inhibition of microtubules [46, 49]. Consistent with this, stabilization of microtubules at integrin adhesions results in sequestration and inactivation of RhoGEF GEF-H1, which subsequently suppresses actomyosin contractility and promotes podosome assembly and FA disassembly [59]. Taken together, microtubules seem to play a major role in invadosome assembly by regulating cellular tension, disassembling FAs and facilitating the transport of FA components to newly formed invadosomes, while maintaining low tensile forces at these sites (Figure 2).

In summary, integrins can form similar yet distinct mechanosensitive adhesions coupled to actin that either push and degrade or pull on the substrate by making use of actin polymerization or actomyosin contractility respectively. The necessity for forming either FAs and/or invadosomes seems to be cell type and situation specific and can be regulated by (local) changes in substrate rigidity, altered actomyosin contractility, microtubule polymerization, and growth factor stimulation.

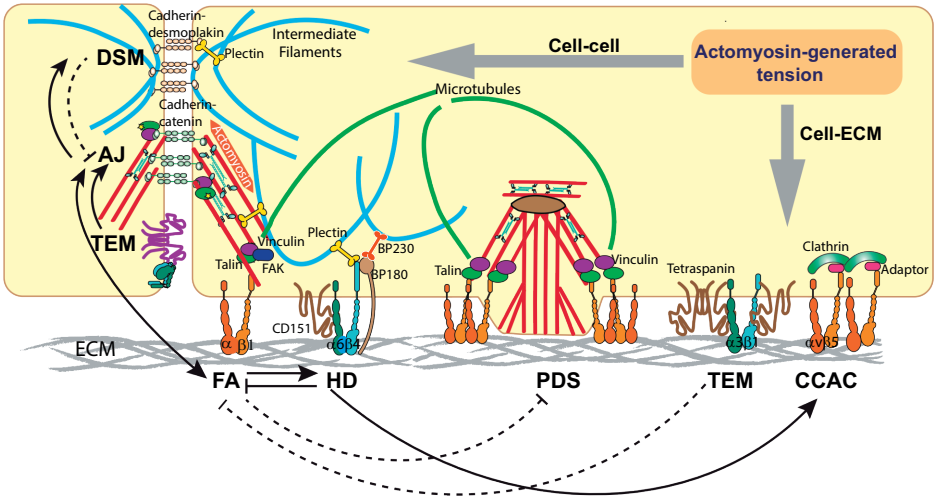


Figure 2 Crosstalk between adhesion complexes integrates cellular mechanotransduction. Actomyosin-generated tension can be transmitted and applied to the ECM by focal adhesions (FAs) and to the cell-cell interface by adherens junctions (AJs). FAs and AJs share similarities in mechanosensing and force transduction due to mechanosensitive proteins and their association with the actomyosin cytoskeleton. The double-sided arrows indicate their reciprocal relationship, which regulates a balanced force distribution between the cell, the ECM, and neighboring cells. Hemidesmosomes (HDs) and desmosomes (DSMs), which are connected to the intermediate filament network, crosstalk with FAs and AJs through plectin that links the IF network to F-actin. Both HDs and DSMs require actomyosin contractility for their assembly. Podosomes/Invadopodia generate local protrusive forces that are generated by actin polymerization and local tensile forces by the integrins surrounding the actin core to balance the protrusive force. Podosomes assemble in response to decreased cellular tension induced by the disassembly of FAs. This process is mediated by microtubules, which facilitate the transport of the shared elements between them and regulate (local) tension. Tetraspanin-enriched-microdomains (TEMs) can be found both at the cell-ECM and cell-cell interface. Tetraspanin CD151 interacts with α6β4 in HDs and/or with α3β1 and α6β1 outside of FAs, which might prevent FA maturation and force transduction on a laminin-rich matrix. Tetraspanins at cell-cell adhesions stabilize the cadherin-catenin complexes and may allow force loading on AJs. Clathrin-containing adhesion complexes (CCACs) are not associated with the actomyosin cytoskeleton and their assembly takes place independently of cellular tension. However, if cellular forces are increased (e.g. by preventing the formation of HDs) integrin αVβ5 is found primarily at FAs instead of CCACs. The dash lines in the figure indicate that the crosstalk between adhesion complexes is less well established.

Hemidesmosomes oppose mechanotransduction by focal adhesions

So far, we have discussed different cell-ECM adhesion complexes that are connected to the actin cytoskeleton, but integrins can also assemble adhesion structures that are not linked to actin. HDs are specialized junctions that mediate stable anchorage of epithelial cells to the underlying basal lamina. The classical type I HDs in (pseudo-) stratified epithelia contain the integrin α6β4, the plakin proteins plectin and BP230 (or BPAG1e), and the transmembrane proteins BP180 (or BPAG2) and tetraspanin CD151. Type II HDs are present in simple epithelia (e.g. the intestine) and consist of only α6β4 and plectin [14, 61]. Recently, we found that cultured keratinocytes also form an alternative HD adhesion structure that, in addition to the type II HD components α6β4 and plectin, contains the integrin α3β1 and CD151 [62]. In contrast to FAs and podosomes, HDs are not associated with intracellular actin bundles but with keratin IFs. IFs can be stretched several times their original length without breaking due to their elastic nature and allow cells to resist external mechanical stress [63-66]. Whether HD components contain mechanosensitive elements, like talin in FAs, is poorly established. Elucidation of the crystal structure of the cytoskeletal cross-linker plectin and subsequent simulations to analyse stretching and unfolding events indicate that plectin contains an auto-inhibited SH3 domain surrounded by spectrin repeats, which elastically deform under tension and unmask the SH3 domain [67, 68]. SH3 domains mediate protein-protein interactions by binding proline-rich regions, yet plectin contains a non-canonical SH3 domain [69]. Furthermore, several tyrosine-phosphorylation sites have been identified in the third and fourth FnIII domains of the β4 cytoplasmic domain that, as judged from the crystal structure of these domains, are not accessible to kinases, but nevertheless have been shown to be phosphorylated [70-73]. Unfolding of these domains due to stretching may expose these cryptic phosphorylation sites and thus promote biochemical signalling events. However, how keratin filaments produce force-induced unfolding of these domains is currently unclear, thereby making the role of these domains in mechanosignaling uncertain.

Although the role of HDs as mechanosensors awaits further investigation, recent findings indicate that HDs in keratinocytes can influence mechanotransduction by opposing force generation by FAs and the actin cytoskeleton [74]. Traction force microscopy measurements demonstrated increased traction forces in keratinocytes in which HDs failed to assemble due to deletion or mutation of integrin β4. In addition, keratinocytes lacking HDs displayed increased actomyosin contractility, FA maturation, and activity of the mechanosensitive transcriptional regulator YAP (Box 1) [74]. These findings build on earlier studies showing an important role of plectin and IFs in modulating cellular tension [75-77]. Because HDs and FAs are often located in close proximity to each other [74, 78], we proposed that these two adhesion complexes are mechanically coupled via plectin,

which is bound to both the HD-associated IF network and the actomyosin cytoskeleton at FAs (Figure 2). This cytoskeletal coupling reduces the cellular tension generated by FAs. However, force modulation by α6β4 and plectin might be limited to epithelial cells. Indeed, the deletion of plectin in myoblasts and fibroblasts resulted in reduced cell contractility and traction force [76, 79, 80]. Additionally, in endothelial cells, vimentin-type IFs have been shown to associate with integrin αVβ3 and plectin in FAs and to stabilize these adhesion complexes in response to shear stress [81, 82].
In summary, integrin α6β4 and plectin in HDs can lower tension and traction force generated by FAs in epithelial cells through the interaction between the actin and keratin IF cytoskeletons. The integrin β4 subunit and plectin might also play a mechanosensory role, as these proteins contain domains that could be mechanically stretched to unmask sites for protein-protein interactions and signalling events. The tensile forces required to stretch these domains might be transmitted by the coupling of the actomyosin fibers to the IF network.

Clathrin-containing adhesion complexes form independently of actomyosin contractility

Intriguingly, it has been observed that HDs in keratinocytes control the subcellular distribution of integrin αVβ5 in FAs versus clathrin lattices by modulating cellular tension [74]. Clathrin molecules have been extensively studied as endocytic entities, with the main function to internalize membrane-bound proteins. Besides forming clathrin-coated vesicles for endocytosis, cells also assemble larger arrays of clathrin molecules, called flat clathrin lattices or plaques [15, 16, 83]. The function of these lattices is not completely understood. Smaller lattices represent intermediate structures during the formation of highly curved clathrin-coated pits that are eventually pinched off from the plasma membrane as endocytic transport vesicles [84]. In addition, more stable and larger arrays of clathrin molecules have been described that do not transform into endocytic vesicles, although occasionally clathrin-coated vesicles can be found in their peripheral regions. The physiological role of these structures remains largely unexplored. Recent studies suggest that they serve as platforms for growth factor receptor signaling [83, 85] and anchorage of desmin IFs in skeletal muscle [86]. Additionally, they may mediate cell-ECM adhesion during mitosis when FAs are disassembled [87] and promote breast cancer cell migration [88].
It is not yet understood why some clathrin lattices become curved pits, while others remain flat [84]. One hypothesis is that stable lattices are the result of frustrated endocytosis, triggered by the binding of integrins to their cognate ligand, but unable to proceed because of structural and/or physical constraints. Many of the large clathrin arrays that are found in close contact with the substratum contain the vitronectin receptor integrin αVβ5 [83, 85, 87, 89]. These αVβ5-containing clathrin lattices have been

referred to as flat clathrin lattices, clathrin plaques, or reticular adhesions, but are considered to be the same type of structure and are referred to as clathrin-containing adhesion complexes (CCACs) [17]. Vitronectin is an abundant plasma protein and the main adhesive protein for cells grown *in vitro* in culture medium supplemented with bovine calf serum. It remains tightly bound after it is adsorbed on the substrate, which will hinder the internalization of vitronectin through receptor-mediated endocytosis and accordingly prolong the presence of αVβ5 and clathrin at the plasma membrane. Moreover, clathrin lattices containing integrin α2β1 assemble on 3D collagen fibers [88], which due to size constraints cannot be internalized by cells using the cell endocytotic machinery. Therefore, like the lattices formed by αVβ5 on vitronectin, the lattices on collagen may be the result of frustrated endocytosis.

Remarkably, it has been shown that the formation of CCACs is dependent on the rigidity of the substrate, suggesting that like FAs, CCACs are mechanosensitive structures [85]. Crosstalk exists between FAs and CCACs, as αVβ5 can shuttle between CCACs and FAs in response to changes in actomyosin-generated tension [74, 89]. Localization of αVβ5 in CCACs is favored upon myosin inhibition or in keratinocytes that assemble HDs and modulate tensile forces generated by FAs (Figure 2) [74, 89]. Integrin αVβ5-containing CCACs can be assembled independently of FAs, as depleting talin increases CCAC formation [85] and mutating β5 to prevent its localization in FAs does not abolish CCAC assembly [89]. These observations indicate that in contrast to FAs, αVβ5-containing CCACs are not linked to the force-generating actomyosin cytoskeleton and their formation occurs independently of actomyosin contractility [85, 89]. Although F-actin can be found associated with these lattices [83, 86, 89], inhibition of actin polymerization does not prevent their formation but rather stabilizes these complexes [83, 85]. Possibly, clathrin-coated pit formation in the peripheral regions of the lattices is prevented or delayed by perturbing the actin cytoskeleton, which can result in the expansion of the flat clathrin lattices. A weaker association of vitronectin with soft substrates (i.e. polyacrylamide gels) might explain why the assembly of CCACs on these substrates is less efficient. In contrast to FAs that can sense substrate rigidity because of their association with the contractile actin cytoskeleton via mechanosensitive proteins such as talin, CCACs are not associated with talin or actomyosin stress fibers. Instead, integrin-containing CCACs interact with clathrin adaptors, including Dab2, ARH, and NUMB, whose binding sites on the integrin β5 cytoplasmic tail (partially) overlap with that of talin [17, 37, 89].

In summary, integrin-based CCACs are sites of cell-ECM adhesion that, in contrast to FAs and podosomes, do not require actomyosin contractility or actin polymerization for their formation but rather form as a result of frustrated endocytosis. Although their assembly is dependent on the mechanical properties of the substratum, it is unlikely that these structures play an active role in mechanosensing or force transduction due to their limited connection to the cytoskeleton. Their contribution to cell-ECM adhesion

is needed for the formation and function of striated muscle [86] and perhaps in other cell types that fail to establish other adhesion structures. Remarkably, integrins that are found in CCACs can also localize in FAs and this localization is promoted by increased cellular tension.

Regulation of cellular tension by integrins in tetraspanin-enriched microdomains

Integrins can also interact with tetraspanins in TEMs that are formed at cell-matrix and cell-cell interfaces. Tetraspanins are a large and widely expressed family of proteins consisting of 4 transmembrane-spanning regions with a conserved structure that interact directly and specifically with proteins, signalling molecules, and other tetraspanins [18]. Although TEMs were initially thought to consist of different types of tetraspanins, recent studies using advanced microscopy indicated that TEMs primarily consist of only one type of tetraspanin together with its partner proteins. The proposed function of TEMs is to regulate the membrane compartmentalization of proteins that interact with tetraspanins in order to regulate their trafficking and function. In this way, tetraspanins contribute to multiple physiological and pathological conditions, including cell-cell fusion, immune response, infectious diseases, and cancer progression [18, 90]. Many integrin subtypes have been described to associate with tetraspanins. Complexes of tetraspanin CD151 with the integrins α3β1 and α6β1, and CD81 with integrin α4β1 are found consistently in epithelial and immune cells, respectively. Integrin α3β1 forms a relatively stable complex with CD151 compared to other integrins, whose interaction with tetraspanins is less robust [91, 92]. Although α3β1 and α6β1 are components of FAs, tetraspanins are excluded from mature FAs and integrins in TEMs are not connected with talin and the contractile actomyosin stress fibers. A possible explanation for this observation is that the lipid composition of TEMs might not be suitable for talin activation and integrin binding. A distinguishing feature of tetraspanins and their partner molecules is a specific post-transcriptional modification (i.e. palmitoylation), which may facilitate their selective incorporation in cholesterol and sphingolipids-rich membrane domains and prevent talin from becoming activated through binding to phosphatidylinositol 4,5-bisphosphate (PIP2) [93-95].

The fact that TEMs are not associated with actomyosin fibers makes it unlikely that integrins in TEMs promote mechanosignaling and force generation. However, tetraspanins could influence cellular tension that drives FA maturation by sequestering integrins in TEMs and/or by modulating Rho GTPase activity (Figure 2). It has been shown that the binding of CD151 to α3β1 and/or α6β1 regulates cellular tension by triggering the activation of Rac1 and Cdc42 [96], while suppressing RhoA activity [96-101]. In contrast to CD151, the tetraspanin CD9 promotes actin arrangement and cell contractility by augmenting RhoA activity [102]. Additionally, a study combining proteomic and biochemical

analyses highlighted a direct interaction of CD81 with Rac. Silencing CD81 leads to increased Rac activity, aberrant FA formation and enhanced adhesion dynamics [103]. Both CD9 and CD81 can indirectly connect to the actin cytoskeleton via association with EWI proteins, which contain binding sites for actin-linking ezrin-radixin-moesin (ERM) proteins [104]. The binding of CD9 with EWI-2 versus integrins was shown to depend on palmitoylation of the tetraspanin and its interaction proteins [105]. These findings indicate that (unpalmitoylated-) CD9/CD81 could indirectly connect to the actin cytoskeleton and Rho GTPases to induce cellular tension, which seems to be favoured when these tetraspanins do not interact with integrins.

Briefly, these studies indicate a role for tetraspanins in adhesion via interactions with integrins and other tetraspanins, and in the regulation of intracellular tension through modulation of Rho GTPase activity and/or recruitment of integrins to TEMs instead of FAs.

Force distribution between cell-ECM and cell-cell junctions

So far, we have discussed how different integrin subtypes in cell-ECM adhesions contribute to, oppose, or do not play an active role in mechanotransduction. Yet many cells in multicellular organisms not only interact with the ECM but also communicate with neighbouring cells by forming cell-cell junctions, including AJs, DSMs, tight junctions, and gap junctions. AJs and DSMs connect the cytoskeleton of adjacent cells to enable the transduction of mechanical forces [20]. Cadherins are the main adhesion receptors in AJs and DSMs, and mediate adhesion primarily through homotypic interactions. Classical cadherins (e.g. E-cadherin) are found in AJs, where they interact with α- and β-catenin to tether the actin cytoskeleton of neighboring cells. Additionally, AJs consist of p120-catenin, which controls the clustering of cadherins [20]. Coupling of AJs to actomyosin cytoskeleton allows these junctions to actively sense and transduce forces between individual cells. Similar to the mechanosensitive protein talin in FAs, α-catenin is partially unfolded by high intracellular force to reveal a cryptic binding site for vinculin [21, 106] and allows vinculin to reinforce the association between cadherin and actin.

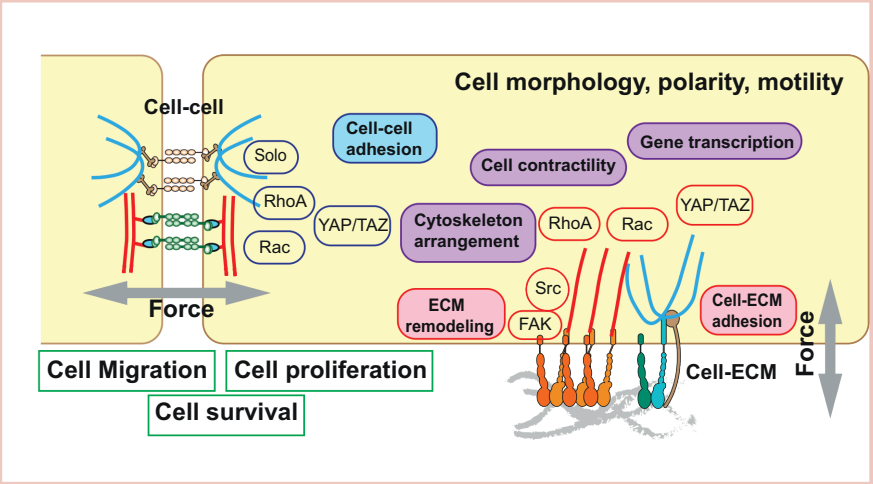
AJs and FAs can have either an antagonistic or cooperative relation, which is mediated by their connection to the actin cytoskeleton and results in a balanced force distribution between sites of cell-cell and cell-ECM attachment (Figure 2). Engagement of integrin-matrix adhesions on fibronectin or collagen increases tension at AJs and subsequently disrupts cell-cell contacts [107, 108]. Additionally, cell-ECM traction force is directly proportional to cell-cell force at E-cadherin junctions in cell pairs [109]. In case three cells are arranged in a linear fashion, cell-ECM traction forces were found to be low in the inner and high in the outer cells. Yet, intercellular forces were higher in the inner cell and equal that of the forces acting at cell-matrix adhesions in the outer cells. Thus, despite the fact that inner and outer cells in the linear three-cell island differ in the extent of cell-cell and cell-matrix adhesions, they experience comparable total forces

[109]. Moreover, the absence of cadherin-based AJs results in changes in the distribution of traction force, which extends from the periphery throughout the cell colony, aiming to rescue the imbalanced cell tension [110]. More details about the crosstalk between AJs and FAs are discussed in several recent reviews [3, 21, 111, 112]. Strikingly, the mechanosensitive FA proteins vinculin and talin are also found in AJs, which raises the question if these proteins could be involved in the crosstalk between FAs and AJs. Vinculin seems unlikely to be the subject of competition between AJs and FAs, as it is expressed at high levels by cells and could therefore distribute to both complexes. Furthermore, its localization to either one of these complexes depends on site-specific phosphorylation mediated by different kinases [113, 114]. Intriguingly, a 70 kDa C-terminal arginylated fragment of talin, generated by calpain-2 cleavage, localizes at cadherin-containing junctions and promotes intercellular adhesion [115]. Although further studies need to be performed to determine the precise role of talin in cell-cell contacts, regulation of force transduction at AJs versus FAs through the cleavage and redistribution of talin is an interesting possibility to consider.

Like HDs, DSMs are adhesive junctions that are associated with the IF system and function to resist mechanical stress [116]. It has long been thought that DSMs have no role in mechanosensing, but recent studies using FRET-based tension sensors showed that the desmosomal cadherin desmoglein 2 and the plakin protein desmoplakin can bear mechanical tension, thus opening the possibility that DSMs can serve as sites of mechanotransduction [116, 117]. By analogy to the role of plectin in force modulation by HDs, desmoplakin in DSMs might initiate mechanosignaling after relief of its auto-inhibited non-canonical SH3 domain by mechanical force [67] and oppose force generation by AJs [118] (Figure 2). Moreover, DSM assembly requires the presence of AJs [119], again similar to the role of FAs in formation of HDs. Recently, Solo (ARHGEF40), a guanine nucleotide exchange factor, which promotes contractility generation via the RhoA-ROCK pathway has been implicated in the formation of DSMs and HDs [120, 121]. Solo also regulates the organization of keratin and decelerates collective cell migration by generating tensile forces that act in the opposite direction of migration and by promoting the assembly of DSMs [121]. These data suggest that Solo integrates IF-associated adhesion complexes and the contractile actin cytoskeleton as part of a mechanism to regulate mechanotransduction during cell migration (Box 1).

Box Transduction of mechanical stimuli

Cells not only sense alterations in their mechanical environment through cell-ECM and cell-cell adhesion complexes, but also can convert this information into biochemical signals. Several proteins in these structures respond to the mechanical stimuli by changing their conformation, altering their phosphorylation status and initiating signaling pathways that regulate gene expression and induce cytoskeletal remodeling. As such, cells can rapidly adjust their behavior to changes in their environment.



Box figure Adhesion receptors that mediate cell-ECM (integrins) and cell-cell (cadherins) adhesion play an important role in mechanotransduction. In response to physical stimuli, they can activate multiple signaling pathways, including FAK-Src signaling that controls the turnover of FAs, cell adhesion and migration and those that involve the activity of the small GTPases RhoA and Rac, which play a role in the organization of the cytoskeleton, actin polymerization, and actomyosin contractility. These pathways regulate the activity YAP/TAZ, which controls gene expression. At cell-cell adhesions, the RhoA activity is controled by the guanine nucleotide exchange factor Solo, which promotes the formation of desmosomes and slows down collective cell migration.

Intriguingly, some integrins localize at cell-cell junctions and can regulate their formation both *in vivo* and *in vitro*. Loss of integrin α3β1 leads to cell-cell adhesion defects in both zebrafish [122] and mouse kidney cells [123]. In lung epithelial cells, α3β1 is a critical regulator of the epithelial-mesenchymal transition in response to injury [124]. In addition to the mechanically driven crosstalk between integrins and cadherins, these molecules also interact with each other through lateral association with other scaffold proteins or molecules within the membrane [111, 125]. This was shown for the interaction

of α3β1 with tetraspanin CD151, which stabilizes cadherin-catenin-based adhesions in epithelial cells [125]. Additionally, integrin α2β1 has been detected at cell-cell junctions in melanoma cells in association with either E- or N-cadherin. Silencing of N-cadherin resulted in the redistribution of α2β1 into cell-matrix adhesions and decreased cell motility [126]. Moreover, α2β1 can interact with an RGD motif in cadherin 17 [127], which could indicate that specific integrins bind proteins in cell-cell junctions as alternative ligands and might play a role in adhesion at these sites. On the other hand, N-cadherin can stabilize integrin α5β1 in an inactive conformation at cell-cell junctions to promote fibronectin assembly by active integrins only at the tissue boundaries during zebrafish development [128].

Taken together, parallels and extensive crosstalk exist between integrin-containing cell-ECM and cadherin-containing cell-cell junctions (Figure 2). Whether integrins at cell-cell junctions are directly involved in mechanotransduction or how their subcellular distribution is orchestrated remains to be resolved.

CONCLUSION

Integrins can localize in a variety of cell-ECM and cell-cell adhesions and impact mechanotransduction. Although most integrins seem to play similar or complementary roles in mechanosensing, their contribution to force generation can differ dramatically. Integrin α5β1 promotes the generation of tensile and traction forces in FAs, while αVβ3 decreases force transduction in this adhesion complex. In HDs, integrin α6β4 reduces cellular tension, FA maturation, and force transduction. The assembly of integrin αVβ5 in FAs or clathrin-containing adhesion complexes is influenced by changes in cellular tension. Moreover, the integrins α2β1, α3β1, α5β1, and α6β1 can be found in multiple adhesion structures, such as FAs, podosomes, TEMs, and/or cadherin-based cell-cell junctions. Their subcellular distribution is determined by the interaction with specific integrin-binding partners and, depending on their localization, these integrins can contribute differently to mechanotransduction. Consequently, inhibition/deletion of specific integrins or other components of adhesion complexes can result in an altered integrin distribution and change the assembly of cell-ECM and cell-cell adhesion complexes. Extensive crosstalk exists between cell-cell and cell-ECM adhesion complexes and the associated cytoskeleton, which might be regulated in a tissue-specific and context-dependent manner. Therefore, the overall contribution of integrins to sensing, responding to, and generating mechanical forces should not be based on one specific integrin or adhesion complex but on the integrated network of the cellular cytoskeleton and the linked cell-ECM and cell-cell adhesions. Future studies will be required to provide further

insight into how the crosstalk between cell-ECM and cell-cell adhesion complexes is regulated and fine-tuned in specific biological processes.

ACKNOWLEDGMENTS

We thank Alessandra Cambi, Reinhard Fässler, Metello Innocenti, Coert Margadant, Jose de Pereda, Veronika Ramovs, and Roy Zent for discussion and critical reading of the manuscript. Lisa te Molder is thanked for contributing one of the immunofluorescence images.

REFERENCES

1. Iskratsch, T., H. Wolfenson, and M.P. Sheetz, *Appreciating force and shape-the rise of mechanotransduction in cell biology.* Nat Rev Mol Cell Biol, 2014. **15**(12): p. 825-33.
2. Paluch, E.K., C.M. Nelson, N. Biais, B. Fabry, J. Moeller, B.L. Pruitt, C. Wollnik, G. Kudryasheva, F. Rehfeldt, and W. Federle, *Mechanotransduction: use the force(s).* BMC Biol, 2015. **13**: p. 47.
3. Han, M.K.L. and J. de Rooij, *Converging and Unique Mechanisms of Mechanotransduction at Adhesion Sites.* Trends Cell Biol, 2016. **26**(8): p. 612-623.
4. Martino, F., A.R. Perestrelo, V. Vinarsky, S. Pagliari, and G. Forte, *Cellular Mechanotransduction: From Tension to Function.* Front Physiol, 2018. **9**: p. 824.
5. Geiger, B. and K.M. Yamada, *Molecular architecture and function of matrix adhesions.* Cold Spring Harb Perspect Biol, 2011. **3**(5).
6. Jansen, K.A., P. Atherton, and C. Ballestrem, *Mechanotransduction at the cell-matrix interface.* Semin Cell Dev Biol, 2017. **71**: p. 75-83.
7. Sun, Z., S.S. Guo, and R. Fassler, *Integrin-mediated mechanotransduction.* J Cell Biol, 2016. **215**(4): p. 445-456.
8. Elosegui-Artola, A., X. Trepat, and P. Roca-Cusachs, *Control of Mechanotransduction by Molecular Clutch Dynamics.* Trends Cell Biol, 2018. **28**(5): p. 356-367.
9. Hynes, R.O., *Integrins: bidirectional, allosteric signaling machines.* Cell, 2002. **110**(6): p. 673-87.
10. Seetharaman, S. and S. Etienne-Manneville, *Integrin diversity brings specificity in mechanotransduction.* Biol Cell, 2018. **110**(3): p. 49-64.
11. Linder, S. and C. Wiesner, *Feel the force: Podosomes in mechanosensing.* Exp Cell Res, 2016. **343**(1): p. 67-72.
12. Litjens, S.H., J.M. de Pereda, and A. Sonnenberg, *Current insights into the formation and breakdown of hemidesmosomes.* Trends Cell Biol, 2006. **16**(7): p. 376-83.
13. de Pereda, J.M., E. Ortega, N. Alonso-Garcia, M. Gomez-Hernandez, and A. Sonnenberg, *Advances and perspectives of the architecture of hemidesmosomes: lessons from structural biology.* Cell Adh Migr, 2009. **3**(4): p. 361-4.
14. Walko, G., M.J. Castanon, and G. Wiche, *Molecular architecture and function of the hemidesmosome.* Cell Tissue Res, 2015. **360**(2): p. 363-78.
15. Grove, J., D.J. Metcalf, A.E. Knight, S.T. Wavre-Shapton, T. Sun, E.D. Protonotarios, L.D. Griffin, J. Lippincott-Schwartz, and M. Marsh, *Flat clathrin lattices: stable features of the plasma membrane.* Mol Biol Cell, 2014. **25**(22): p. 3581-94.
16. Lampe, M., S. Vassilopoulos, and C. Merrifield, *Clathrin coated pits, plaques and adhesion.* J Struct Biol, 2016. **196**(1): p. 48-56.
17. Lock, J.G., F. Baschieri, M.C. Jones, J.D. Humphries, G. Montagnac, S. Stromblad, and M.J. Humphries, *Clathrin-containing adhesion complexes.* J Cell Biol, 2019. **218**(7): p. 2086-2095.
18. Charrin, S., S. Jouannet, C. Boucheix, and E. Rubinstein, *Tetraspanins at a glance.* J Cell Sci, 2014. **127**(Pt 17): p. 3641-8.
19. Hemler, M.E., *Tetraspanin functions and associated microdomains.* Nat Rev Mol Cell Biol, 2005. **6**(10): p. 801-11.
20. Pannekoek, W.J., J. de Rooij, and M. Gloerich, *Force transduction by cadherin adhesions in morphogenesis.* F1000Res, 2019. **8**.

21. Mui, K.L., C.S. Chen, and R.K. Assoian, *The mechanical regulation of integrin-cadherin crosstalk organizes cells, signaling and forces.* J Cell Sci, 2016. **129**(6): p. 1093-100.
22. Kowalczyk, A.P. and K.J. Green, *Structure, function, and regulation of desmosomes.* Prog Mol Biol Transl Sci, 2013. **116**: p. 95-118.
23. Burridge, K., *Focal adhesions: a personal perspective on a half century of progress.* FEBS J, 2017. **284**(20): p. 3355-3361.
24. Manninen, A. and M. Varjosalo, *A proteomics view on integrin-mediated adhesions.* Proteomics, 2017. **17**(3-4).
25. Danen, E.H., J. van Rheenen, W. Franken, S. Huveneers, P. Sonneveld, K. Jalink, and A. Sonnenberg, *Integrins control motile strategy through a Rho-cofilin pathway.* J Cell Biol, 2005. **169**(3): p. 515-26.
26. Schiller, H.B., M.R. Hermann, J. Polleux, T. Vignaud, S. Zanivan, C.C. Friedel, Z. Sun, A. Raducanu, K.E. Gottschalk, M. Thery, M. Mann, and R. Fassler, *beta1- and alphav-class integrins cooperate to regulate myosin II during rigidity sensing of fibronectin-based microenvironments.* Nat Cell Biol, 2013. **15**(6): p. 625-36.
27. Milloud, R., O. Destaing, R. de Mets, I. Bourrin-Reynard, C. Oddou, A. Delon, I. Wang, C. Albiges-Rizo, and M. Balland, *alphavbeta3 integrins negatively regulate cellular forces by phosphorylation of its distal NPXY site.* Biol Cell, 2017. **109**(3): p. 127-137.
28. Benito-Jardon, M., S. Klapproth, L.I. Gimeno, T. Petzold, M. Bharadwaj, D.J. Muller, G. Zuchtriegel, C.A. Reichel, and M. Costell, *The fibronectin synergy site re-enforces cell adhesion and mediates a crosstalk between integrin classes.* Elife, 2017. **6**.
29. Bachmann, M., M. Schafer, V.V. Mykuliak, M. Ripamonti, L. Heiser, K. Weissenbruch, S. Krubel, C.M. Franz, V.P. Hytonen, B. Wehrle-Haller, and M. Bastmeyer, *Induction of ligand promiscuity of alphaVbeta3 integrin by mechanical force.* J Cell Sci, 2020.
30. De Mets, R., I. Wang, M. Balland, C. Oddou, P. Moreau, B. Fourcade, C. Albiges-Rizo, A. Delon, and O. Destaing, *Cellular tension encodes local Src-dependent differential beta1 and beta3 integrin mobility.* Mol Biol Cell, 2019. **30**(2): p. 181-190.
31. Lee, S.E., R.D. Kamm, and M.R. Mofrad, *Force-induced activation of talin and its possible role in focal adhesion mechanotransduction.* J Biomech, 2007. **40**(9): p. 2096-106.
32. del Rio, A., R. Perez-Jimenez, R. Liu, P. Roca-Cusachs, J.M. Fernandez, and M.P. Sheetz, *Stretching single talin rod molecules activates vinculin binding.* Science, 2009. **323**(5914): p. 638-41.
33. Austen, K., P. Ringer, A. Mehlich, A. Chrostek-Grashoff, C. Kluger, C. Klingner, B. Sabass, R. Zent, M. Rief, and C. Grashoff, *Extracellular rigidity sensing by talin isoform-specific mechanical linkages.* Nat Cell Biol, 2015. **17**(12): p. 1597-606.
34. Anthis, N.J., K.L. Wegener, D.R. Critchley, and I.D. Campbell, *Structural diversity in integrin/talin interactions.* Structure, 2010. **18**(12): p. 1654-66.
35. Roca-Cusachs, P., A. del Rio, E. Puklin-Faucher, N.C. Gauthier, N. Biais, and M.P. Sheetz, *Integrin-dependent force transmission to the extracellular matrix by alpha-actinin triggers adhesion maturation.* Proc Natl Acad Sci U S A, 2013. **110**(15): p. E1361-70.
36. Shams, H. and M.R.K. Mofrad, *alpha-Actinin Induces a Kink in the Transmembrane Domain of beta3-Integrin and Impairs Activation via Talin.* Biophys J, 2017. **113**(4): p. 948-956.

37. Calderwood, D.A., Y. Fujioka, J.M. de Pereda, B. Garcia-Alvarez, T. Nakamoto, B. Margolis, C.J. McGlade, R.C. Liddington, and M.H. Ginsberg, *Integrin beta cytoplasmic domain interactions with phosphotyrosine-binding domains: a structural prototype for diversity in integrin signaling.* Proc Natl Acad Sci U S A, 2003. **100**(5): p. 2272-7.
38. Wickstrom, S.A., A. Lange, E. Montanez, and R. Fassler, *The ILK/PINCH/parvin complex: the kinase is dead, long live the pseudokinase!* EMBO J, 2010. **29**(2): p. 281-91.
39. Jahed, Z., Z. Haydari, A. Rathish, and M.R.K. Mofrad, *Kindlin Is Mechanosensitive: Force-Induced Conformational Switch Mediates Cross-Talk among Integrins.* Biophys J, 2019. **116**(6): p. 1011-1024.
40. Bandyopadhyay, A., G. Rothschild, S. Kim, D.A. Calderwood, and S. Raghavan, *Functional differences between kindlin-1 and kindlin-2 in keratinocytes.* J Cell Sci, 2012. **125**(Pt 9): p. 2172-84.
41. van der Bijl, I., K. Nawaz, U. Kazlauskaite, A.M. van Stalborch, S. Tol, A. Jimenez Orgaz, I. van den Bout, N.R. Reinhard, A. Sonnenberg, and C. Margadant, *Reciprocal integrin/integrin antagonism through kindlin-2 and Rho GTPases regulates cell cohesion and collective migration.* Matrix Biol, 2020.
42. Schiller, H.B. and R. Fassler, *Mechanosensitivity and compositional dynamics of cell-matrix adhesions.* EMBO Rep, 2013. **14**(6): p. 509-19.
43. Kuo, J.C., X. Han, C.T. Hsiao, J.R. Yates, 3rd, and C.M. Waterman, *Analysis of the myosin-II-responsive focal adhesion proteome reveals a role for beta-Pix in negative regulation of focal adhesion maturation.* Nat Cell Biol, 2011. **13**(4): p. 383-93.
44. Moreno-Layseca, P., J. Icha, H. Hamidi, and J. Ivaska, *Integrin trafficking in cells and tissues.* Nat Cell Biol, 2019. **21**(2): p. 122-132.
45. David-Pfeuty, T. and S.J. Singer, *Altered distributions of the cytoskeletal proteins vinculin and alpha-actinin in cultured fibroblasts transformed by Rous sarcoma virus.* Proc Natl Acad Sci U S A, 1980. **77**(11): p. 6687-91.
46. Murphy, D.A. and S.A. Courtneidge, *The 'ins' and 'outs' of podosomes and invadopodia: characteristics, formation and function.* Nat Rev Mol Cell Biol, 2011. **12**(7): p. 413-26.
47. Paterson, E.K. and S.A. Courtneidge, *Invadosomes are coming: new insights into function and disease relevance.* FEBS J, 2018. **285**(1): p. 8-27.
48. Destaing, O., E. Planus, D. Bouvard, C. Oddou, C. Badowski, V. Bossy, A. Raducanu, B. Fourcade, C. Albiges-Rizo, and M.R. Block, *beta1A integrin is a master regulator of invadosome organization and function.* Mol Biol Cell, 2010. **21**(23): p. 4108-19.
49. Seano, G., G. Chiaverina, P.A. Gagliardi, L. di Blasio, A. Puliafito, C. Bouvard, R. Sessa, G. Tarone, L. Sorokin, D. Helley, R.K. Jain, G. Serini, F. Bussolino, and L. Primo, *Endothelial podosome rosettes regulate vascular branching in tumour angiogenesis.* Nat Cell Biol, 2014. **16**(10): p. 931-41, 1-8.
50. Kedziora, K.M., T. Isogai, K. Jalink, and M. Innocenti, *Invadosomes - shaping actin networks to follow mechanical cues.* Front Biosci (Landmark Ed), 2016. **21**: p. 1092-117.
51. Labernadie, A., A. Bouissou, P. Delobelle, S. Balor, R. Voituriez, A. Proag, I. Fourquaux, C. Thibault, C. Vieu, R. Poincloux, G.M. Charriere, and I. Maridonneau-Parini, *Protrusion force microscopy reveals oscillatory force generation and mechanosensing activity of human macrophage podosomes.* Nat Commun, 2014. **5**: p. 5343.

52. Block, M.R., C. Badowski, A. Millon-Fremillon, D. Bouvard, A.P. Bouin, E. Faurobert, D. Gerber-Scokaert, E. Planus, and C. Albiges-Rizo, *Podosome-type adhesions and focal adhesions, so alike yet so different.* Eur J Cell Biol, 2008. **87**(8-9): p. 491-506.
53. Glazier, R., J.M. Brockman, E. Bartle, A.L. Mattheyses, O. Destaing, and K. Salaita, *DNA mechanotechnology reveals that integrin receptors apply pN forces in podosomes on fluid substrates.* Nat Commun, 2019. **10**(1): p. 4507.
54. Bouissou, A., A. Proag, N. Bourg, K. Pingris, C. Cabriel, S. Balor, T. Mangeat, C. Thibault, C. Vieu, G. Dupuis, E. Fort, S. Leveque-Fort, I. Maridonneau-Parini, and R. Poincloux, *Podosome Force Generation Machinery: A Local Balance between Protrusion at the Core and Traction at the Ring.* ACS Nano, 2017. **11**(4): p. 4028-4040.
55. van den Dries, K., L. Nahidiazar, J.A. Slotman, M.B.M. Meddens, E. Pandzic, B. Joosten, M. Ansems, J. Schouwstra, A. Meijer, R. Steen, M. Wijers, J. Fransen, A.B. Houtsmuller, P.W. Wiseman, K. Jalink, and A. Cambi, *Modular actin nano-architecture enables podosome protrusion and mechanosensing.* Nat Commun, 2019. **10**(1): p. 5171.
56. van den Dries, K., S. Linder, I. Maridonneau-Parini, and R. Poincloux, *Probing the mechanical landscape - new insights into podosome architecture and mechanics.* J Cell Sci, 2019. **132**(24).
57. Sit, B., D. Gutmann, and T. Iskratsch, *Costameres, dense plaques and podosomes: the cell matrix adhesions in cardiovascular mechanosensing.* J Muscle Res Cell Motil, 2019. **40**(2): p. 197-209.
58. Bouchet, B.P., R.E. Gough, Y.C. Ammon, D. van de Willige, H. Post, G. Jacquemet, A.M. Altelaar, A.J. Heck, B.T. Goult, and A. Akhmanova, *Talin-KANK1 interaction controls the recruitment of cortical microtubule stabilizing complexes to focal adhesions.* Elife, 2016. **5**.
59. Rafiq, N.B.M., Y. Nishimura, S.V. Plotnikov, V. Thiagarajan, Z. Zhang, S. Shi, M. Natarajan, V. Viasnoff, P. Kanchanawong, G.E. Jones, and A.D. Bershadsky, *A mechano-signalling network linking microtubules, myosin IIA filaments and integrin-based adhesions.* Nat Mater, 2019. **18**(6): p. 638-649.
60. Sun, Z., H.Y. Tseng, S. Tan, F. Senger, L. Kurzawa, D. Dedden, N. Mizuno, A.A. Wasik, M. Thery, A.R. Dunn, and R. Fassler, *Kank2 activates talin, reduces force transduction across integrins and induces central adhesion formation.* Nat Cell Biol, 2016. **18**(9): p. 941-53.
61. Uematsu, J., Y. Nishizawa, A. Sonnenberg, and K. Owaribe, *Demonstration of type II hemidesmosomes in a mammary gland epithelial cell line, BMGE-H.* J Biochem, 1994. **115**(3): p. 469-76.
62. Te Molder, L., J. Juksar, R. Harkes, W. Wang, M. Kreft, and A. Sonnenberg, *Tetraspanin CD151 and integrin alpha3beta1 contribute to the stabilization of integrin alpha6beta4-containing cell-matrix adhesions.* J Cell Sci, 2019. **132**(19).
63. Sanghvi-Shah, R. and G.F. Weber, *Intermediate Filaments at the Junction of Mechanotransduction, Migration, and Development.* Front Cell Dev Biol, 2017. **5**: p. 81.
64. De Pascalis, C., C. Perez-Gonzalez, S. Seetharaman, B. Boeda, B. Vianay, M. Burute, C. Leduc, N. Borghi, X. Trepat, and S. Etienne-Manneville, *Intermediate filaments control collective migration by restricting traction forces and sustaining cell-cell contacts.* J Cell Biol, 2018. **217**(9): p. 3031-3044.
65. Goldmann, W.H., *Intermediate filaments and cellular mechanics.* Cell Biol Int, 2018. **42**(2): p. 132-138.
66. Charrier, E.E. and P.A. Janmey, *Mechanical Properties of Intermediate Filament Proteins.* Methods Enzymol, 2016. **568**: p. 35-57.

67. Daday, C., K. Kolsek, and F. Grater, *The mechano-sensing role of the unique SH3 insertion in plakin domains revealed by Molecular Dynamics simulations.* Sci Rep, 2017. **7**(1): p. 11669.
68. Suman, S.K., C. Daday, T. Ferraro, T. Vuong-Brender, S. Tak, S. Quintin, F. Robin, F. Grater, and M. Labouesse, *The plakin domain of C. elegans VAB-10/plectin acts as a hub in a mechanotransduction pathway to promote morphogenesis.* Development, 2019. **146**(24).
69. Ortega, E., R.M. Buey, A. Sonnenberg, and J.M. de Pereda, *The structure of the plakin domain of plectin reveals a non-canonical SH3 domain interacting with its fourth spectrin repeat.* J Biol Chem, 2011. **286**(14): p. 12429-38.
70. Alonso-Garcia, N., I. Garcia-Rubio, J.A. Manso, R.M. Buey, H. Urien, A. Sonnenberg, G. Jeschke, and J.M. de Pereda, *Combination of X-ray crystallography, SAXS and DEER to obtain the structure of the FnIII-3,4 domains of integrin alpha6beta4.* Acta Crystallogr D Biol Crystallogr, 2015. **71**(Pt 4): p. 969-85.
71. Shaw, L.M., *Identification of insulin receptor substrate 1 (IRS-1) and IRS-2 as signaling intermediates in the alpha6beta4 integrin-dependent activation of phosphoinositide 3-OH kinase and promotion of invasion.* Mol Cell Biol, 2001. **21**(15): p. 5082-93.
72. Dans, M., L. Gagnoux-Palacios, P. Blaikie, S. Klein, A. Mariotti, and F.G. Giancotti, *Tyrosine phosphorylation of the beta 4 integrin cytoplasmic domain mediates Shc signaling to extracellular signal-regulated kinase and antagonizes formation of hemidesmosomes.* J Biol Chem, 2001. **276**(2): p. 1494-502.
73. Bertotti, A., P.M. Comoglio, and L. Trusolino, *Beta4 integrin activates a Shp2-Src signaling pathway that sustains HGF-induced anchorage-independent growth.* J Cell Biol, 2006. **175**(6): p. 993-1003.
74. Wang, W., A. Zuidema, L. Te Molder, L. Nahidiazar, L. Hoekman, T. Schmidt, S. Coppola, and A. Sonnenberg, *Hemidesmosomes modulate force generation via focal adhesions.* J Cell Biol, 2020. **219**(2).
75. Jiu, Y., J. Peranen, N. Schaible, F. Cheng, J.E. Eriksson, R. Krishnan, and P. Lappalainen, *Vimentin intermediate filaments control actin stress fiber assembly through GEF-H1 and RhoA.* J Cell Sci, 2017. **130**(5): p. 892-902.
76. Bonakdar, N., A. Schilling, M. Sporrer, P. Lennert, A. Mainka, L. Winter, G. Walko, G. Wiche, B. Fabry, and W.H. Goldmann, *Determining the mechanical properties of plectin in mouse myoblasts and keratinocytes.* Exp Cell Res, 2015. **331**(2): p. 331-7.
77. Osmanagic-Myers, S., S. Rus, M. Wolfram, D. Brunner, W.H. Goldmann, N. Bonakdar, I. Fischer, S. Reipert, A. Zuzuarregui, G. Walko, and G. Wiche, *Plectin reinforces vascular integrity by mediating crosstalk between the vimentin and the actin networks.* J Cell Sci, 2015. **128**(22): p. 4138-50.
78. Myllymaki, S.M., U.R. Kamarainen, X. Liu, S.P. Cruz, S. Miettinen, M. Vuorela, M. Varjosalo, and A. Manninen, *Assembly of the beta4-Integrin Interactome Based on Proximal Biotinylation in the Presence and Absence of Heterodimerization.* Mol Cell Proteomics, 2019. **18**(2): p. 277-293.
79. Gregor, M., S. Osmanagic-Myers, G. Burgstaller, M. Wolfram, I. Fischer, G. Walko, G.P. Resch, A. Jorgl, H. Herrmann, and G. Wiche, *Mechanosensing through focal adhesion-anchored intermediate filaments.* FASEB J, 2014. **28**(2): p. 715-29.
80. Na, S., F. Chowdhury, B. Tay, M. Ouyang, M. Gregor, Y. Wang, G. Wiche, and N. Wang, *Plectin contributes to mechanical properties of living cells.* Am J Physiol Cell Physiol, 2009. **296**(4): p. C868-77.

81. Gonzales, M., B. Weksler, D. Tsuruta, R.D. Goldman, K.J. Yoon, S.B. Hopkinson, F.W. Flitney, and J.C. Jones, *Structure and function of a vimentin-associated matrix adhesion in endothelial cells.* Mol Biol Cell, 2001. **12**(1): p. 85-100.
82. Tsuruta, D. and J.C. Jones, *The vimentin cytoskeleton regulates focal contact size and adhesion of endothelial cells subjected to shear stress.* J Cell Sci, 2003. **116**(Pt 24): p. 4977-84.
83. Leyton-Puig, D., T. Isogai, E. Argenzio, B. van den Broek, J. Klarenbeek, H. Janssen, K. Jalink, and M. Innocenti, *Flat clathrin lattices are dynamic actin-controlled hubs for clathrin-mediated endocytosis and signalling of specific receptors.* Nat Commun, 2017. **8**: p. 16068.
84. Sochacki, K.A. and J.W. Taraska, *From Flat to Curved Clathrin: Controlling a Plastic Ratchet.* Trends Cell Biol, 2019. **29**(3): p. 241-256.
85. Baschieri, F., S. Dayot, N. Elkhatib, N. Ly, A. Capmany, K. Schauer, T. Betz, D.M. Vignjevic, R. Poincloux, and G. Montagnac, *Frustrated endocytosis controls contractility-independent mechanotransduction at clathrin-coated structures.* Nat Commun, 2018. **9**(1): p. 3825.
86. Franck, A., J. Laine, G. Moulay, E. Lemerle, M. Trichet, C. Gentil, S. Benkhelifa-Ziyyat, E. Lacene, M.T. Bui, G. Brochier, P. Guicheney, N. Romero, M. Bitoun, and S. Vassilopoulos, *Clathrin plaques and associated actin anchor intermediate filaments in skeletal muscle.* Mol Biol Cell, 2019. **30**(5): p. 579-590.
87. Lock, J.G., M.C. Jones, J.A. Askari, X. Gong, A. Oddone, H. Olofsson, S. Goransson, M. Lakadamyali, M.J. Humphries, and S. Stromblad, *Reticular adhesions are a distinct class of cell-matrix adhesions that mediate attachment during mitosis.* Nat Cell Biol, 2018. **20**(11): p. 1290-1302.
88. Elkhatib, N., E. Bresteau, F. Baschieri, A.L. Rioja, G. van Niel, S. Vassilopoulos, and G. Montagnac, *Tubular clathrin/AP-2 lattices pinch collagen fibers to support 3D cell migration.* Science, 2017. **356**(6343).
89. Zuidema, A., W. Wang, M. Kreft, L. Te Molder, L. Hoekman, O.B. Bleijerveld, L. Nahidiazar, H. Janssen, and A. Sonnenberg, *Mechanisms of integrin alphaVbeta5 clustering in flat clathrin lattices.* J Cell Sci, 2018. **131**(21).
90. Termini, C.M. and J.M. Gillette, *Tetraspanins Function as Regulators of Cellular Signaling.* Front Cell Dev Biol, 2017. **5**: p. 34.
91. Berditchevski, F., *Complexes of tetraspanins with integrins: more than meets the eye.* J Cell Sci, 2001. **114**(Pt 23): p. 4143-51.
92. Yauch, R.L., F. Berditchevski, M.B. Harler, J. Reichner, and M.E. Hemler, *Highly stoichiometric, stable, and specific association of integrin alpha3beta1 with CD151 provides a major link to phosphatidylinositol 4-kinase, and may regulate cell migration.* Mol Biol Cell, 1998. **9**(10): p. 2751-65.
93. Chinthalapudi, K., E.S. Rangarajan, and T. Izard, *The interaction of talin with the cell membrane is essential for integrin activation and focal adhesion formation.* Proc Natl Acad Sci U S A, 2018. **115**(41): p. 10339-10344.
94. McLaughlin, S., J. Wang, A. Gambhir, and D. Murray, *PIP(2) and proteins: interactions, organization, and information flow.* Annu Rev Biophys Biomol Struct, 2002. **31**: p. 151-75.
95. Ye, X., M.A. McLean, and S.G. Sligar, *Phosphatidylinositol 4,5-Bisphosphate Modulates the Affinity of Talin-1 for Phospholipid Bilayers and Activates Its Autoinhibited Form.* Biochemistry, 2016. **55**(36): p. 5038-48.

96. Hong, I.K., D.I. Jeoung, K.S. Ha, Y.M. Kim, and H. Lee, *Tetraspanin CD151 stimulates adhesion-dependent activation of Ras, Rac, and Cdc42 by facilitating molecular association between beta1 integrins and small GTPases.* J Biol Chem, 2012. **287**(38): p. 32027-39.
97. Yamada, M., Y. Sumida, A. Fujibayashi, K. Fukaguchi, N. Sanzen, R. Nishiuchi, and K. Sekiguchi, *The tetraspanin CD151 regulates cell morphology and intracellular signaling on laminin-511.* FEBS J, 2008. **275**(13): p. 3335-51.
98. Varzavand, A., W. Hacker, D. Ma, K. Gibson-Corley, M. Hawayek, O.J. Tayh, J.A. Brown, M.D. Henry, and C.S. Stipp, *alpha3beta1 Integrin Suppresses Prostate Cancer Metastasis via Regulation of the Hippo Pathway.* Cancer Res, 2016. **76**(22): p. 6577-6587.
99. Zhang, F., J.E. Michaelson, S. Moshiach, N. Sachs, W. Zhao, Y. Sun, A. Sonnenberg, J.M. Lahti, H. Huang, and X.A. Zhang, *Tetraspanin CD151 maintains vascular stability by balancing the forces of cell adhesion and cytoskeletal tension.* Blood, 2011. **118**(15): p. 4274-84.
100. Novitskaya, V., H. Romanska, R. Kordek, P. Potemski, R. Kusinska, M. Parsons, E. Odintsova, and F. Berditchevski, *Integrin alpha3beta1-CD151 complex regulates dimerization of ErbB2 via RhoA.* Oncogene, 2014. **33**(21): p. 2779-89.
101. Johnson, J.L., N. Winterwood, K.A. DeMali, and C.S. Stipp, *Tetraspanin CD151 regulates RhoA activation and the dynamic stability of carcinoma cell-cell contacts.* J Cell Sci, 2009. **122**(Pt 13): p. 2263-73.
102. Herr, M.J., S.E. Mabry, and L.K. Jennings, *Tetraspanin CD9 regulates cell contraction and actin arrangement via RhoA in human vascular smooth muscle cells.* PLoS One, 2014. **9**(9): p. e106999.
103. Tejera, E., V. Rocha-Perugini, S. Lopez-Martin, D. Perez-Hernandez, A.I. Bachir, A.R. Horwitz, J. Vazquez, F. Sanchez-Madrid, and M. Yanez-Mo, *CD81 regulates cell migration through its association with Rac GTPase.* Mol Biol Cell, 2013. **24**(3): p. 261-73.
104. Sala-Valdes, M., A. Ursa, S. Charrin, E. Rubinstein, M.E. Hemler, F. Sanchez-Madrid, and M. Yanez-Mo, *EWI-2 and EWI-F link the tetraspanin web to the actin cytoskeleton through their direct association with ezrin-radixin-moesin proteins.* J Biol Chem, 2006. **281**(28): p. 19665-75.
105. Yang, X.H., O.V. Kovalenko, T.V. Kolesnikova, M.M. Andzelm, E. Rubinstein, J.L. Strominger, and M.E. Hemler, *Contrasting effects of EWI proteins, integrins, and protein palmitoylation on cell surface CD9 organization.* J Biol Chem, 2006. **281**(18): p. 12976-85.
106. Buckley, C.D., J. Tan, K.L. Anderson, D. Hanein, N. Volkmann, W.I. Weis, W.J. Nelson, and A.R. Dunn, *Cell adhesion. The minimal cadherin-catenin complex binds to actin filaments under force.* Science, 2014. **346**(6209): p. 1254211.
107. Wang, Y., G. Jin, H. Miao, J.Y. Li, S. Usami, and S. Chien, *Integrins regulate VE-cadherin and catenins: dependence of this regulation on Src, but not on Ras.* Proc Natl Acad Sci U S A, 2006. **103**(6): p. 1774-9.
108. de Rooij, J., A. Kerstens, G. Danuser, M.A. Schwartz, and C.M. Waterman-Storer, *Integrin-dependent actomyosin contraction regulates epithelial cell scattering.* J Cell Biol, 2005. **171**(1): p. 153-64.
109. Maruthamuthu, V., B. Sabass, U.S. Schwarz, and M.L. Gardel, *Cell-ECM traction force modulates endogenous tension at cell-cell contacts.* Proc Natl Acad Sci U S A, 2011. **108**(12): p. 4708-13.

110. Mertz, A.F., Y. Che, S. Banerjee, J.M. Goldstein, K.A. Rosowski, S.F. Revilla, C.M. Niessen, M.C. Marchetti, E.R. Dufresne, and V. Horsley, *Cadherin-based intercellular adhesions organize epithelial cell-matrix traction forces.* Proc Natl Acad Sci U S A, 2013. **110**(3): p. 842-7.
111. Weber, G.F., M.A. Bjerke, and D.W. DeSimone, *Integrins and cadherins join forces to form adhesive networks.* J Cell Sci, 2011. **124**(Pt 8): p. 1183-93.
112. Changede, R. and M. Sheetz, *Integrin and cadherin clusters: A robust way to organize adhesions for cell mechanics.* Bioessays, 2017. **39**(1): p. 1-12.
113. Auernheimer, V., L.A. Lautscham, M. Leidenberger, O. Friedrich, B. Kappes, B. Fabry, and W.H. Goldmann, *Vinculin phosphorylation at residues Y100 and Y1065 is required for cellular force transmission.* J Cell Sci, 2015. **128**(18): p. 3435-43.
114. Bays, J.L., X. Peng, C.E. Tolbert, C. Guilluy, A.E. Angell, Y. Pan, R. Superfine, K. Burridge, and K.A. DeMali, *Vinculin phosphorylation differentially regulates mechanotransduction at cell-cell and cell-matrix adhesions.* J Cell Biol, 2014. **205**(2): p. 251-63.
115. Zhang, F., S. Saha, and A. Kashina, *Arginylation-dependent regulation of a proteolytic product of talin is essential for cell-cell adhesion.* J Cell Biol, 2012. **197**(6): p. 819-36.
116. Price, A.J., A.L. Cost, H. Ungewiss, J. Waschke, A.R. Dunn, and C. Grashoff, *Mechanical loading of desmosomes depends on the magnitude and orientation of external stress.* Nat Commun, 2018. **9**(1): p. 5284.
117. Baddam, S.R., P.T. Arsenovic, V. Narayanan, N.R. Duggan, C.R. Mayer, S.T. Newman, D.A. Abutaleb, A. Mohan, A.P. Kowalczyk, and D.E. Conway, *The Desmosomal Cadherin Desmoglein-2 Experiences Mechanical Tension as Demonstrated by a FRET-Based Tension Biosensor Expressed in Living Cells.* Cells, 2018. **7**(7).
118. Yang, R., J.A. Broussard, K.J. Green, and H.D. Espinosa, *Techniques to stimulate and interrogate cell-cell adhesion mechanics.* Extreme Mech Lett, 2018. **20**: p. 125-139.
119. Michels, C., T. Buchta, W. Bloch, T. Krieg, and C.M. Niessen, *Classical cadherins regulate desmosome formation.* J Invest Dermatol, 2009. **129**(8): p. 2072-5.
120. Fujiwara, S., T.S. Matsui, K. Ohashi, S. Deguchi, and K. Mizuno, *Solo, a RhoA-targeting guanine nucleotide exchange factor, is critical for hemidesmosome formation and acinar development in epithelial cells.* PLoS One, 2018. **13**(4): p. e0195124.
121. Isozaki, Y., K. Sakai, K. Kohiro, K. Kagoshima, Y. Iwamura, H. Sato, D. Rindner, S. Fujiwara, K. Yamashita, K. Mizuno, and K. Ohashi, *The Rho-guanine nucleotide exchange factor Solo decelerates collective cell migration by modulating the Rho-ROCK pathway and keratin networks.* Mol Biol Cell, 2020. **31**(8): p. 741-752.
122. Postel, R., C. Margadant, B. Fischer, M. Kreft, H. Janssen, P. Secades, G. Zambruno, and A. Sonnenberg, *Kindlin-1 mutant zebrafish as an in vivo model system to study adhesion mechanisms in the epidermis.* J Invest Dermatol, 2013. **133**(9): p. 2180-90.
123. Wang, Z., J.M. Symons, S.L. Goldstein, A. McDonald, J.H. Miner, and J.A. Kreidberg, *(Alpha)3(beta)1 integrin regulates epithelial cytoskeletal organization.* J Cell Sci, 1999. **112 (Pt 17)**: p. 2925-35.
124. Kim, K.K., Y. Wei, C. Szekeres, M.C. Kugler, P.J. Wolters, M.L. Hill, J.A. Frank, A.N. Brumwell, S.E. Wheeler, J.A. Kreidberg, and H.A. Chapman, *Epithelial cell alpha3beta1 integrin links beta-catenin and Smad signaling to promote myofibroblast formation and pulmonary fibrosis.* J Clin Invest, 2009. **119**(1): p. 213-24.

125. Chattopadhyay, N., Z. Wang, L.K. Ashman, S.M. Brady-Kalnay, and J.A. Kreidberg, *alpha3beta1 integrin-CD151, a component of the cadherin-catenin complex, regulates PTPmu expression and cell-cell adhesion.* J Cell Biol, 2003. **163**(6): p. 1351-62.
126. Siret, C., C. Terciolo, A. Dobric, M.C. Habib, S. Germain, R. Bonnier, D. Lombardo, V. Rigot, and F. Andre, *Interplay between cadherins and alpha2beta1 integrin differentially regulates melanoma cell invasion.* Br J Cancer, 2015. **113**(10): p. 1445-53.
127. Bartolome, R.A., A. Pelaez-Garcia, I. Gomez, S. Torres, M.J. Fernandez-Acenero, B. Escudero-Paniagua, J.I. Imbaud, and J.I. Casal, *An RGD motif present in cadherin 17 induces integrin activation and tumor growth.* J Biol Chem, 2014. **289**(50): p. 34801-14.
128. Julich, D., G. Cobb, A.M. Melo, P. McMillen, A.K. Lawton, S.G. Mochrie, E. Rhoades, and S.A. Holley, *Cross-Scale Integrin Regulation Organizes ECM and Tissue Topology.* Dev Cell, 2015. **34**(1): p. 33-44.