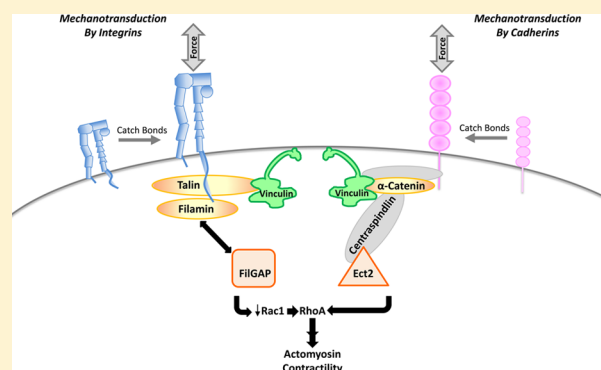


Force Transmission at Cell–Cell and Cell–Matrix Adhesions

Kris A. DeMali,* Xiaowen Sun, and Gabrielle A. Bui

Department of Biochemistry and Interdisciplinary Program in Molecular and Cellular Biology, Roy J. and Lucille A. Carver College of Medicine, Iowa City, Iowa 52242, United States

ABSTRACT: All cells are subjected to mechanical forces throughout their lifetimes. These forces are sensed by cell surface adhesion receptors and trigger robust actin cytoskeletal rearrangements and growth of the associated adhesion complex to counter the applied force. In this review, we discuss how integrins and cadherins sense force and transmit these forces into the cell interior. We focus on the complement of proteins each adhesion complex recruits to bear the force and the signal transduction pathways activated to allow the cell to tune its contractility. A discussion of the similarities, differences, and crosstalk between cadherin- and integrin-mediated force transmission is also presented.



The forces cells experience come in two varieties—those applied from the environment and those that the cell itself generates.^{1,2} Externally applied forces include shear stress generated by fluid flow over cells as well as the forces that cells experience when they are compressed, extended, or stretched.¹ In response to external forces or other stimuli, cells can generate internal forces either by extending membranes or by rearranging their actin cytoskeletons, thereby producing endogenous contractile forces.

Externally applied forces are sensed by numerous cell surface adhesion receptors.^{3–8} Here, we limit our discussion to forces sensed by integrins (adhesion receptors present at sites where cells bind to the extracellular matrix or focal adhesions) and cadherins (adhesion receptors that mediate the strong attachment of cells to neighboring cells or cell–cell adhesions). The ability of these two receptors to respond to external forces governs cell behavior and tissue homeostasis.

How the forces sensed by cadherins and integrins are translated into biochemical signals, a process known as mechanotransduction, has been the subject of intense scrutiny. From this work, it is well appreciated that forces applied to these adhesion receptors trigger robust actin cytoskeletal rearrangements, activate the small GTPase RhoA, and enhance the activity of myosin II culminating in the generation of a cell contraction force through the mutual sliding of actin and myosin II filaments.^{1,8,9} These events allow for growth of the associated adhesion complex and tuning of internal tension to counter the applied force. This process is known as reinforcement or cell stiffening. The cytoskeletal rearrangements and signal transduction pathways culminating in cell stiffening are complex and are dependent upon the type of adhesion receptor that senses the force. In this review, we will present a general overview of how integrins and cadherins sense and transduce forces to the cell interior, compare and contrast the response of both receptors, and discuss the interplay

between force transmission at cell–cell and cell–matrix adhesions. We refer readers to reviews on cadherin-mediated^{5,10,11} or integrin-mediated mechanotransduction^{7,8,12} for a comprehensive description of the signaling and cytoskeletal components involved in force transmission.

MECHANOTRANSDUCTION AT CELL–MATRIX ADHESIONS

Mechanical forces applied at the cell–matrix interface are sensed and transmitted to the cell interior by transmembrane, dimeric adhesion receptors known as integrins. The integrin response to force involves three mechanochemical steps.¹³ Integrins must first bind to extracellular matrix molecules (or become activated). Second, these forces have to be transmitted to the cell interior where they are converted into biochemical signals (i.e., mechanotransduction). Lastly, integrins link to the cytoskeleton to transmit the forces throughout the cell and reinforce their adhesions to resist the force.¹⁴ To facilitate their activation and response to force, integrins recruit (on the inside of the cell) large molecular assemblies of cytoskeletal and/or signaling proteins to form a complex known as a focal adhesion. Many of the cytoplasmic components of focal adhesions sense, respond to, and bear the force applied to integrins. Here, we consider each of the mechanochemical steps with an emphasis on the cytoskeletal and signaling components that allow integrins to withstand force exertion.

Integrin Activation in Response to Force. Integrins are transmembrane-spanning heterodimers of α and β subunits that exist in a bent and upright conformation depending upon their interaction with extracellular matrix ligands. A final step in adopting the upright conformation is binding of talin, a 270

Received: September 19, 2014

Revised: November 20, 2014

Published: December 4, 2014



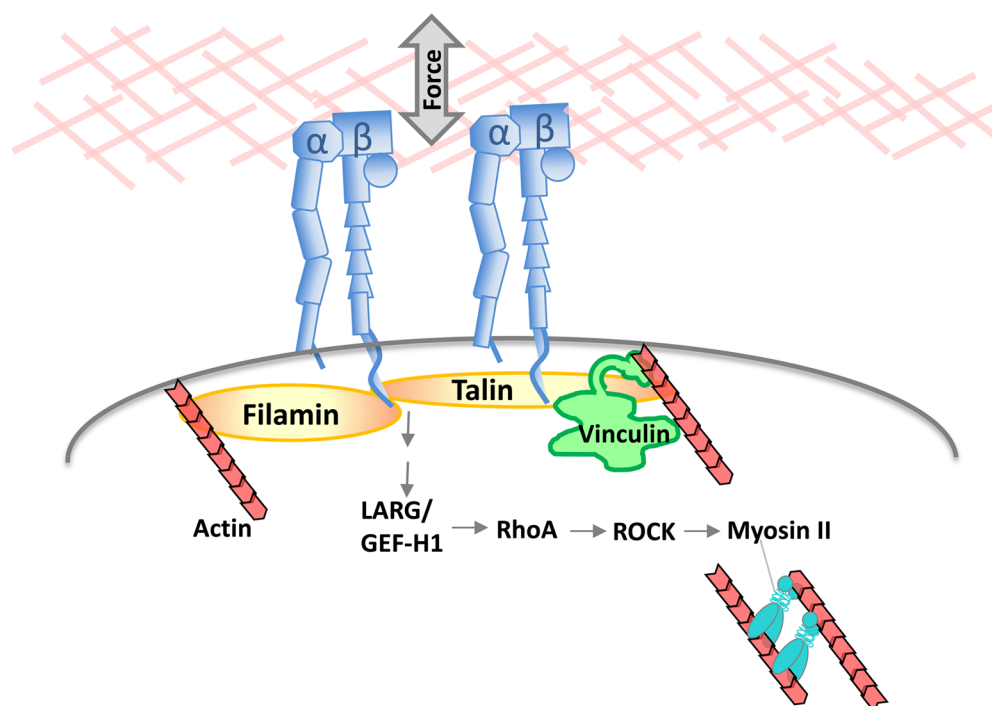


Figure 1. Integrin-mediated force transmission. Integrins (blue) are heterodimers of α and β subunits that form bonds with the extracellular matrix⁹⁵ on the outside of the cell. In response to force, several proteins are recruited to the integrin cytoplasmic β domain. Critical among these are talin and filamin. Talin, in turn, recruits vinculin, a prominent mechanotransducing protein. Upon force exertion, integrins also activate GEF-H1 and LARG. These guanine nucleotide exchange factors catalyze the exchange of GDP for GTP and activate the small GTPase, RhoA, as well as its downstream effector, Rho kinase. Increases in the level of Rho kinase ultimately lead to an increased level of phosphorylation of the regulatory subunit of myosin II and its association with actin filaments. Myosin II cross-links actin filaments and generates tension on actin filaments, thereby promoting changes in the cytoskeleton necessary to withstand force.

kDa actin binding protein, to the cytoplasmic domain of the integrin β subunit.^{15,16} Talin binding occurs in the earliest cell–matrix adhesions observed, transpires independently of tension,^{17,18} and separates the integrin α and β cytoplasmic tails.¹⁹ This separation triggers conformational changes that increase the affinity of integrins for ligands and that initiate the assembly of nascent adhesions.¹⁶ Talin then binds F-actin directly and indirectly through vinculin, a 116 kDa actin binding protein.²⁰ Vinculin stabilizes talin binding, thereby supporting integrin activation and continued force transmission.^{21,22}

Linkages to the Actin Cytoskeleton. As described above, talin can serve as a link between integrins and the actin cytoskeleton; however, its binding partner, vinculin, may play a more prominent role (Figure 1). Vinculin is recruited to focal adhesions when tension is applied to integrins directly²³ or is generated during cell migration.²⁴ Vinculin recruitment requires talin, but another focal adhesion protein known as paxillin may also be involved.¹⁸ Direct binding to the actin cytoskeleton allows vinculin to bear the force and regulate the recruitment and the release of several proteins, thereby stabilizing and promoting the growth of focal adhesions.^{25,26} Consequently, it is not surprising that cells lacking vinculin are unable to generate force on the ECM, are less stiff, and do not reinforce their focal adhesions in response to externally applied force.^{23,27,28}

Filamin, another focal adhesion component, directly binds to the integrin cytoplasmic domain and F-actin, making it poised to transduce the force experienced by integrins onto the cytoskeleton^{29–31} (Figure 1). Evidence of filamin in mechanotransduction arises from the observation that application of

shear stress or mechanical deformation increases the level of binding of filamin to integrins.³² In addition, mouse embryo fibroblasts from mice harboring a deletion of the two filamin isoforms exhibited a severe disruption in force transmission.^{33,34}

Signaling Components (RhoA pathway). Exertion of force on integrins also triggers signaling cascades. Key among these pathways is activation of the small GTPase RhoA.^{1,8} RhoA exists in either an active (GTP-bound) or an inactive (GDP-bound) state, and the oscillation between these states is regulated predominantly by the activity of guanine nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAPs). Two GEFs, leukemia-associated Rho GEF (LARG) and guanine nucleotide exchange factor H1 (GEF-H1), are required for RhoA activation in response to force on integrins³⁵ (Figure 1). Inhibition of either GEF alone weakens the ability of integrins to activate RhoA in response to mechanical force, but depletion of both proteins is required to completely block RhoA activation.³⁵

Once GTP-bound, RhoA activates the Rho kinase (ROCK) family members⁹ (Figure 1). The ROCK1 and ROCK2 isoforms directly phosphorylate myosin light chain (MLC) and indirectly regulate MLC by phosphorylating and inhibiting the myosin light chain phosphatase. The activation of MLC ultimately results in assembly of myosin II into filaments and promotes the interaction of myosin II with actin filaments.³⁶ Myosin II couples the hydrolysis of ATP to conformational changes that result in the sliding of myosin II and actin filaments against each other, thereby providing the force that rearranges the actin cytoskeleton. In addition, myosin II bundles actin filaments³⁷ and may regulate actin polymer-

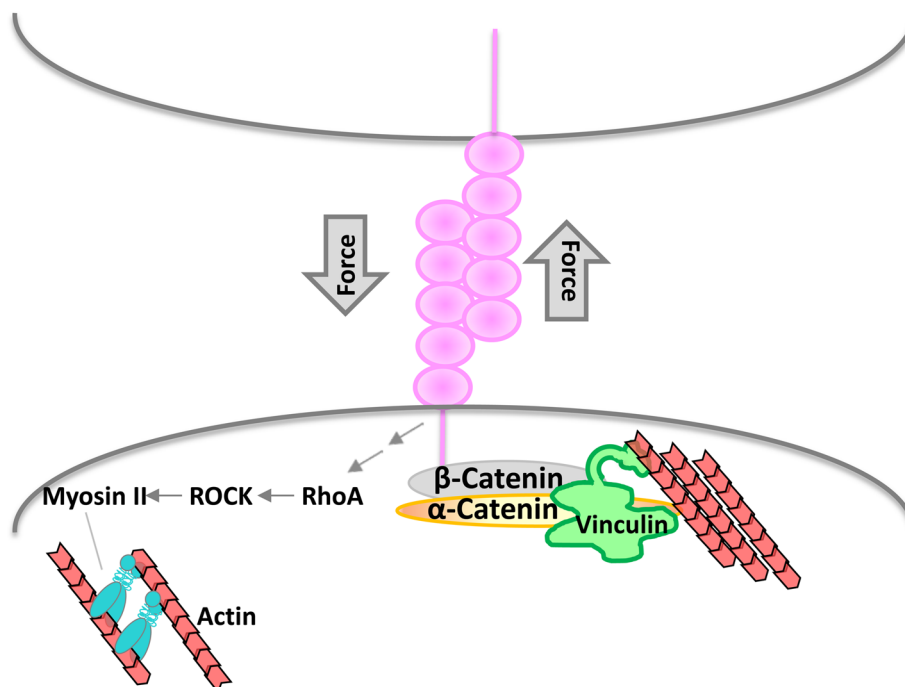


Figure 2. Cadherin-mediated force transmission. E-Cadherin⁹⁵ binds E-cadherins on neighboring cells. The E-cadherin cytoplasmic domain binds a number of proteins that are critical for transmitting forces into the cell. These include β -catenin, α -catenin, and vinculin. Both vinculin and α -catenin directly bind actin, and evidence supports the idea these linkages are required for force transmission. In addition to recruiting actin binding proteins, E-cadherin regulates myosin II-dependent contractility, presumably by activating a RhoA-dependent signaling cascade.

ization.³⁸ These myosin-induced changes allow a cell to rearrange and reinforce its cytoskeleton, thereby promoting the formation of mature adhesions that can withstand force.

MECHANOTRANSDUCTION AT CELL–CELL ADHESIONS

Unlike integrins that have well-appreciated roles in sensing and eliciting cellular responses upon exertion of force, cadherins have only recently begun to be recognized as being mechanoresponsive. Initial clues that cell–cell adhesions might be able to respond to force came from the observation that myosin II is required for the integrity of cadherin-containing cell–cell junctions.^{39–42} This major tension generator is present in adherens junctions, and the size⁴³ and strength of cell–cell adhesions can be regulated by mechanical force.^{44,45} Ultimately, more direct evidence of cadherins as mechanosensors arose from studies showing that cells stiffened or reinforced their cell–cell adhesions when twisting forces were applied to E-cadherin.⁴⁶

Knowledge that cadherins could sense and transmit forces into the cell interior led to an intense search to identify the cadherin cytoplasmic components that bear and dissipate force on the actin cytoskeleton. Coupling between cadherins and actin occurs through proteins that directly or indirectly bind actin. Here, we limit our discussion to β -catenin, α -catenin, and vinculin. β -catenin is recruited directly to the cadherin cytoplasmic tail⁴⁷ and directly binds α -catenin⁴⁸ and vinculin.⁴⁹ α -catenin, in turn, directly binds vinculin,⁵⁰ and both vinculin and α -catenin bind actin.^{51,52}

α -catenin is critical for cadherins to respond to force exertion. In cells with depressed α -catenin levels, cell stiffening and actin accumulation beneath beads coated with cadherin extracellular domains are significantly attenuated.⁵³ Additionally, α -catenin deficient cells rescued with mutant forms of α -

catenin that do not bind vinculin exhibit altered mechanobiology.⁵³ How α -catenin regulates E-cadherin-mediated force transmission is emerging. α -catenin depletion produces a modest reduction in the affinity of E-cadherin for ligands, lending support to the idea that α -catenin might contribute to force-activated adhesion strengthening by increasing the strength of the anchoring of cadherin to the cytoskeleton.⁵³ A requirement for α -catenin in establishing and maintaining linkages to the actin cytoskeleton is further supported by studies of force transmission in developing *Drosophila* embryos.^{54,55}

α -catenin is not the sole modulator of force transmission in cell–cell junctions. Its binding partner, vinculin, becomes enriched in cell–cell adhesions when stretching⁴⁴ or twisting forces are applied to E-cadherin,⁴⁶ and its localization is lost when cells are treated with agents that disrupt cellular tension.^{46,56,57} Vinculin does not bind directly to cadherins. The protein(s) responsible for its recruitment to the cadherin adhesion complex has been the subject of much debate. For many years, α -catenin was thought to recruit vinculin to cell–cell contacts as vinculin localization was disrupted in cancer cells lacking α -catenin.^{50,58} Additional supporting evidence comes from the observation that force exertion causes α -catenin to unfold, thereby increasing the level of binding to vinculin.⁵⁷ In contrast, other work supports a role for β -catenin in recruiting vinculin. Indeed, vinculin still binds to the cadherin adhesion complex in cells lacking α -catenin⁴⁹ or in cells expressing mutant vinculins unable to bind α -catenin.⁵⁹ More direct evidence of β -catenin comes from recent studies showing that vinculin is not recruited to cell–cell junctions when force is applied to cells lacking β -catenin.⁶⁰ More work is needed to resolve the question of whether β -catenin and α -catenin represent two distinct recruitment pathways for vinculin or if they act together. One possibility is that β -

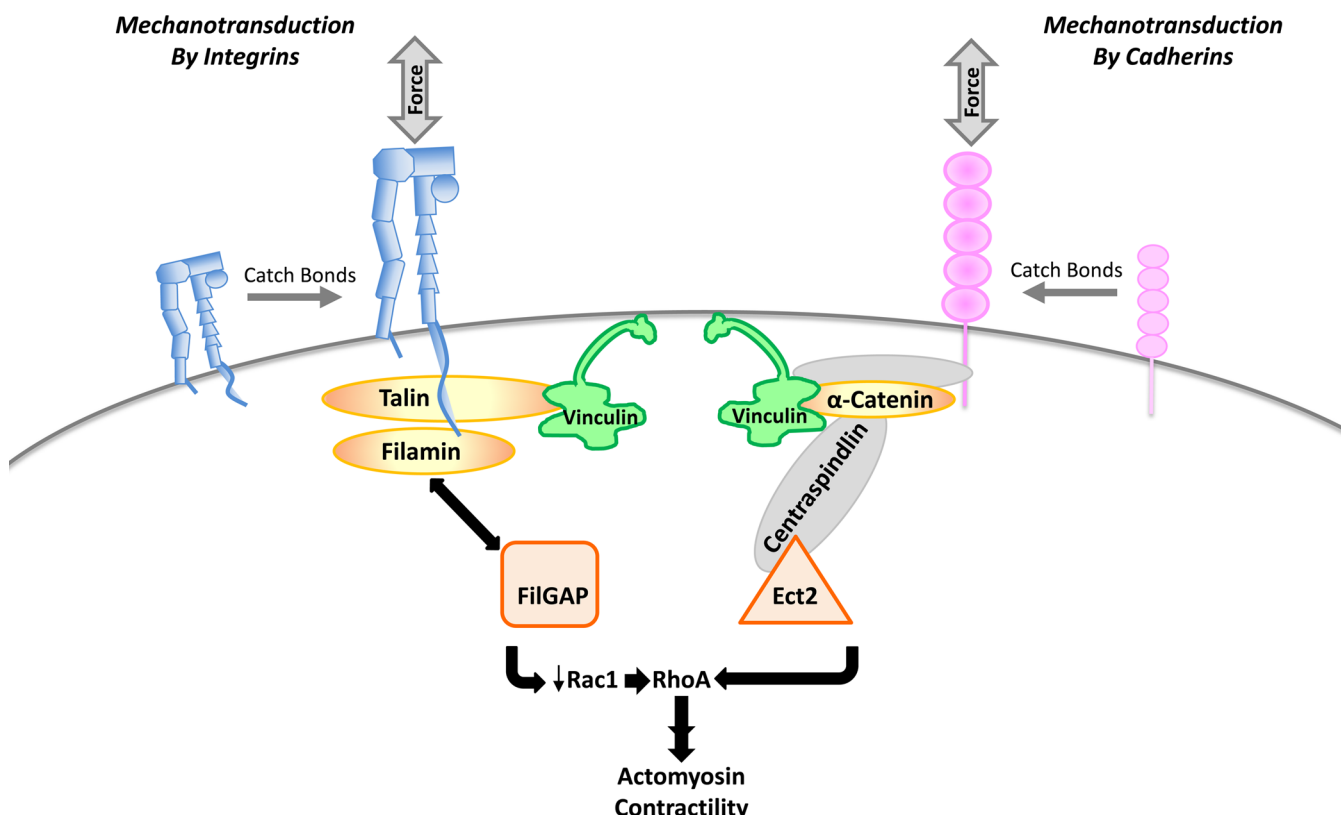


Figure 3. Similarities in how integrins and cadherins respond to and transmit force. First, in response to force, both integrins (blue) and cadherins (pink)⁹⁵ form catch bonds with their ligands. The frequency of these bonds increases as tension is elevated until a maximal force is reached. Second, a number of proteins (including talin, filamin, and α -catenin) are recruited to the cytoplasmic domains of cadherins and integrins and undergo force-induced conformational changes that expose binding sites for additional adhesive components. Third, both integrins and cadherins share a dependency on vinculin, an actin binding protein recruited to both complexes, for transmitting force to the cytoskeleton. Finally, both integrins and cadherins link their cytoskeletal components to RhoA-dependent signaling pathways by targeting the activities of upstream activators/inhibitors (orange). Cadherins activate RhoA by recruiting a GEF known as Ect2 to α -catenin, and integrins bind filamin in response to force and release the FilGAP, a GTPase activating protein for Rac1. FilGAP decreases the level of Rac1, and this can lead to an activation of RhoA.

catenin recruits vinculin and α -catenin stabilizes it at cell–cell junctions. Such a model would explain why in the absence of either protein vinculin is lost from adherens junctions. However, this model is likely only part of the story as myosin VI is required for stable association of vinculin with the cadherin adhesion complex.⁶¹

In addition to recruiting vinculin, β -catenin may also directly mediate the response of cadherins to force. β -catenin unfolds its armadillo repeats when stretched⁶² and is phosphorylated in response to the application of shear stress.⁶³ Moreover, cells lacking β -catenin fail to reinforce their adherens junctions or to increase their barrier function in response to externally applied stress.⁶⁰ The mechanism for the effects of β -catenin on cadherin mechanotransduction is not fully understood but likely involves a regulation of the strength of E-cadherin–E-cadherin interactions.⁶⁴

Signaling to Myosin II. Myosin II is present in cell–cell junctions, and disrupting its activities interferes with cadherin mechanotransduction. As noted above, myosin II is activated downstream of the small GTPase RhoA. It is generally assumed that cadherins activate myosin II using a RhoA-dependent pathway (Figure 2). Several lines of evidence support a role for the RhoA pathway. First, the engagement of cadherins activates RhoA,^{65,66} and this activation is prolonged when mechanical force is exerted onto the cell–cell adhesions.⁶⁷ Second, direct inhibition of RhoA using C3-transferase or indirect inhibition

by depletion of a RhoA activator reduces cell–cell junctional tension.⁶⁸ Finally, inhibition of the RhoA effector, ROCK, decreases junctional tension.⁶⁹ Together, these data suggest cadherins modulate junctional tension by activating RhoA and its downstream effectors. Direct evidence of a role for RhoA awaits the outcome of experiments showing that direct application of force on cadherins increases RhoA-GTP levels.

■ RECURRING THEMES IN FORCE TRANSMISSION BY INTEGRINS AND CADHERINS

It is now becoming increasingly apparent that integrins and cadherins transmit force in similar ways (Figure 3). One recurring theme is how the adhesion receptors themselves respond to force. Both integrins and cadherins form non-covalent interactions, known as catch bonds, whose lifetimes increase until a maximal force is reached, at which point they begin to decrease.^{3,70} For integrins, the lifetime of catch bond formation increases until a force of 10–30 pN is reached.⁷⁰ A similar maximal force (i.e., 30 pN) is the point at which cadherin catch bond lifetimes begin to decrease.³ Additionally, Förster resonance energy transfer probes that report on the amount of tension experienced by E-cadherin or vinculin show that the E-cadherin cytoplasmic domain is under a 1–2 pN constitutive load from the cytoskeleton; this value is on the same order of magnitude observed for vinculin in focal

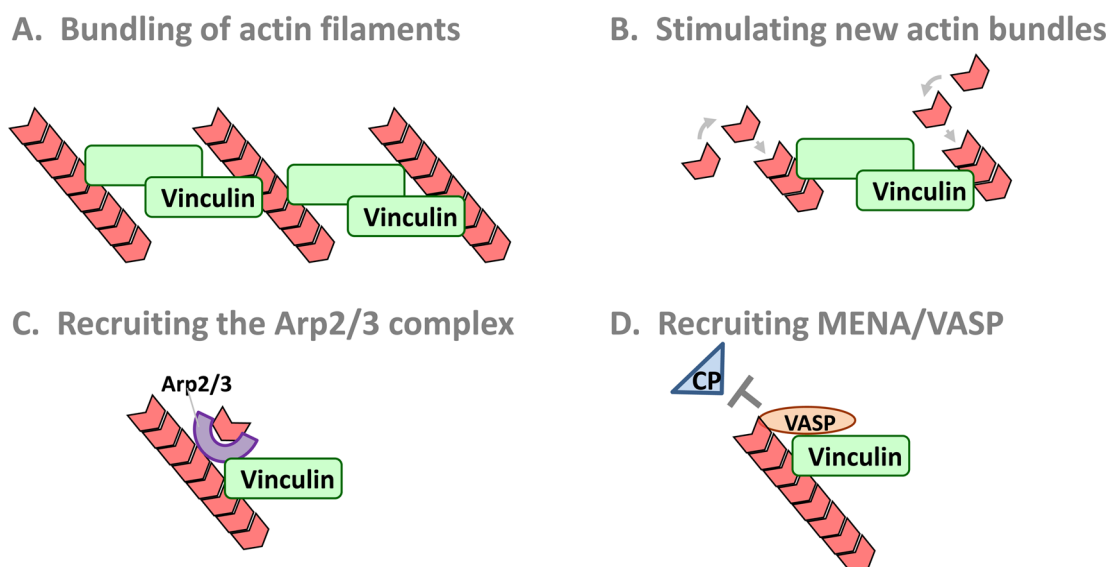


Figure 4. Potential mechanisms for vinculin-mediated stabilization of adhesions. Vinculin can bind to the sides of existing filaments and bundle them (A) and can stimulate the formation of new actin bundles (B). Additionally, at sites of nascent cell–matrix adhesions, vinculin can bind to the Arp2/3 complex, an actin nucleation factor that induces branches on the sides of actin filaments (C). Branched actin filaments can provide a protrusive force and can develop into other actin structures that can stabilize cell adhesions. Finally, vinculin may stabilize cell adhesions by recruiting VASP, an actin binding protein that promotes actin filament length by preventing capping of the barbed ends (D).

adhesions.^{25,71} Hence, both cadherins and integrins experience and withstand forces of the same magnitude.

A second and prevalent similarity is that many of the mechanotransducing components of cell–matrix and cell–cell adhesions undergo conformational changes that affect their interactions with ligands (Figure 3). For example, at sites of cell–cell contact, a central inhibitory domain in α -catenin precludes its binding to vinculin.⁷² This region of α -catenin is accessible to antibody binding only when tension is elevated.⁵⁷ These observations led to the idea that force triggers the exposure of a cryptic vinculin binding site in α -catenin that in turn recruits vinculin.^{57,73} This idea was directly tested by applying physiological levels of force (using magnetic tweezers) to an α -catenin molecule tethered to a magnetic bead on one end and a glass coverslip on the other.⁷⁴ These studies showed that the two subdomains of the α catenin central inhibitory domain unfold, thereby allowing vinculin to bind. Importantly, binding of vinculin to this unfolded conformation prevents α -catenin from refolding when the force is removed.⁷⁴

Similarly, force causes the cell–matrix adhesion proteins, talin and filamin, to unfold. Talin has an N-terminal FERM domain and a C-terminal rod domain that contains many hidden binding sites for vinculin. When force is applied, these binding sites are exposed, thereby allowing talin to interact with vinculin.^{21,22} By increasing the force that is applied in a linear fashion, Yao et al. showed an initial unfolding of talin at 5 pN and complete unfolding at 25 pN.²² Additionally, the authors showed that talin refolds at a low level of force, and this refolding can be prevented by vinculin binding.²² Filamin, another focal adhesion protein, has an amino-terminal actin binding domain followed by a rod domain composed of 24 Ig domains. In its unfolded conformation, the A-strand of filamin IgG domain 20 binds to IgG domain 21, thereby precluding IgG domain 21 from binding to integrins. This intramolecular interaction is released when force is applied to filamin, thereby increasing the level of interaction of filamin with integrins.⁷⁵ The relief of this autoinhibition can be accelerated and/or can

require less force if filamin is first phosphorylated at a critical serine residue in IgG domain 20.⁷⁶ Hence, force modulates the composition of cell–cell and cell–matrix adhesions by governing access of binding partners to their mechanoresponsive counterparts.

A third recurring theme is that both integrins and cadherins share a dependency on vinculin to transmit force (Figure 3). It is not completely clear how vinculin stabilizes cell–cell or cell–matrix adhesions, but several possibilities exist (Figure 4). Vinculin can bind to the sides of existing filaments and bundle them^{77,78} and can stimulate the formation of new actin bundles.⁷⁹ Additionally, at sites of nascent cell–matrix adhesions, vinculin can bind to the Arp2/3 complex, an actin nucleation factor that binds to the sides of actin filaments and induces branch formation.⁸⁰ Branched actin filaments can provide a protrusive force and can develop into other actin structures that can stabilize cell adhesions. Finally, vinculin may stabilize cell adhesions by recruiting other actin modifiers. Vinculin binds VASP, an actin binding protein that promotes actin filament length by preventing capping of the barbed ends.^{81,82} This interaction supports tension-sensitive actin assembly in cell–cell junctions.⁸³ Hence, vinculin is critical for force transmission by virtue of its ability to modify actin filaments.

Finally, both cadherins and integrins have mechanisms to couple force-activated signaling pathways to adaptor proteins that link adhesion receptors to the cytoskeleton. For example, linkages between integrins and the actin cytoskeleton are formed by filamin, and filamin can indirectly activate RhoA and its downstream effectors (Figure 3). Indeed, force triggers increases in the level of binding of filamin to β -integrins and decreases the level of binding to the Rac1 GTPase activating protein, FilGAP.³² The liberated FilGAP can then suppress Rac1, and this inhibition can lead to activation of RhoA through multiple pathways.⁸⁴ Similarly, the elements linking cadherins to the actin cytoskeleton are directly coupled to its signaling pathways. In response to application of force to cadherins, α -

catenin binds centralspindlin, a protein complex that links the mitotic spindle to the plasma membrane during cytokinesis.⁶⁸ Centralspindlin, in turn, recruits a guanine nucleotide exchange factor⁸⁵ for RhoA, known as Ect2.⁶⁸ Ect2 activates RhoA and supports junctional integrity through myosin IIA. Centralspindlin also inhibits the junctional localization of p190B, a RhoA GAP that can inactivate RhoA.⁶⁸ Thus, the cytoskeletal and signaling components of the cadherin and integrin force-transducing machinery are coordinated by GEFs and GAPs. Importantly, this level of regulation is likely only part of the story as some cytoskeletal components directly bind other signaling components of the RhoA pathway.⁸⁶

■ INTERPLAY BETWEEN CELL–CELL AND CELL–MATRIX ADHESIONS

There is a large body of evidence demonstrating the existence of crosstalk between integrins and cadherins in mediating the adhesion and migration of cells (reviewed in ref 87). Lending support to this notion is evidence suggesting that integrin adhesion complexes can modulate tension on cadherin-based adhesions.^{88–90} For example, elevations in the magnitude of integrin-mediated traction forces are accompanied by increases in myosin-dependent tension at cadherin-based adhesions.^{88,90} Additional evidence suggests that engagement of integrins increases the strength of cadherin-mediated adhesion.⁸⁹ Inhibiting myosin II activity (directly or indirectly) decreases the integrin-dependent enhancement of cadherin function.⁸⁹ Hence, tension on integrin-based adhesions is transferred to cadherins.

The transfer of tension is reciprocal: tension on cadherins can be transferred to integrin-based adhesions. Specifically, cells expressing cadherins can generate more traction forces than cells lacking them.⁹¹ Additionally, groups of cells with strong cell–cell adhesions localize their traction forces to the colony periphery, and interrupting cadherin function produces high traction forces throughout the colony.⁹² Furthermore, interfering with mechanotransduction at sites of cell–cell adhesion increases the degree of stiffening of cells in response to integrin ligands.⁹³ These observations suggest that the mechanical properties of integrins and cadherins are intimately coupled.

The transfer of tension is not always reciprocal. An emerging view is that a cell fine-tunes its mechanical properties to allow force transmission at one adhesion site to proceed independently of other adhesion complexes.⁹³ As noted above, vinculin is a shared component of the force-transducing machinery at cell–cell and cell–matrix adhesions. In response to direct application of force on cadherins, but not integrins, Abl tyrosine kinase is activated and phosphorylates vinculin at Y822.⁹³ Furthermore, when vinculin phosphorylation at Y822 is prevented using phosphorylation deficient mutants of vinculin, cell stiffening in response to force on cadherins, but not integrins, is blocked. Therefore, phosphorylation of Y822 vinculin represents a mechanism for differentially regulating force transmission.

■ SUMMARY

Integrins and cadherins strengthen their adhesions in response to applied forces by promoting the recruitment of new components and by activating signaling pathways that remodel the actin cytoskeleton. There are striking similarities in how integrins and cadherins respond and transmit forces to cell interior, and an exquisite level of crosstalk between these two

adhesion receptors is necessary for coordinated mechanotransduction.

■ FUTURE PERSPECTIVES

The key players regulating cadherin- and integrin-mediated force transmission have emerged, and it is clear that others will be uncovered. Attention is beginning to shift toward understanding how these events unfold in model systems and how cadherin- and integrin-mediated force transmission are integrated. Also growing is the need to understand how the force applied to either adhesion receptor produces different biological responses. For example, how does applying force to cadherins or integrins individually cause cells to stiffen while producing different effects on cell growth?⁹⁴ Finally, while much attention has focused on how integrins and cadherins transmit force, more work is needed to define the signals that turn these pathways off and to understand how these signals are integrated with other systems in the cell.

■ AUTHOR INFORMATION

Corresponding Author

*Department of Biochemistry, University of Iowa Carver College of Medicine, 51 Newton Rd., 4-470 BSB, Iowa City, IA 52242. E-mail: kris-demali@uiowa.edu.

Funding

Research in our group is funded by National Science Foundation Grant 1120478 (to K.A.D.). Salary support for X.S. is provided by Iowa Department of Public Health Grant 5885CC12.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to Caitlin Runne, Jennifer Bays, and Ernesto Fuentes for critical comments.

■ REFERENCES

- (1) Lessey, E. C., Guilly, C., and Burridge, K. (2012) From mechanical force to RhoA activation. *Biochemistry* 51, 7420–7432.
- (2) Plotnikov, S. V., and Waterman, C. M. (2013) Guiding cell migration by tugging. *Curr. Opin. Cell Biol.* 25, 619–626.
- (3) Rakshit, S., and Sivasankar, S. (2014) Biomechanics of cell adhesion: How force regulates the lifetime of adhesive bonds at the single molecule level. *Phys. Chem. Chem. Phys.* 16, 2211–2223.
- (4) Thomas, W. (2008) Catch bonds in adhesion. *Annu. Rev. Biomed. Eng.* 10, 39–57.
- (5) Leckband, D. E., and de Rooij, J. (2014) Cadherin Adhesion and Mechanotransduction. *Annu. Rev. Cell Dev. Biol.* 30, 291–315.
- (6) Stapleton, S. C., Chopra, A., and Chen, C. S. (2014) Force measurement tools to explore cadherin mechanotransduction. *Cell Commun. Adhes.* 21, 193–205.
- (7) Ross, T. D., Coon, B. G., Yun, S., Baeyens, N., Tanaka, K., Ouyang, M., and Schwartz, M. A. (2013) Integrins in mechanotransduction. *Curr. Opin. Cell Biol.* 25, 613–618.
- (8) Marjoram, R. J., Lessey, E. C., and Burridge, K. (2014) Regulation of RhoA activity by adhesion molecules and mechanotransduction. *Curr. Mol. Med.* 14, 199–208.
- (9) Julian, L., and Olson, M. F. (2014) Rho-associated coiled-coil containing kinases (ROCK): Structure, regulation, and functions. *Small GTPases* 5, e29846.
- (10) Twiss, F., and de Rooij, J. (2013) Cadherin mechanotransduction in tissue remodeling. *Cell. Mol. Life Sci.* 70, 4101–4116.

- (11) Leerberg, J. M., and Yap, A. S. (2013) Vinculin, cadherin mechanotransduction and homeostasis of cell-cell junctions. *Plasma* 250, 817–829.
- (12) Roca-Cusachs, P., Iskratsch, T., and Sheetz, M. P. (2012) Finding the weakest link: Exploring integrin-mediated mechanical molecular pathways. *J. Cell Sci.* 125, 3025–3038.
- (13) Roca-Cusachs, P., Gauthier, N. C., Del Rio, A., and Sheetz, M. P. (2009) Clustering of $\alpha_5\beta_1$ integrins determines adhesion strength whereas $\alpha_5\beta_3$ and talin enable mechanotransduction. *Proc. Natl. Acad. Sci. U.S.A.* 106, 16245–16250.
- (14) Choquet, D., Felsenfeld, D. P., and Sheetz, M. P. (1997) Extracellular matrix rigidity causes strengthening of integrin-cytoskeleton linkages. *Cell* 88, 39–48.
- (15) Calderwood, D. A., Zent, R., Grant, R., Rees, D. J., Hynes, R. O., and Ginsberg, M. H. (1999) The Talin head domain binds to integrin β subunit cytoplasmic tails and regulates integrin activation. *J. Biol. Chem.* 274, 28071–28074.
- (16) Tadokoro, S., Shattil, S. J., Eto, K., Tai, V., Liddington, R. C., de Pereda, J. M., Ginsberg, M. H., and Calderwood, D. A. (2003) Talin binding to integrin β tails: A final common step in integrin activation. *Science* 302, 103–106.
- (17) Partridge, M. A., and Marcantonio, E. E. (2006) Initiation of attachment and generation of mature focal adhesions by integrin-containing filopodia in cell spreading. *Mol. Biol. Cell* 17, 4237–4248.
- (18) Pasapera, A. M., Schneider, I. C., Rericha, E., Schlaepfer, D. D., and Waterman, C. M. (2010) Myosin II activity regulates vinculin recruitment to focal adhesions through FAK-mediated paxillin phosphorylation. *J. Cell Biol.* 188, 877–890.
- (19) Zhu, J., Luo, B. H., Xiao, T., Zhang, C., Nishida, N., and Springer, T. A. (2008) Structure of a complete integrin ectodomain in a physiologic resting state and activation and deactivation by applied forces. *Mol. Cell* 32, 849–861.
- (20) Horwitz, A., Duggan, K., Buck, C., Beckerle, M. C., and Burridge, K. (1986) Interaction of plasma membrane fibronectin receptor with talin: A transmembrane linkage. *Nature* 320, 531–533.
- (21) del Rio, A., Perez-Jimenez, R., Liu, R., Roca-Cusachs, P., Fernandez, J. M., and Sheetz, M. P. (2009) Stretching single talin rod molecules activates vinculin binding. *Science* 323, 638–641.
- (22) Yao, M., Goult, B. T., Chen, H., Cong, P., Sheetz, M. P., and Yan, J. (2014) Mechanical activation of vinculin binding to talin locks talin in an unfolded conformation. *Sci. Rep.* 4, 4610.
- (23) Galbraith, C. G., Yamada, K. M., and Sheetz, M. P. (2002) The relationship between force and focal complex development. *J. Cell Biol.* 159, 695–705.
- (24) Balaban, N. Q., Schwarz, U. S., Riveline, D., Goichberg, P., Tzur, G., Sabanay, I., Mahalu, D., Safran, S., Bershadsky, A., Addadi, L., and Geiger, B. (2001) Force and focal adhesion assembly: A close relationship studied using elastic micropatterned substrates. *Nat. Cell Biol.* 3, 466–472.
- (25) Grashoff, C., Hoffman, B. D., Brenner, M. D., Zhou, R., Parsons, M., Yang, M. T., McLean, M. A., Sligar, S. G., Chen, C. S., Ha, T., and Schwartz, M. A. (2010) Measuring mechanical tension across vinculin reveals regulation of focal adhesion dynamics. *Nature* 466, 263–266.
- (26) Carisey, A., Tsang, R., Greiner, A. M., Nijenhuis, N., Heath, N., Nazgiewicz, A., Kemkemmer, R., Derby, B., Spatz, J., and Ballestrem, C. (2013) Vinculin regulates the recruitment and release of core focal adhesion proteins in a force-dependent manner. *Curr. Biol.* 23, 271–281.
- (27) Alenghat, F. J., Fabry, B., Tsai, K. Y., Goldmann, W. H., and Ingber, D. E. (2000) Analysis of cell mechanics in single vinculin-deficient cells using a magnetic tweezer. *Biochem. Biophys. Res. Commun.* 277, 93–99.
- (28) Mierke, C. T., Kollmannsberger, P., Zitterbart, D. P., Smith, J., Fabry, B., and Goldmann, W. H. (2008) Mechano-coupling and regulation of contractility by the vinculin tail domain. *Biophys. J.* 94, 661–670.
- (29) Calderwood, D. A., Huttenlocher, A., Kiosses, W. B., Rose, D. M., Woodside, D. G., Schwartz, M. A., and Ginsberg, M. H. (2001) Increased filamin binding to β -integrin cytoplasmic domains inhibits cell migration. *Nat. Cell Biol.* 3, 1060–1068.
- (30) Hartwig, J. H., Tyler, J., and Stossel, T. P. (1980) Actin-binding protein promotes the bipolar and perpendicular branching of actin filaments. *J. Cell Biol.* 87, 841–848.
- (31) Niederman, R., Amrein, P. C., and Hartwig, J. (1983) Three-dimensional structure of actin filaments and of an actin gel made with actin-binding protein. *J. Cell Biol.* 96, 1400–1413.
- (32) Ehrlicher, A. J., Nakamura, F., Hartwig, J. H., Weitz, D. A., and Stossel, T. P. (2011) Mechanical strain in actin networks regulates FilGAP and integrin binding to filamin A. *Nature* 478, 260–263.
- (33) Lynch, C. D., Gauthier, N. C., Biais, N., Lazar, A. M., Roca-Cusachs, P., Yu, C. H., and Sheetz, M. P. (2011) Filamin depletion blocks endoplasmic spreading and destabilizes force-bearing adhesions. *Mol. Biol. Cell* 22, 1263–1273.
- (34) Lynch, C. D., and Sheetz, M. P. (2011) Cellular mechanotransduction: Filamin A strains to regulate motility. *Curr. Biol.* 21, R916–R918.
- (35) Guilluy, C., Swaminathan, V., Garcia-Mata, R., O'Brien, E. T., Superfine, R., and Burridge, K. (2011) The Rho GEFs LARG and GEF-H1 regulate the mechanical response to force on integrins. *Nat. Cell Biol.* 13, 722–727.
- (36) Clark, K., Langeslag, M., Figdor, C. G., and van Leeuwen, F. N. (2007) Myosin II and mechanotransduction: A balancing act. *Trends Cell Biol.* 17, 178–186.
- (37) Laevsky, G., and Knecht, D. A. (2003) Cross-linking of actin filaments by myosin II is a major contributor to cortical integrity and cell motility in restrictive environments. *J. Cell Sci.* 116, 3761–3770.
- (38) Rex, C. S., Gavin, C. F., Rubio, M. D., Kramar, E. A., Chen, L. Y., Jia, Y., Haganir, R. L., Muzyczka, N., Gall, C. M., Miller, C. A., Lynch, G., and Rumbaugh, G. (2010) Myosin IIb regulates actin dynamics during synaptic plasticity and memory formation. *Neuron* 67, 603–617.
- (39) Shewan, A. M., Maddugoda, M., Kraemer, A., Stehbins, S. J., Verma, S., Kovacs, E. M., and Yap, A. S. (2005) Myosin 2 is a key Rho kinase target necessary for the local concentration of E-cadherin at cell-cell contacts. *Mol. Biol. Cell* 16, 4531–4542.
- (40) Watanabe, T., Hosoya, H., and Yonemura, S. (2007) Regulation of myosin II dynamics by phosphorylation and dephosphorylation of its light chain in epithelial cells. *Mol. Biol. Cell* 18, 605–616.
- (41) Ivanov, A. I., Bachar, M., Babbini, B. A., Adelstein, R. S., Nusrat, A., and Parkos, C. A. (2007) A unique role for nonmuscle myosin heavy chain IIA in regulation of epithelial apical junctions. *PLoS One* 2, e658.
- (42) Smutny, M., Cox, H. L., Leerberg, J. M., Kovacs, E. M., Conti, M. A., Ferguson, C., Hamilton, N. A., Parton, R. G., Adelstein, R. S., and Yap, A. S. (2010) Myosin II isoforms identify distinct functional modules that support integrity of the epithelial zonula adherens. *Nat. Cell Biol.* 12, 696–702.
- (43) Liu, Z., Tan, J. L., Cohen, D. M., Yang, M. T., Sniadecki, N. J., Ruiz, S. A., Nelson, C. M., and Chen, C. S. (2010) Mechanical tugging force regulates the size of cell-cell junctions. *Proc. Natl. Acad. Sci. U.S.A.* 107, 9944–9949.
- (44) Thomas, W. A., Boscher, C., Chu, Y. S., Cuvelier, D., Martinez-Rico, C., Seddiki, R., Heysch, J., Ladoux, B., Thiery, J. P., Mege, R. M., and Dufour, S. (2013) α -Catenin and vinculin cooperate to promote high E-cadherin-based adhesion strength. *J. Biol. Chem.* 288, 4957–4969.
- (45) Tabdili, H., Langer, M., Shi, Q., Poh, Y. C., Wang, N., and Leckband, D. (2012) Cadherin-dependent mechanotransduction depends on ligand identity but not affinity. *J. Cell Sci.* 125, 4362–4371.
- (46) le Duc, Q., Shi, Q., Blonk, I., Sonnenberg, A., Wang, N., Leckband, D., and de Rooij, J. (2010) Vinculin potentiates E-cadherin mechanosensing and is recruited to actin-anchored sites within adherens junctions in a myosin II-dependent manner. *J. Cell Biol.* 189, 1107–1115.
- (47) McCrear, P. D., Turck, C. W., and Gumbiner, B. (1991) A homolog of the armadillo protein in *Drosophila* (plakoglobin) associated with E-cadherin. *Science* 254, 1359–1361.

- (48) Aberle, H., Butz, S., Stappert, J., Weissig, H., Kemler, R., and Hoschuetzky, H. (1994) Assembly of the cadherin-catenin complex in vitro with recombinant proteins. *J. Cell Sci.* 107 (Part 12), 3655–3663.
- (49) Hazan, R. B., Kang, L., Roe, S., Borgen, P. I., and Rimm, D. L. (1997) Vinculin is associated with the E-cadherin adhesion complex. *J. Biol. Chem.* 272, 32448–32453.
- (50) Watabe-Uchida, M., Uchida, N., Imamura, Y., Nagafuchi, A., Fujimoto, K., Uemura, T., Vermeulen, S., van Roy, F., Adamson, E. D., and Takeichi, M. (1998) α -Catenin-vinculin interaction functions to organize the apical junctional complex in epithelial cells. *J. Cell Biol.* 142, 847–857.
- (51) Jockusch, B. M., and Isenberg, G. (1981) Interaction of α -actinin and vinculin with actin: Opposite effects on filament network formation. *Proc. Natl. Acad. Sci. U.S.A.* 78, 3005–3009.
- (52) Rimm, D. L., Koslov, E. R., Kebriaei, P., Ciani, C. D., and Morrow, J. S. (1995) α 1(E)-catenin is an actin-binding and -bundling protein mediating the attachment of F-actin to the membrane adhesion complex. *Proc. Natl. Acad. Sci. U.S.A.* 92, 8813–8817.
- (53) Barry, A. K., Tabdili, H., Muhamed, I., Wu, J., Shashikanth, N., Gomez, G. A., Yap, A. S., Gottardi, C. J., de Rooij, J., Wang, N., and Leckband, D. E. (2014) α -Catenin cytomechanics: Role in cadherin-dependent adhesion and mechanotransduction. *J. Cell Sci.* 127, 1779–1791.
- (54) Maitre, J. L., Berthoumieux, H., Krens, S. F., Salbreux, G., Julicher, F., Paluch, E., and Heisenberg, C. P. (2012) Adhesion functions in cell sorting by mechanically coupling the cortices of adhering cells. *Science* 338, 253–256.
- (55) Desai, R., Sarpal, R., Ishiyama, N., Pellikka, M., Ikura, M., and Tepass, U. (2013) Monomeric α -catenin links cadherin to the actin cytoskeleton. *Nat. Cell Biol.* 15, 261–273.
- (56) Miyake, Y., Inoue, N., Nishimura, K., Kinoshita, N., Hosoya, H., and Yonemura, S. (2006) Actomyosin tension is required for correct recruitment of adherens junction components and zonula occludens formation. *Exp. Cell Res.* 312, 1637–1650.
- (57) Yonemura, S., Wada, Y., Watanabe, T., Nagafuchi, A., and Shibata, M. (2010) α -Catenin as a tension transducer that induces adherens junction development. *Nat. Cell Biol.* 12, 533–542.
- (58) Sheikh, F., Chen, Y., Liang, X., Hirschy, A., Stenbit, A. E., Gu, Y., Dalton, N. D., Yajima, T., Lu, Y., Knowlton, K. U., Peterson, K. L., Perriard, J. C., and Chen, J. (2006) α -E-catenin inactivation disrupts the cardiomyocyte adherens junction, resulting in cardiomyopathy and susceptibility to wall rupture. *Circulation* 114, 1046–1055.
- (59) Peng, X., Cuff, L. E., Lawton, C. D., and DeMali, K. A. (2010) Vinculin regulates cell-surface E-cadherin expression by binding to β -catenin. *J. Cell Sci.* 123, 567–577.
- (60) Ray, S., Foote, H. P., and Lechler, T. (2013) β -Catenin protects the epidermis from mechanical stresses. *J. Cell Biol.* 202, 45–52.
- (61) Maddugoda, M. P., Crompton, M. S., Shewan, A. M., and Yap, A. S. (2007) Myosin VI and vinculin cooperate during the morphogenesis of cadherin cell cell contacts in mammalian epithelial cells. *J. Cell Biol.* 178, 529–540.
- (62) Valbuena, A., Vera, A. M., Oroz, J., Menendez, M., and Carrion-Vazquez, M. (2012) Mechanical properties of β -catenin revealed by single-molecule experiments. *Biophys. J.* 103, 1744–1752.
- (63) Avvisato, C. L., Yang, X., Shah, S., Hoxter, B., Li, W., Gaynor, R., Pestell, R., Tozeren, A., and Byers, S. W. (2007) Mechanical force modulates global gene expression and β -catenin signaling in colon cancer cells. *J. Cell Sci.* 120, 2672–2682.
- (64) Bajpai, S., Feng, Y., Wirtz, D., and Longmore, G. D. (2013) β -Catenin serves as a clutch between low and high intercellular E-cadherin bond strengths. *Biophys. J.* 105, 2289–2300.
- (65) Lampugnani, M. G., Zanetti, A., Breviario, F., Balconi, G., Orsenigo, F., Corada, M., Spagnuolo, R., Betson, M., Braga, V., and Dejana, E. (2002) VE-cadherin regulates endothelial actin activating Rac and increasing membrane association of Tiam. *Mol. Biol. Cell* 13, 1175–1189.
- (66) Noren, N. K., Niessen, C. M., Gumbiner, B. M., and Burridge, K. (2001) Cadherin engagement regulates Rho family GTPases. *J. Biol. Chem.* 276, 33305–33308.
- (67) Nelson, C. M., Pirone, D. M., Tan, J. L., and Chen, C. S. (2004) Vascular endothelial-cadherin regulates cytoskeletal tension, cell spreading, and focal adhesions by stimulating RhoA. *Mol. Biol. Cell* 15, 2943–2953.
- (68) Ratheesh, A., Gomez, G. A., Priya, R., Verma, S., Kovacs, E. M., Jiang, K., Brown, N. H., Akhmanova, A., Stehbens, S. J., and Yap, A. S. (2012) Centralspindlin and α -catenin regulate Rho signalling at the epithelial zonula adherens. *Nat. Cell Biol.* 14, 818–828.
- (69) Fernandez-Gonzalez, R., Simoes Sde, M., Roper, J. C., Eaton, S., and Zallen, J. A. (2009) Myosin II dynamics are regulated by tension in intercalating cells. *Dev. Cell* 17, 736–743.
- (70) Kong, F., Garcia, A. J., Mould, A. P., Humphries, M. J., and Zhu, C. (2009) Demonstration of catch bonds between an integrin and its ligand. *J. Cell Biol.* 185, 1275–1284.
- (71) Borghi, N., Sorokina, M., Shcherbakova, O. G., Weis, W. I., Pruitt, B. L., Nelson, W. J., and Dunn, A. R. (2012) E-Cadherin is under constitutive actomyosin-generated tension that is increased at cell-cell contacts upon externally applied stretch. *Proc. Natl. Acad. Sci. U.S.A.* 109, 12568–12573.
- (72) Rangarajan, E. S., and Izard, T. (2013) Dimer asymmetry defines α -catenin interactions. *Nat. Struct. Mol. Biol.* 20, 188–193.
- (73) Ishiyama, N., Tanaka, N., Abe, K., Yang, Y. J., Abbas, Y. M., Umitsu, M., Nagar, B., Bueler, S. A., Rubinstein, J. L., Takeichi, M., and Ikura, M. (2013) An autoinhibited structure of α -catenin and its implications for vinculin recruitment to adherens junctions. *J. Biol. Chem.* 288, 15913–15925.
- (74) Yao, M., Qiu, W., Liu, R., Efremov, A. K., Cong, P., Seddiki, R., Payre, M., Lim, C. T., Ladoux, B., Mege, R. M., and Yan, J. (2014) Force-dependent conformational switch of α -catenin controls vinculin binding. *Nat. Commun.* 5, 4525.
- (75) Rognoni, L., Most, T., Zoldak, G., and Rief, M. (2014) Force-dependent isomerization kinetics of a highly conserved proline switch modulates the mechanosensing region of filamin. *Proc. Natl. Acad. Sci. U.S.A.* 111, 5568–5573.
- (76) Chen, H. S., Kolahi, K. S., and Mofrad, M. R. (2009) Phosphorylation facilitates the integrin binding of filamin under force. *Biophys. J.* 97, 3095–3104.
- (77) Isenberg, G., Leonard, K., and Jockusch, B. M. (1982) Structural aspects of vinculin-actin interactions. *J. Mol. Biol.* 158, 231–249.
- (78) Jockusch, B. M., and Isenberg, G. (1982) Vinculin and α -actinin: Interaction with actin and effect on microfilament network formation. *Cold Spring Harbor Symp. Quant. Biol.* 46 (Part 2), 613–623.
- (79) Wen, K. K., Rubenstein, P. A., and DeMali, K. A. (2009) Vinculin nucleates actin polymerization and modifies actin filament structure. *J. Biol. Chem.* 284, 30463–30473.
- (80) DeMali, K. A., Barlow, C. A., and Burridge, K. (2002) Recruitment of the Arp2/3 complex to vinculin: Coupling membrane protrusion to matrix adhesion. *J. Cell Biol.* 159, 881–891.
- (81) Brindle, N. P., Holt, M. R., Davies, J. E., Price, C. J., and Critchley, D. R. (1996) The focal-adhesion vasodilator-stimulated phosphoprotein (VASP) binds to the proline-rich domain in vinculin. *Biochem. J.* 318 (Part 3), 753–757.
- (82) Bear, J. E., Svitkina, T. M., Krause, M., Schafer, D. A., Loureiro, J. J., Strasser, G. A., Maly, I. V., Chaga, O. Y., Cooper, J. A., Borisy, G. G., and Gertler, F. B. (2002) Antagonism between Ena/VASP proteins and actin filament capping regulates fibroblast motility. *Cell* 109, 509–521.
- (83) Leerberg, J. M., Gomez, G. A., Verma, S., Moussa, E. J., Wu, S. K., Priya, R., Hoffman, B. D., Grashoff, C., Schwartz, M. A., and Yap, A. S. (2014) Tension-sensitive actin assembly supports contractility at the epithelial zonula adherens. *Curr. Biol.* 24, 1689–1699.
- (84) Burridge, K., and Wennerberg, K. (2004) Rho and Rac take center stage. *Cell* 116, 167–179.
- (85) Chatrchyan, S., Khachatryan, V., Sirunyan, A. M., Tumasyan, A., Adam, W., Bergauer, T., Dragicevic, M., Ero, J., Fabjan, C., Friedl, M., Fruhwirth, R., Ghete, V. M., Hammer, J., Hansel, S., Hoch, M., Hormann, N., Hrubec, J., Jeitler, M., Kiesenhofer, W., Krammer, M., Liko, D., Mikulec, I., Pernicka, M., Rohringer, H., Schofbeck, R., Strauss, J., Taurok, A., Teischinger, F., Wagner, P., Waltenberger, W.,

Walzel, G., Widl, E., Wulz, C. E., Mossolov, V., Shumeiko, N., Gonzalez, J. S., Bansal, S., Benucci, L., De Wolf, E. A., Janssen, X., Maes, J., Maes, T., Mucibello, L., Ochesanu, S., Roland, B., Rougny, R., Selvaggi, M., Van Haevermaet, H., Van Mechelen, P., Van Remortel, N., Blekman, F., Blyweert, S., D'Hondt, J., Devroede, O., Suarez, R. G., Kalogeropoulos, A., Maes, M., Van Doninck, W., Van Mulders, P., Van Onsem, G. P., Villella, I., Charaf, O., Clerbaux, B., De Lentdecker, G., Dero, V., Gay, A. P., Hammad, G. H., Hreus, T., Marage, P. E., Thomas, L., Velde, C. V., Vanlaer, P., Adler, V., Cimmino, A., Costantini, S., Grunewald, M., Klein, B., Lellouch, J., Marinov, A., McCartin, J., Ryckbosch, D., Thyssen, F., Tytgat, M., Vanelderen, L., Verwilligen, P., Walsh, S., Zaganidis, N., Basegmez, S., Bruno, G., Caudron, J., Ceard, L., Gil, E. C., De Favereau De Jeneret, J., Delaere, C., Favart, D., Giammanco, A., Gregoire, G., Hollar, J., Lemaitre, V., Liao, J., Militaru, O., Nuttens, C., Oryn, S., Pagano, D., Pin, A., Piotrkowski, K., Schul, N., Beliy, N., Caebegs, T., Daubie, E., Alves, G. A., Brito, L., De Jesus Damiao, D., Pol, M. E., Souza, M. H., Alda Junior, W. L., Carvalho, W., Da Costa, E. M., Martins Cde, O., Fonseca De Souza, S., Mundim, L., Nogima, H., Oguri, V., Prado Da Silva, W. L., Santoro, A., Silva Do Amaral, S. M., Sznajder, A., Bernardes, C. A., Dias, F. A., Tomei, T. R., Gregores, E. M., Lagana, C., Marinho, F., Mercadante, P. G., Novaes, S. F., Padula, S. S., Darmenov, N., Genchev, V., Iaydjiev, P., Piperov, S., Rodozov, M., Stoykova, S., Sultanov, G., Tcholakov, V., Trayanov, R., Dimitrov, A., Hadjiiska, R., Karadzchinova, A., Kozuharov, V., Litov, L., Mateev, M., Pavlov, B., Petkov, P., Bian, J. G., Chen, G. M., Chen, H. S., Jiang, C. H., Liang, D., Liang, S., Meng, X., Tao, J., Wang, J., Wang, J., Wang, X., Wang, Z., Xiao, H., Xu, M., Zang, J., Zhang, Z., Ban, Y., Guo, S., Guo, Y., Li, W., Mao, Y., Qian, S. J., Teng, H., Zhu, B., Zou, W., Cabrera, A., Moreno, B. G., Rios, A. A., Oliveros, A. F., Sanabria, J. C., Godinovic, N., Lelas, D., Lelas, K., Plestina, R., Polic, D., Puljak, I., Antunovic, Z., Dzelalija, M., Brigljevic, V., Duric, S., Kadija, K., Morovic, S., Attikis, A., Galanti, M., Mousa, J., Nicolaou, C., Ptochos, F., Razis, P. A., Finger, M., Finger, M., Jr., Awad, A., Khalil, S., Radi, A., Hektor, A., Kadastik, M., Muntel, M., Raidal, M., Rebane, L., Tiko, A., Azzolini, V., Eerola, P., Fedi, G., Czellar, S., Harkonen, J., Heikkinen, A., Karimaki, V., Kinnunen, R., Kortelainen, M. J., Lampen, T., Lassila-Perini, K., Lehti, S., Linden, T., Luukka, P., Maenpaa, T., Tuominen, E., Tuominiemi, J., Tuovinen, E., Ungaro, D., Wendland, L., Banzuzi, K., Karjalainen, A., Korpela, A., Tuuva, T., Sillou, D., Besancon, M., Choudhury, S., Dejardin, M., Denegri, D., Fabbro, B., Faure, J. L., Ferri, F., Ganjour, S., Gentit, F. X., Givernaud, A., Gras, P., Hamel de Monchenault, G., Jaray, P., Locci, E., Malcles, J., Marionneau, M., Millischer, L., Rander, J., Rosowsky, A., Shreyber, I., Titov, M., Verrecchia, P., Baffioni, S., Beaudette, F., Benhabib, L., Bianchini, L., Bluj, M., Broutin, C., Bussan, P., Chabot, C., Dahms, T., Dobrzynski, L., Elgammal, S., Granier de Cassagnac, R., Haguenaer, M., Mine, P., Mironov, C., Ochando, C., Paganini, P., Sabes, D., Salerno, R., Sirois, Y., Thiebaut, C., Wyslouch, B., Zabi, A., Agram, J. L., Andrea, J., Bloch, D., Bodin, D., Brom, J. M., Cardaci, M., Chabert, E. C., Collard, C., Conte, E., Drouhin, F., Ferro, C., Fontaine, J. C., Gele, D., Goerlach, U., Greder, S., Juillot, P., Karim, M., Le Bihan, A. C., Mikami, Y., Van Hove, P., Fassi, F., Mercier, D., Baty, C., Beauceron, S., Beaupere, N., Bedjidian, M., Bondu, O., Boudoul, G., Boumediene, D., Brun, H., Chasserat, J., Chierici, R., Contardo, D., Depasse, P., El Mamouni, H., Fay, J., Gascon, S., Ille, B., Kurca, T., Le Grand, T., Lethuillier, M., Mirabito, L., Perries, S., Sordini, V., Tosi, S., Tschudi, Y., Verdier, P., Lomidze, D., Anagnostou, G., Beranek, S., Edelhoff, M., Feld, L., Heracleous, N., Hindrichs, O., Jussen, R., Klein, K., Merz, J., Mohr, N., Ostapchuk, A., Perieanu, A., Raupach, F., Sammet, J., Schael, S., Sprenger, D., Weber, H., Weber, M., Wittmer, B., Ata, M., Dietz-Laursonn, E., Erdmann, M., Hebbeker, T., Hinzmann, A., Hoepfner, K., Klimkovich, T., Klingebiel, D., Kreuzer, P., Lanks, D., Lingemann, J., Magass, C., Merschmeyer, M., Meyer, A., Papacz, P., Pieta, H., Reithler, H., Schmitz, S. A., Sonnenschein, L., Steggemann, J., Teyssier, D., Bontenackels, M., Davids, M., Duda, M., Flugge, G., Geenen, H., Giffels, M., Ahmad, W. H., Heydhausen, D., Hoehle, F., Kargoll, B., Kress, T., Kuessel, Y., Linn, A., Nowack, A., Perchalla, L., Pooth, O., Rennefeld, J., Sauerland, P., Stahl, A., Thomas, M., Tornier, D., Zoeller, M. H., Martin, M. A.,

Behrenhoff, W., Behrens, U., Bergholz, M., Bethani, A., Borrás, K., Cakir, A., Campbell, A., Castro, E., Dammann, D., Eckert, G., Eckstein, D., Flossdorf, A., Flucke, G., Geiser, A., Hauk, J., Jung, H., Kasemann, M., Katkov, I., Katsas, P., Kleinwort, C., Kluge, H., Knutsson, A., Kramer, M., Krucker, D., Kuznetsova, E., Lange, W., Lohmann, W., Mankel, R., Marienfeld, M., Melzer-Pellmann, I. A., Meyer, A. B., Mnich, J., Mussgiller, A., Olzem, J., Petrukhin, A., Pitzl, D., Raspereza, A., Raval, A., Rosin, M., Schmidt, R., Schoerner-Sadenius, T., Sen, N., Spiridonov, A., Stein, M., Tomaszewska, J., Walsh, R., Wissing, C., Autermann, C., Blobel, V., Bobrovskiy, S., Draeger, J., Enderle, H., Gebbert, U., Gerner, M., Kaschube, K., Kaussen, G., Kirschenmann, H., Klanner, R., Lange, J., Mura, B., Naumann-Emme, S., Nowak, F., Pietsch, N., Sander, C., Schettler, H., Schleper, P., Schlieckau, E., Schroder, M., Schum, T., Schwandt, J., Stadie, H., Steinbrück, G., Thomsen, J., Barth, C., Bauer, J., Berger, J., Buege, V., Chwalek, T., De Boer, W., Dierlamm, A., Dirkes, G., Feindt, M., Gruschke, J., Hackstein, C., Hartmann, F., Heinrich, M., Held, H., Hoffmann, K. H., Honc, S., Komaragiri, J. R., Kuhr, T., Martschei, D., Mueller, S., Muller, T., Niegel, M., Oberst, O., Oehler, A., Ott, J., Peiffer, T., Quast, G., Rabbertz, K., Ratnikov, F., Ratnikova, N., Renz, M., Saout, C., Scheurer, A., Schieferdecker, P., Schilling, F. P., Schott, G., Simonis, H. J., Stober, F. M., Troendle, D., Wagner-Kuhr, J., Weiler, T., Zeise, M., Zhukov, V., Ziebarth, E. B., Daskalakis, G., Gerasis, T., Kesisoglou, S., Kyriakis, A., Loukas, D., Manolakis, I., Markou, A., Markou, C., Mavrommatis, C., Ntomari, E., Petrakou, E., Gouskos, L., Mertziemakis, T. J., Panagiotou, A., Stiliaris, E., Evangelou, I., Foudas, C., Kokkas, P., Manthos, N., Papadopoulos, I., Patras, V., Triantis, F. A., Aranyi, A., Bencze, G., Boldizsar, L., Hajdu, C., Hidas, P., Horvath, D., Kapusi, A., Krajczar, K., Sikler, F., Veres, G. I., Vesztergombi, G., Beni, N., Molnar, J., Palinkas, J., Szilasi, Z., Veszpremi, V., Raics, P., Trocsanyi, Z. L., Ujvari, B., Beri, S. B., Bhatnagar, V., Dhinra, N., Gupta, R., Jindal, M., Kaur, M., Kohli, J. M., Mehta, M. Z., Nishu, N., Saini, L. K., Sharma, A., Singh, A. P., Singh, J., Singh, S. P., Ahuja, S., Choudhary, B. C., Gupta, P., Jain, S., Jain, S., Kumar, A., Kumar, A., Naimuddin, M., Ranjan, K., Shivpuri, R. K., Banerjee, S., Bhattacharya, S., Dutta, S., Gomber, B., Khurana, R., Sarkar, S., Choudhury, R. K., Dutta, D., Kailas, S., Kumar, V., Mehta, P., Mohanty, A. K., Pant, L. M., Shukla, P., Aziz, T., Guchait, M., Gurtu, A., Maity, M., Majumder, D., Majumder, G., Mazumdar, K., Mohanty, G. B., Saha, A., Sudhakar, K., Wickramage, N., Banerjee, S., Dugad, S., Mondal, N. K., Arfaei, H., Bakhshiansohi, H., Etesami, S. M., Fahim, A., Hashemi, M., Jafari, A., Khakzad, M., Mohammadi, A., Najafabadi, M. M., Mehdiabadi, S. P., Safarzadeh, B., Zeinali, M., Abbrescia, M., Barbone, L., Calabria, C., Colaleo, A., Creanza, D., De Filippis, N., De Palma, M., Fiore, L., Iaselli, G., Lusito, L., Maggi, G., Maggi, M., Manna, N., Marangelli, B., My, S., Nuzzo, S., Pacifico, N., Pierro, G. A., Pompili, A., Pugliese, G., Romano, F., Roselli, G., Selvaggi, G., Silvestris, L., Trentadue, R., Tupputi, S., Zito, G., Abbiendi, G., Benvenuti, A. C., Bonacorsi, D., Braibant-Giacomelli, S., Brigliadori, L., Capiluppi, P., Castro, A., Cavallo, F. R., Cuffiani, M., Dallavalle, G. M., Fabbri, F., Fanfani, A., Fasanella, D., Giacomelli, P., Giunta, M., Grandi, C., Marcellini, S., Masetti, G., Meneghelli, M., Montanari, A., Navarria, F. L., Odorici, F., Perrotta, A., Primavera, F., Rossi, A. M., Rovelli, T., Siroli, G., Travaglini, R., Albergo, S., Cappello, G., Chiorboli, M., Costa, S., Tricomi, A., Tuve, C., Barbagli, G., Ciulli, V., Civinini, C., D'Alessandro, R., Focardi, E., Frosali, S., Gallo, E., Gonzi, S., Lenzi, P., Meschini, M., Paoletti, S., Sguazzoni, G., Tropiano, A., Benussi, L., Bianco, S., Colafranceschi, S., Fabbri, F., Piccolo, D., Fabbriatore, P., Musenich, R., Benaglia, A., De Guio, F., Di Matteo, L., Gennai, S., Ghezzi, A., Malvezzi, S., Martelli, A., Massironi, A., Menasce, D., Moroni, L., Paganoni, M., Pedrini, D., Ragazzi, S., Redaelli, N., Sala, S., Tabarelli de Fatis, T., Buontempo, S., Montoya, C. A., Cavallo, N., De Cosa, A., Fabozzi, F., Iorio, A. O., Lista, L., Merola, M., Paolucci, P., Azzi, P., Bacchetta, N., Bellan, P., Biasotto, M., Bisello, D., Branca, A., Carlin, R., Checchia, P., Dorigo, T., Gasparini, F., Gozzelino, A., Gulmini, M., Lacaparra, S., Lazzizzera, I., Margoni, M., Maron, G., Meneguzzo, A. T., Nespolo, M., Perrozzi, L., Pozzobon, N., Ronchese, P., Simonetto, F., Torassa, E., Tosi, M., Triossi, A., Vanini, S., Zotto, P., Zumerle, G., Baesso, P., Berzano, U.,

- Ratti, S. P., Riccardi, C., Torre, P., Vitulo, P., Viviani, C., Biasini, M., Bilei, G. M., Caponeri, B., Fano, L., Lariccia, P., Lucaroni, A., Mantovani, G., Menichelli, M., Nappi, A., Romeo, F., Santocchia, A., Taroni, S., Valdata, M., Azzurri, P., Bagliesi, G., Bernardini, J., Boccali, T., Broccolo, G., Castaldi, R., D'Agno, R. T., Dell'Oso, R., Fiori, F., Foa, L., Giassi, A., Kraan, A., Ligabue, F., Lomtadze, T., Martini, L., Messineo, A., Palla, F., Segneri, G., Serban, A. T., Spagnolo, P., Tenchini, R., Tonelli, G., Venturi, A., Verdini, P. G., Barone, L., Cavallari, F., Del Re, D., Di Marco, E., Diemoz, M., Franci, D., Grassi, M., Longo, E., Meridiani, P., Nourbakhsh, S., Organtini, G., Pandolfi, F., Paramatti, R., Rahatlou, S., Rovelli, C., Amapane, N., Arcidiacono, R., Argiro, S., Arneodo, M., Biino, C., Botta, C., Cartiglia, N., Castello, R., Costa, M., Demaria, N., Graziano, A., Mariotti, C., Marone, M., Maselli, S., Migliore, E., Mila, G., Monaco, V., Musich, M., Obertino, M. M., Pastrone, N., Pelliccioni, M., Potenza, A., Romero, A., Ruspa, M., Sacchi, R., Sola, V., Solano, A., Staiano, A., Pereira, A. V., Belforte, S., Cossutti, F., Della Ricca, G., Gobbo, B., Montanino, D., Penzo, A., Heo, S. G., Nam, S. K., Chang, S., Chung, J., Kim, D. H., Kim, G. N., Kim, J. E., Kong, D. J., Park, H., Ro, S. R., Son, D., Son, D. C., Son, T., Kim, Z., Kim, J. Y., Song, S., Choi, S., Hong, B., Jo, M., Kim, H., Kim, J. H., Kim, T. J., Lee, K. S., Moon, D. H., Park, S. K., Sim, K. S., Choi, M., Kang, S., Kim, H., Park, C., Park, I. C., Park, S., Ryu, G., Choi, Y., Choi, Y. K., Goh, J., Kim, M. S., Lee, J., Lee, S., Seo, H., Yu, I., Bilinskas, M. J., Grigelionis, I., Janulis, M., Martisiute, D., Petrov, P., Sabonis, T., Castilla-Valdez, H., De La Cruz-Burelo, E., Heredia-de La Cruz, I., Lopez-Fernandez, R., Villalba, R. M., Sanchez-Hernandez, A., Villaseñor-Cendejas, L. M., Moreno, S. C., Valencia, F. V., Ibarguen, H. A., Linares, E. C., Pineda, A. M., Reyes-Santos, M. A., Krofcheck, D., Tam, J., Butler, P. H., Doesburg, R., Silverwood, H., Ahmad, M., Ahmed, I., Asghar, M. I., Hoorani, H. R., Khan, W. A., Khurshid, T., Qazi, S., Brona, G., Cwiok, M., Dominik, W., Doroba, K., Kalinowski, A., Konecki, M., Krolkowski, J., Frueboes, T., Gokiel, R., Gorski, M., Kazana, M., Nawrocki, K., Romanowska-Rybinska, K., Szeleper, M., Wrochna, G., Zalewski, P., Almeida, N., Bargassa, P., David, A., Faccioli, P., Parracho, P. G., Gallinaro, M., Musella, P., Nayak, A., Pela, J., Ribeiro, P. Q., Seixas, J., Varela, J., Afanasiev, S., Belotelov, I., Bunin, P., Golutvin, I., Karjavin, V., Kozlov, G., Lanev, A., Moisenz, P., Palichik, V., Pereygin, V., Savina, M., Shmatov, S., Smirnov, V., Volodko, A., Zarubin, A., Golovtsov, V., Ivanov, Y., Kim, V., Levchenko, P., Murzin, V., Oreshkin, V., Smirnov, I., Sulimov, V., Uvarov, L., Vavilov, S., Vorobyev, A., Vorobyev, A., Andreev, Y., Dermenev, A., Gninenko, S., Golubev, N., Kirsanov, M., Krasnikov, N., Matveev, V., Pashenkov, A., Toropin, A., Troitsky, S., Epshteyn, V., Gavrilov, V., Kaftanov, V., Kossov, M., Krokhotin, A., Lychkovskaya, N., Popov, V., Safronov, G., Semenov, S., Stolin, V., Vlasov, E., Zhokin, A., Boos, E., Dubinin, M., Dudko, L., Ershov, A., Gribovshin, A., Kodolova, O., Lokhtin, I., Markina, A., Obraztsov, S., Perfilov, M., Petrushanko, S., Sarycheva, L., Savrin, V., Snigirev, A., Andreev, V., Azarkin, M., Dremin, I., Kirakosyan, M., Leonidov, A., Rusakov, S. V., Vinogradov, A., Azhgirey, I., Bayshev, I., Bitiukov, S., Grishin, V., Kachanov, V., Konstantinov, D., Korablev, A., Krychkin, V., Petrov, V., Ryutin, R., Sobol, A., Tourtchanovitch, L., Troshin, S., Tyurin, N., Uzunian, A., Volkov, A., Adzic, P., Djordjevic, M., Krpic, D., Milosevic, J., Aguilar-Benitez, M., Maestre, J. A., Arce, P., Battilana, C., Calvo, E., Cepeda, M., Cerrada, M., Llatas, M. C., Colino, N., De La Cruz, B., Peris, A. D., Pardos, C. D., Vazquez, D. D., Bedoya, C. F., Ramos, J. P., Ferrando, A., Flix, J., Fouz, M. C., Garcia-Abia, P., Lopez, O. G., Lopez, S. G., Hernandez, J. M., Josa, M. I., Merino, G., Pelayo, J. P., Redondo, I., Romero, L., Santaolalla, J., Soares, M. S., Willmott, C., Albajar, C., Codispoti, G., de Troconiz, J. F., Cuevas, J., Menendez, J. F., Folgueras, S., Caballero, I. G., Iglesias, L. L., Garcia, J. M., Cifuentes, J. A., Cabrillo, I. J., Calderon, A., Chuang, S. H., Campderos, J. D., Felcini, M., Fernandez, M., Gomez, G., Sanchez, J. G., Jorda, C., Pardo, P. L., Virto, A. L., Marco, J., Marco, R., Rivero, C. M., Matorras, F., Sanchez, F. J., Gomez, J. P., Rodrigo, T., Rodriguez-Marrero, A. Y., Ruiz-Jimeno, A., Scodellaro, L., Sanudo, M. S., Vila, I., Cortabitarte, R. V., Abbaneo, D., Auffray, E., Auzinger, G., Baillon, P., Ball, A. H., Barney, D., Bell, A. J., Benedetti, D., Berner, C., Bialas, W., Bloch, P., Bocci, A., Bolognesi, S., Bona, M., Breuker, H., Bunkowski, K., Camporesi, T., Cerninara, G., Christiansen, T., Perez, J. A., Cure, B., D'Enterria, D., De Roeck, A., Di Guida, S., Dupont-Sagorin, N., Elliott-Peisert, A., Frisch, B., Funk, W., Gaddi, A., Georgiou, G., Gerwig, H., Gigi, D., Gill, K., Giordano, D., Glege, F., Garrido, R. G., Gouzevitch, M., Govoni, P., Gowdy, S., Guiducci, L., Hansen, M., Hartl, C., Harvey, J., Hegeman, J., Hegner, B., Hoffmann, H. F., Honma, A., Innocente, V., Janot, P., Kaadze, K., Karavakis, E., Lecoq, P., Lourenco, C., Maki, T., Malberti, M., Malgeri, L., Mannelli, M., Masetti, L., Maurisset, A., Meijers, F., Mersi, S., Meschi, E., Moser, R., Mozer, M. U., Mulders, M., Nesvold, E., Nguyen, M., Orimoto, T., Orsini, L., Perez, E., Petrilli, A., Pfeiffer, A., Pierini, M., Pimia, M., Piparo, D., Polese, G., Racz, A., Antunes, J. R., Rolandi, G., Rommelskirchen, T., Rovere, M., Sakulin, H., Schafer, C., Schwick, C., Segoni, I., Sharma, A., Siegrist, P., Simon, M., Spicas, P., Spirropulu, M., Stoye, M., Tropea, P., Tsiros, A., Vichoudis, P., Voutilainen, M., Zeuner, W. D., Bertl, W., Deiters, K., Erdmann, W., Gabathuler, K., Horisberger, R., Ingram, Q., Kaestli, H. C., Konig, S., Kotlinski, D., Langenegger, U., Meier, F., Renker, D., Rohe, T., Sibille, J., Starodumov, A., Bani, L., Bortignon, P., Caminada, L., Chanon, N., Chen, Z., Cittolin, S., Dissertori, G., Dittmar, M., Eugster, J., Freudenreich, K., Grab, C., Hintz, W., Lecomte, P., Lustermann, W., Marchica, C., Ruiz del Arbol, P. M., Milenovic, P., Moortgat, F., Nageli, C., Nef, P., Nessi-Tedaldi, F., Pape, L., Pauss, F., Punz, T., Rizzi, A., Ronga, F. J., Rossini, M., Sala, L., Sanchez, A. K., Sawley, M. C., Stieger, B., Tauscher, L., Thea, A., Theofilatos, K., Treille, D., Urscheler, C., Wallny, R., Weber, M., Wehrli, L., Weng, J., Aguilo, E., Amsler, C., Chiochia, V., De Visser, S., Favaro, C., Rikova, M. I., Mejias, B. M., Otoungova, P., Regenfus, C., Robmann, P., Schmidt, A., Snoek, H., Chang, Y. H., Chen, K. H., Kuo, C. M., Li, S. W., Lin, W., Liu, Z. K., Lu, Y. J., Mekterovic, D., Volpe, R., Wu, J. H., Yu, S. S., Bartolini, P., Chang, P., Chang, Y. H., Chang, Y. W., Chao, Y., Chen, K. F., Hou, W. S., Hsiung, Y., Kao, K. Y., Lei, Y. J., Lu, R. S., Shiu, J. G., Tzeng, Y. M., Wang, M., Adiguzel, A., Bakirci, M. N., Cerci, S., Dozen, C., Dumanoglu, I., Eskut, E., Gargis, S., Gokbulut, G., Hos, I., Kangal, E. E., Topaksu, A. K., Onengut, G., Ozdemir, K., Ozturk, S., Polatoz, A., Sogut, K., Cerci, D. S., Tali, B., Topakli, H., Uzun, D., Vergili, L. N., Vergili, M., Akin, I. V., Aliev, T., Bilin, B., Bilmis, S., Deniz, M., Gamsizkan, H., Guler, A. M., Ocalan, K., Ozpineci, A., Serin, M., Sever, R., Surat, U. E., Yildirim, E., Zeyrek, M., Delimiroglu, M., Demir, D., Gulmez, E., Isildak, B., Kaya, M., Kaya, O., Ozbek, M., Ozkorucuklu, S., Sonmez, N., Levchuk, L., Bostock, F., Brooke, J. J., Cheng, T. L., Clement, E., Cussans, D., Frazier, R., Goldstein, J., Grimes, M., Hansen, M., Hartley, D., Heath, G. P., Heath, H. F., Kreczko, L., Metson, S., Newbold, D. M., Nirunpong, K., Poll, A., Senkin, S., Smith, V. J., Ward, S., Basso, L., Bell, K. W., Belyaev, A., Brew, C., Brown, R. M., Camanzi, B., Cockerill, D. J., Coughlan, J. A., Harder, K., Harper, S., Jackson, J., Kennedy, B. W., Olaiya, E., Petyt, D., Radburn-Smith, B. C., Shepherd-Themistocleous, C. H., Tomalin, I. R., Womersley, W. J., Worm, S. D., Bainbridge, R., Ball, G., Ballin, J., Beuselinck, R., Buchmuller, O., Colling, D., Cripps, N., Cutajar, M., Davies, G., Della Negra, M., Ferguson, W., Fulcher, J., Futyan, D., Gilbert, A., Bryer, A. G., Hall, G., Hatherell, Z., Hays, J., Iles, G., Jarvis, M., Karapostoli, G., Lyons, L., MacEvoy, B. C., Magnan, A. M., Marrouche, J., Mathias, B., Nandi, R., Nash, J., Nikitenko, A., Papageorgiou, A., Pesaresi, M., Petridis, K., Pioppi, M., Raymond, D. M., Rogerson, S., Rombotis, N., Rose, A., Ryan, M. J., Seer, C., Sharp, P., Sparrow, A., Tapper, A., Tourneur, S., Acosta, M. V., Virdee, T., Wakefield, S., Wardle, N., Wardrope, D., Whyntie, T., Barrett, M., Chadwick, M., Cole, J. E., Hobson, P. R., Khan, A., Kyberd, P., Leslie, D., Martin, W., Reid, I. D., Teodorescu, L., Hatakeyama, K., Liu, H., Henderson, C., Bose, T., Jarrin, E. C., Fantasia, C., Heister, A., St John, J., Lawson, P., Lazic, D., Rohlf, J., Sperka, D., Sulak, L., Avetisyan, A., Bhattacharya, S., Chou, J. P., Cutts, D., Ferapontov, A., Heintz, U., Jabeen, S., Kukartsev, G., Landsberg, G., Luk, M., Narain, M., Nguyen, D., Segala, M., Sinthuprasith, T., Speer, T., Tsang, K. V., Breton, J., Breto, G., Calderon De La Barca Sanchez, M., Chauhan, S., Chertok, M., Conway, J., Cox, P. T., Dolen, J., Erbacher, R., Friis, E., Ko, W., Kopecky, A., Lander, R., Liu, H., Maruyama, S., Miceli, T., Nikolic, M., Pellett, D., Robles, J., Salur, S., Schwarz, T., Searle, M., Smith, J., Squires, M., Tripathi, M., Sierra, R. V., Veelken, C., Andreev, V.,

- Arisaka, K., Cline, D., Cousins, R., Deisher, A., Duris, J., Erhan, S., Farrell, C., Hauser, J., Ignatenko, M., Jarvis, C., Plager, C., Rakness, G., Schlein, P., Tucker, J., Valuev, V., Babb, J., Chandra, A., Clare, R., Ellison, J., Gary, J. W., Giordano, F., Hanson, G., Jeng, G. Y., Kao, S. C., Liu, F., Liu, H., Long, O. R., Luthra, A., Nguyen, H., Shen, B. C., Stringer, R., Sturdy, J., Sumowidagdo, S., Wilken, R., Wimpenny, S., Andrews, W., Branson, J. G., Cerati, G. B., Evans, D., Golf, F., Holzner, A., Kelley, R., Lebourgeois, M., Letts, J., Mangano, B., Padhi, S., Palmer, C., Petrucciani, G., Pi, H., Pieri, M., Ranieri, R., Sani, M., Sharma, V., Simon, S., Sudano, E., Tadel, M., Tu, Y., Vartak, A., Wasserbaech, S., Wurthwein, F., Yagil, A., Yoo, J., Barge, D., Bellan, R., Campagnari, C., D'Alfonso, M., Danielson, T., Flowers, K., Geffert, P., Incandela, J., Justus, C., Kalavase, P., Koay, S. A., Kovalskyi, D., Krutlyov, V., Lowette, S., McColl, N., Pavlunin, V., Rebassoo, F., Ribnik, J., Richman, J., Rossin, R., Stuart, D., To, W., Vlimant, J. R., Apresyan, A., Bornheim, A., Bunn, J., Chen, Y., Gataullin, M., Ma, Y., Mott, A., Newman, H. B., Rogan, C., Shin, K., Timciuc, V., Traczyk, P., Veverka, J., Wilkinson, R., Yang, Y., Zhu, R. Y., Akgun, B., Carroll, R., Ferguson, T., Iiyama, Y., Jang, D. W., Jun, S. Y., Liu, Y. F., Paulini, M., Russ, J., Vogel, H., Vorobiev, I., Cumalat, J. P., Dinardo, M. E., Drell, B. R., Edelmaier, C. J., Ford, W. T., Gaz, A., Heyburn, B., Lopez, E. L., Nauenberg, U., Smith, J. G., Stenson, K., Ulmer, K. A., Wagner, S. R., Zang, S. L., Agostino, L., Alexander, J., Cassel, D., Chatterjee, A., Das, S., Eggert, N., Gibbons, L. K., Heltsley, B., Hopkins, W., Khukhunaishvili, A., Kreis, B., Kaufman, G. N., Patterson, J. R., Puigh, D., Ryd, A., Salvati, E., Shi, X., Sun, W., Teo, W. D., Thom, J., Thompson, J., Vaughan, J., Weng, Y., Winstrom, L., Wittich, P., Biselli, A., Cirino, G., Winn, D., Abdullin, S., Albrow, M., Anderson, J., Apollinari, G., Atac, M., Bakken, J. A., Bauerdick, L. A., Beretvas, A., Berryhill, J., Bhat, P. C., Bloch, I., Borchering, F., Burkett, K., Butler, J. N., Chetlur, V., Cheung, H. W., Chlebana, F., Cihangir, S., Cooper, W., Eartly, D. P., Elvira, V. D., Esen, S., Fisk, I., Freeman, J., Gao, Y., Gottschalk, E., Green, D., Gunthoti, K., Gutsche, O., Hanlon, J., Harris, R. M., Hirschauer, J., Hooberman, B., Jensen, H., Johnson, M., Joshi, U., Khatiwada, R., Klima, B., Kousouris, K., Kunori, S., Kwan, S., Leonidopoulos, C., Limon, P., Lincoln, D., Lipton, R., Lykken, J., Maeshima, K., Marraffino, J. M., Mason, D., McBride, P., Miao, T., Mishra, K., Mrenna, S., Musienko, Y., Newman-Holmes, C., O'Dell, V., Pordes, R., Prokofyev, O., Saoulidou, N., Sexton-Kennedy, E., Sharma, S., Spalding, W. J., Spiegel, L., Tan, P., Taylor, L., Tkaczyk, S., Upplegger, L., Vaandering, E. W., Vidal, R., Whitmore, J., Wu, W., Yang, F., Yumiceva, F., Yun, J. C., Acosta, D., Avery, P., Bourilkov, D., Chen, M., De Gruttola, M., Di Giovanni, G. P., Dobur, D., Drozdetskiy, A., Field, R. D., Fisher, M., Fu, Y., Furic, I. K., Gartner, J., Kim, B., Konigsberg, J., Korytov, A., Kropivnitskaya, A., Kypreos, T., Matchev, K., Mitselmakher, G., Muniz, L., Prescott, C., Remington, R., Schmitt, M., Scurlock, B., Sellers, P., Skhirtladze, N., Snowball, M., Wang, D., Yelton, J., Zakaria, M., Ceron, C., Gaultney, V., Kramer, L., Lebolo, L. M., Linn, S., Markowitz, P., Martinez, G., Mesa, D., Rodriguez, J. L., Adams, T., Askew, A., Bochenek, J., Chen, J., Diamond, B., Gleyzer, S. V., Haas, J., Hagopian, S., Hagopian, V., Jenkins, M., Johnson, K. F., Prosper, H., Quertenmont, L., Sekmen, S., Veeraraghavan, V., Baarmand, M. M., Dorney, B., Guragain, S., Hohlmann, M., Kalakhety, H., Ralich, R., Vodopiyarov, I., Adams, M. R., Anghel, I. M., Apanasevich, L., Bai, Y., Bazterra, V. E., Betts, R. R., Callner, J., Cavanaugh, R., Dragoiu, C., Gauthier, L., Gerber, C. E., Hofman, D. J., Khalatyan, S., Kunde, G. J., Lacroix, F., Malek, M., O'Brien, C., Silkworth, C., Silvestre, C., Smoron, A., Strom, D., Varelas, N., Akgun, U., Albayrak, E. A., Bilki, B., Clarida, W., Duru, F., Lae, C. K., McCliment, E., Merlo, J. P., Mermerkaya, H., Mestvirishvili, A., Moeller, A., Nachtman, J., Newsom, C. R., Norbeck, E., Olson, J., Onel, Y., Ozok, F., Sen, S., Wetzel, J., Yetkin, T., Yi, K., Barnett, B. A., Blumenfeld, B., Bonato, A., Eskew, C., Fehling, D., Giurgiu, G., Gribsan, A. V., Guo, Z. J., Hu, G., Maksimovic, P., Rappoccio, S., Swartz, M., Tran, N. V., Whitbeck, A., Baringer, P., Bean, A., Benelli, G., Grachov, O., Kenny, R. P., III, Murray, M., Noonan, D., Sanders, S., Wood, J. S., Zhukova, V., Barfuss, A. F., Bolton, T., Chakaberia, I., Ivanov, A., Khalil, S., Makouski, M., Maravin, Y., Shrestha, S., Svintradze, I., Wan, Z., Gronberg, J., Lange, D., Wright, D., Baden, A., Bouteleur, M., Eno, S. C., Ferencek, D., Gomez, J. A., Hadley, N. J., Kellogg, R. G., Kim, M., Lu, Y., Mignerey, A. C., Rossato, K., Rumerio, P., Santanastasio, F., Skuja, A., Temple, J., Tonjes, M. B., Tonwar, S. C., Twedt, E., Alver, B., Bauer, G., Bendavid, J., Busza, W., Butz, E., Cali, I. A., Chan, M., Dutta, V., Everaerts, P., Ceballos, G. G., Goncharov, M., Hahn, K. A., Harris, P., Kim, Y., Klute, M., Lee, Y. J., Li, W., Loizides, C., Luckey, P. D., Ma, T., Nahn, S., Paus, C., Ralph, D., Roland, C., Roland, G., Rudolph, M., Stephens, G. S., Stockli, F., Sumorok, K., Sung, K., Wenger, E. A., Wolf, R., Xie, S., Yang, M., Yilmaz, Y., Yoon, A. S., Zanetti, M., Cooper, S. I., Cushman, P., Dahmes, B., De Benedetti, A., Duder, P. R., Franzoni, G., Haupt, J., Klapoetke, K., Kubota, Y., Mans, J., Pastika, N., Rekovic, V., Rusack, R., Sasseville, M., Singovsky, A., Tambe, N., Cremaldi, L. M., Godang, R., Kroeger, R., Perera, L., Rahmat, R., Sanders, D. A., Summers, D., Bloom, K., Bose, S., Butt, J., Claes, D. R., Dominguez, A., Eads, M., Keller, J., Kelly, T., Kravchenko, I., Lazo-Flores, J., Malbouisson, H., Malik, S., Snow, G. R., Baur, U., Godshalk, A., Iashvili, I., Jain, S., Kharchilava, A., Kumar, A., Shipkowski, S. P., Smith, K., Zennaro, J., Alverson, G., Barberis, E., Baumgartel, D., Boeriu, O., Chasco, M., Reucroft, S., Swain, J., Trocino, D., Wood, D., Zhang, J., Anastasov, A., Kubik, A., Odell, N., Ofierzynski, R. A., Pollack, B., Pozdnyakov, A., Schmitt, M., Stoynev, S., Velasco, M., Won, S., Antonelli, L., Berry, D., Brinkerhoff, A., Hildreth, M., Jessop, C., Karmgard, D. J., Kolb, J., Kolberg, T., Lannon, K., Luo, W., Lynch, S., Marinelli, N., Morse, D. M., Pearson, T., Ruchti, R., Slaunwhite, J., Valls, N., Wayne, M., Ziegler, J., Bylsma, B., Durkin, L. S., Gu, J., Hill, C., Killewald, P., Kotov, K., Ling, T. Y., Rodenburg, M., Williams, G., Adam, N., Berry, E., Elmer, P., Gerbaudo, D., Halyo, V., Hebda, P., Hunt, A., Jones, J., Laird, E., Pegna, D. L., Marlow, D., Medvedeva, T., Mooney, M., Olsen, J., Piroué, P., Quan, X., Saka, H., Stickland, D., Tully, C., Werner, J. S., Zuranski, A., Acosta, J. G., Huang, X. T., Lopez, A., Mendez, H., Oliveros, S., Vargas, J. E., Zatserklyaniy, A., Alagöz, E., Barnes, V. E., Bolla, G., Borrello, L., Bortoletto, D., De Mattia, M., Everett, A., Garfinkel, A. F., Gutay, L., Hu, Z., Jones, M., Koybasi, O., Kress, M., Laasänen, A. T., Leonardo, N., Liu, C., Maroussov, V., Merkel, P., Miller, D. H., Neumeister, N., Shipsey, I., Silvers, D., Svyatkovskiy, A., Yoo, H. D., Zablocki, J., Zheng, Y., Jindal, P., Parashar, N., Boulahouache, C., Ecklund, K. M., Geurts, F. J., Padley, B. P., Redjimi, R., Roberts, J., Zabel, J., Betchart, B., Bodek, A., Chung, Y. S., Covarelli, R., de Barbaro, P., Demina, R., Eshaq, Y., Flacher, H., Garcia-Bellido, A., Goldenzweig, P., Gotra, Y., Han, J., Harel, A., Miner, D. C., Orbaker, D., Petrillo, G., Sakumoto, W., Vishnevskiy, D., Zielinski, M., Bhatti, A., Ciesielski, R., Demortier, L., Goulianos, K., Lungu, G., Malik, S., Mesropian, C., Yan, M., Atramentov, O., Barker, A., Duggan, D., Gershtein, Y., Gray, R., Halkiadakis, E., Hidas, D., Hits, D., Lath, A., Panwalkar, S., Patel, R., Rose, K., Schnetzer, S., Somalwar, S., Stone, R., Thomas, S., Cerizza, G., Hollingsworth, M., Spanier, S., Yang, Z. C., York, A., Eusebi, R., Flanagan, W., Gilmore, J., Gurrola, A., Kamon, T., Khotilovich, V., Montalvo, R., Osipenko, I., Pakhotin, Y., Pivarski, J., Safonov, A., Sengupta, S., Tatarinov, A., Toback, D., Weinberger, M., Akchurin, N., Bardak, C., Damgov, J., Jeong, C., Kovitangsoo, K., Lee, S. W., Libeiro, T., Mane, P., Roh, Y., Sill, A., Volobouev, I., Wigmans, R., Yazgan, E., Appelt, E., Brownson, E., Engh, D., Florez, C., Gabella, W., Issah, M., Johns, W., Kurt, P., Maguire, C., Melo, A., Sheldon, P., Snook, B., Tuo, S., Velkovska, J., Arenton, M. W., Balazs, M., Boutle, S., Cox, B., Francis, B., Hirosky, R., Ledovskoy, A., Lin, C., Neu, C., Yohay, R., Gollapinni, S., Harr, R., Karchin, P. E., Lamichhane, P., Mattson, M., Milstene, C., Sakharov, A., Anderson, M., Bachtis, M., Bellinger, J. N., Carlsmith, D., Dasu, S., Efron, J., Flood, K., Gray, L., Grogg, K. S., Grothe, M., Hall-Wilton, R., Herndon, M., Herve, A., Klabbers, P., Klukas, J., Lanaro, A., Lazaris, C., Leonard, J., Loveless, R., Mohapatra, A., Palmonari, F., Reeder, D., Ross, I., Savin, A., Smith, W. H., Swanson, J., Weinberg, M., and Collaboration, C. M. S. (2011) Search for new physics with a monojet and missing transverse energy in pp collisions at $\sqrt{s} = 7$ TeV. *Phys. Rev. Lett.* 107, 201804.
- (86) Ueda, K., Ohta, Y., and Hosoya, H. (2003) The carboxy-terminal pleckstrin homology domain of ROCK interacts with filamin-A. *Biochem. Biophys. Res. Commun.* 301, 886–890.

- (87) Weber, G. F., Bjerke, M. A., and DeSimone, D. W. (2011) Integrins and cadherins join forces to form adhesive networks. *J. Cell Sci.* 124, 1183–1193.
- (88) de Rooij, J., Kerstens, A., Danuser, G., Schwartz, M. A., and Waterman-Storer, C. M. (2005) Integrin-dependent actomyosin contraction regulates epithelial cell scattering. *J. Cell Biol.* 171, 153–164.
- (89) Martinez-Rico, C., Pincet, F., Thiery, J. P., and Dufour, S. (2010) Integrins stimulate E-cadherin-mediated intercellular adhesion by regulating Src-kinase activation and actomyosin contractility. *J. Cell Sci.* 123, 712–722.
- (90) Maruthamuthu, V., Sabass, B., Schwarz, U. S., and Gardel, M. L. (2011) Cell-ECM traction force modulates endogenous tension at cell-cell contacts. *Proc. Natl. Acad. Sci. U.S.A.* 108, 4708–4713.
- (91) Jasaitis, A., Estevez, M., Heysch, J., Ladoux, B., and Dufour, S. (2012) E-Cadherin-dependent stimulation of traction force at focal adhesions via the Src and PI3K signaling pathways. *Biophys. J.* 103, 175–184.
- (92) Mertz, A. F., Che, Y., Banerjee, S., Goldstein, J. M., Rosowski, K. A., Revilla, S. F., Niessen, C. M., Marchetti, M. C., Dufresne, E. R., and Horsley, V. (2013) Cadherin-based intercellular adhesions organize epithelial cell-matrix traction forces. *Proc. Natl. Acad. Sci. U.S.A.* 110, 842–847.
- (93) Bays, J. L., Peng, X., Tolbert, C. E., Guilluy, C., Angell, A. E., Pan, Y., Superfine, R., Burridge, K., and DeMali, K. A. (2014) Vinculin phosphorylation differentially regulates mechanotransduction at cell-cell and cell-matrix adhesions. *J. Cell Biol.* 205, 251–263.
- (94) Uda, Y., Poh, Y. C., Chowdhury, F., Wu, D. C., Tanaka, T. S., Sato, M., and Wang, N. (2011) Force via integrins but not E-cadherin decreases Oct3/4 expression in embryonic stem cells. *Biochem. Biophys. Res. Commun.* 415, 396–400.
- (95) Curtin, J. A., Busam, K., Pinkel, D., and Bastian, B. C. (2006) Somatic activation of KIT in distinct subtypes of melanoma. *J. Clin. Oncol.* 24, 4340–4346.