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Mechanosensing at integrin-mediated cell–matrix adhesions: from molecular to integrated mechanisms

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Integrin-mediated adhesions between cells and the extracellular matrix are fundamental for cell function, and one of their main roles is to sense and respond to mechanical force. Here we discuss the different mechanisms that can confer mechanosensitivity to adhesions. We first address molecular mechanisms mediated by force-induced changes in molecular properties, such as binding dynamics or protein conformation. Then, we discuss recent evidence on how these mechanisms are integrated with cellular and extracellular parameters such as myosin and actin activity, membrane tension, and ECM properties, endowing cells with an exquisite ability to both detect and respond to physical and mechanical cues from their environment.

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Introduction

The molecular nature of the structures conferring adhesion between cells and their surrounding extracellular matrix (ECM) began to be elucidated over 40 years ago, when Abercrombie et al. [1] identified dense 'plaques' at the cell–substrate interface of migrating cells. Since then, the study of cell–matrix adhesions has flourished, leading to the identification of multiple types of adhesive structures, and of their roles in cell migration [2], signaling [3], and disease progression [4]. Cell–matrix adhesions can be classified according to their shape and molecular complexity, and for instance focal complexes, focal adhesions, and fibrillar adhesions progressively increase in size and complexity. Despite this diversity, most types of cell–matrix adhesions share a common basic architecture, characterized on one end by the transmembrane proteins, integrins, that bind the ECM, and on the other end by actin fibers that indirectly bind to integrins via a set of adaptor proteins (Figure 1a). These adaptor proteins can include over a hundred different types of molecules, which function as a major hub for biochemical signaling events [5]. However, beyond mediating biochemical signaling, one of the main functions of cell–matrix adhesions is to detect, transmit, and respond to mechanical signals. Such signals include the rigidity of the ECM or forces transmitted from it, as well as mechanical cues originating within the cell, like cytoskeletal contraction or changes in membrane tension.

Cell–matrix adhesions are described as mechanosensitive because they grow and mature in response to applied forces or increased substrate rigidity, and shrink or disassemble in the absence of such stimuli [6,7••]. Once formed, mature focal adhesions connect to the cytoskeleton via the formation of stress fibers. Focal adhesions and stress fibers in turn affect nuclear shuttling and the activity of different transcriptional regulators, for instance by changing their binding affinity to either focal adhesions [8] or actin [9], or by transmitting force to the nucleus, opening nuclear pores, and promoting their nuclear entry [10••]. Thus, mechanosensitive adhesion growth and maturation can directly drive gene transcription. Due to the complexity of cell–matrix adhesions, the mechanosensing process is mediated by a rich network of molecular interactions and biochemical pathways, which have been the subject of recent extensive reviews [11,12]. Given the concise nature of this review, we will not cover those interactions in detail. Instead, we will focus on a more fundamental question: what are conceptually the different types of mechanisms that can confer mechanosensitivity to cell–matrix adhesions, and what is the experimental evidence for them?

Mechanosensitivity through regulation of binding dynamics

Force applied to cell–matrix adhesions is transmitted through their molecular elements, from ECM–integrin bonds, to adaptor proteins, and finally to the actin cytoskeleton (Figure 1a). For this force to be detected, it needs to trigger some sort of event in the affected molecules. The most common type of molecular event affected by force is bond dissociation. In the most intuitive scenario, known as 'slip bond', force applied to a bond weakens it, promoting dissociation. However, some bonds behave as 'catch bonds', which strengthen under force up to a given threshold, and only weaken if this

Figure 1
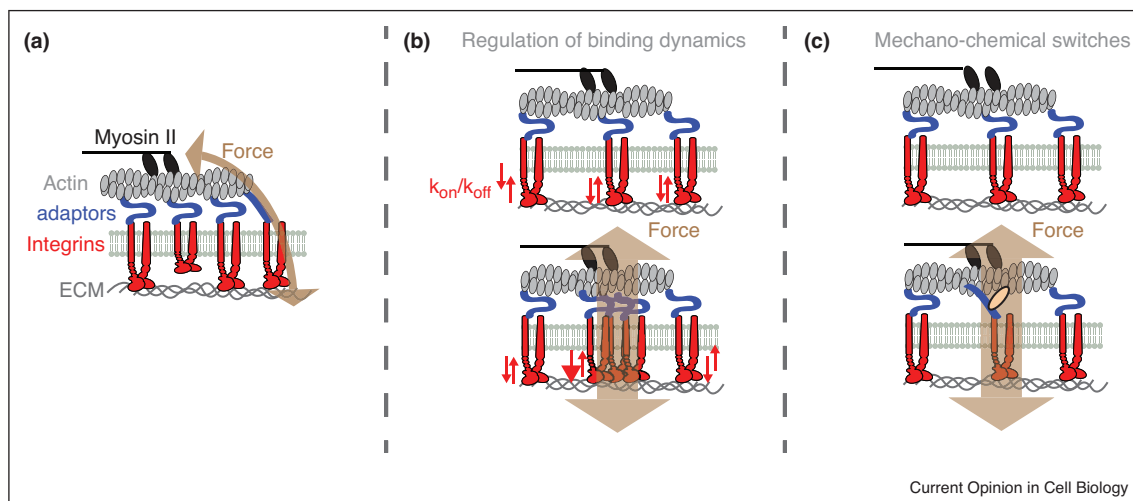
Molecular mechanosensing mechanisms. **(a)** Cell–matrix adhesions link the ECM to actin through integrins and adaptor proteins. As myosin exerts force on actin, this is transmitted through adaptor proteins and integrins. **(b)** Force application increases the lifetime of catch bonds between integrins and the ECM, potentially increasing clustering. **(c)** Force application induces conformational changes in adaptor proteins (such as protein unfolding), leading to downstream biochemical events such as protein binding to newly exposed unfolded domains in adaptor proteins.

threshold is surpassed. Catch bonds have been mostly described for integrin–ECM interactions such as the bond between fibronectin and integrins, α5β1 and αvβ3 [13,14], but they have recently been found also in adaptor protein interactions, such as the bond between vinculin and actin [15••]. Regardless of whether they operate as catch or slip bonds, in both cases force is a key regulator of bond lifetime. In the case of integrin–ECM adhesion, this means that the number of ligand-bound integrins, and the stability of the binding, will depend on force. In turn, this will determine subsequent integrin clustering (Figure 1b), and the likelihood of triggering downstream integrin-mediated events which depend on integrin ligation and clustering, such as activation of FAK and Src [16•], or recruitment of adaptor proteins like vinculin or zyxin [17].

Force-dependent bond lifetimes provide sensitivity not only to externally applied forces, but also to passive ECM mechanical properties such as its rigidity. Indeed and as predicted by the molecular clutch model [18], as cells pull on the ECM through contraction of the actomyosin cytoskeleton, different matrix rigidities lead to different regimes of force transmission. This then affects the dynamics of cell–matrix bond formation and rupture, regulating force transmission itself and subsequently, cell migration, actin dynamics, and adhesion formation [7••,18–20]. Adhesion-dependent mechanosensitivity, particularly for integrins, can be further tuned by cells through several strategies, conferring the ability to respond to specific mechanical conditions. These strategies include binding to the matrix through different integrin types with different mechanosensitivities [21,22], the action of

different integrin binding partners such as talin [23], sharpin [24], shank [25], kank [26••], kindlin [27], ICAP-1 [28], or ZO-1 [29], which regulate integrin activation and thereby force-dependent ligand binding [13], or the regulation of the steric hindrance to ligand binding provided by the glycocalyx [30] (discussed below).

Mechanosensitivity through activation of mechano-chemical switches
Beyond affecting bond lifetime, another major molecular effect of force is to regulate protein conformation (Figure 1c). The best known example of this effect is with talin, an adaptor molecule linking actin to integrins that is submitted to cell–ECM forces [31,32]. Upon force application, several domains of talin unfold, exposing previously hidden binding sites to vinculin [33,34]. Subsequent vinculin binding then reinforces the adhesion site, possibly through interactions with both integrins and actin [15••,35], and leads to adhesion maturation. Whereas the detailed mechanism by which vinculin binding leads to adhesion maturation is unclear, this constitutes a prime example of a mechano-chemical switch, in which a mechanical signal (force) is converted into a biochemical one (a protein–protein interaction). Several other examples of mechano-chemical switches in adaptor proteins have been described. For instance, force-induced events include changes in filamin crosslinking angles affecting integrin binding [36], stretching of p130Cas leading to its phosphorylation [37], and activation of focal adhesion kinase by dissociating auto-inhibitory interactions [38], although this latter effect remains to date a computational prediction. Interestingly, talin has recently

been reported to respond to force not only by unfolding but also by cleaving, producing a rod domain needed for cell growth [39[••]]. Outside of adaptor proteins, mechanical stretching can also induce chemical events in ECM proteins such as fibronectin (by promoting the binding of interleukin 7 [40[•]]), or in integrins, by inducing conformational changes that in turn regulate ECM binding [14].
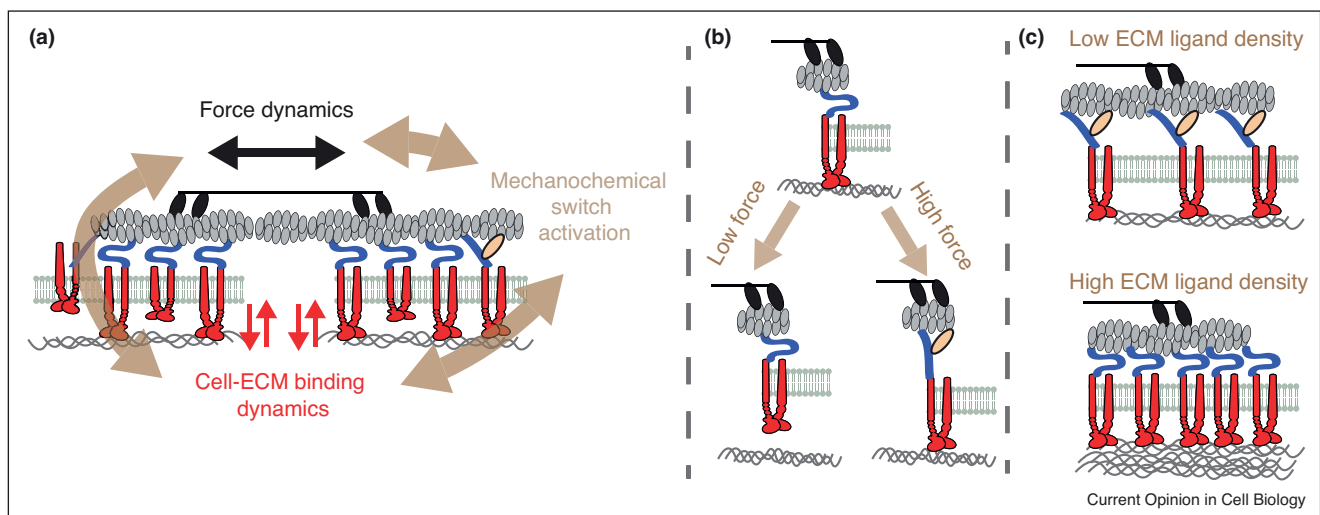
Mechanosensitivity integration through contractility and ECM properties

In cells, the different types of molecular mechanosensing mechanisms described above are coupled to each other, to biochemical signaling pathways, and to higher order force regulation, giving rise to complex feedback mechanisms (Figure 2a). Some fundamental design rules, however, are beginning to emerge. For instance, cytoskeletal structure, dynamics, and integrity will affect how force is transmitted to adhesions, in turn regulating mechanosensing [41]. Some recent examples of this principle include the regulation of actin stress fiber mechanics by zyxin, which tunes force transmission [42[•]], the alignment and re-orientation of integrins by actin flows, which affects their clustering and thereby their function [43[•]], and the re-ordering of the actin cytoskeleton induced by stiffness [44]. The collective behavior of ensembles of several ECM-integrin-adaptor protein–actin links (often referred to as 'clutches') is also affected by force, as observed and predicted theoretically by the molecular clutch theory [18,45]. This framework could explain the mechanosensitive oscillations observed in force transmission in focal adhesions [46,47], and potentially also the nano-scale

force contraction cycles observed in maturing adhesions [48]. Such nano-scale contractions depend on substrate rigidity [49] and are associated with altered activity of receptor tyrosine kinases [50]. Further, they may sense rigidity through the duration of the force cycles applied, although the underlying mechanisms are unclear.

Additionally, a fundamental aspect that determines adhesion mechanosensing is the coupling between binding dynamics and mechano-chemical switches. In our recent work, we have determined that the differential response to force of talin unfolding and integrin–fibronectin unbinding enables cell sensing of the rigidity [7[••]], ligand density, and ligand distribution [51[••]] of the ECM. If we consider a given actin–talin–integrin–fibronectin clutch, this differential response entails that a low applied force will tend to trigger integrin–fibronectin unbinding first, disengaging the clutch and preventing talin unfolding (Figure 2b). In contrast, applying force above a given threshold (of about 5 pN) will first lead to talin unfolding, enabling vinculin binding and subsequent mechanosensing. Thus, this coupled system allows talin unfolding only above a threshold force, conferring sensitivity to force, but also to substrate rigidity and ligand distribution. This is because clutch forces are increased both by high substrate rigidity and low ligand density, since total cell applied force is distributed among fewer ligands (Figure 2c). Interestingly, this framework confirms that cell spatial sensing of ligands is also mediated by mechanosensing, and not by a direct length measurement as previously hypothesized [51[••]]. This concept of

Figure 2

Integration of mechanosensing through contractility and ECM properties. **(a)** The regulation of force dynamics, both at the nano-scale and at the cell level, both affects and is impacted by cell–ECM binding dynamics, and the activation of mechanochemical switches. This leads to a feedback mechanism integrating cell response. **(b)** If force is transmitted through an adaptor protein (talin) and an integrin–ECM bond, the different properties under force of talin and the integrin–ECM bond lead to integrin unbinding if the force is low, and talin unfolding (and subsequent vinculin binding) if the force is high. **(c)** If ECM coating density is low, contractility is distributed among few ligands, leading to a high force per molecule that triggers talin unfolding. If ECM density is high, more integrins bind, distributing the force and preventing talin unfolding.

differential mechanosensing has so far been explored by using the talin-integrin system, but it could apply in several other cases. A particularly interesting example is the complex between glycoprotein Ib, and the ECM protein Willebrand factor, which contains three mechanosensitive elements in series: a catch bond between both proteins, and two unfoldable domains within glycoprotein Ib [52•].

Mechanosensitivity integration through actin dynamics and membrane tension

Any machinery adhering cells to the extracellular environment is intimately linked to the main guardian of cell integrity: the plasma membrane. The lipid bilayer supports all adhesive molecules and numerous studies show that membrane mechanics is also a key element in the mechanosensitivity of cell–substrate adhesions. Membrane tension, and particularly in our focus here, plasma membrane tension, is a mechanical property of the cell based on four driving sources: osmotic forces, cytoskeletal forces, membrane bending rigidity (stiffness, composition) and attachment to the underlying cytoskeleton through different lipids and proteins (see our recent review [53]). These four elements are linked to the physical properties of the lipid bilayer as a fluid, but barely stretchable material (about 4% before lysis). Recent work has shown that membrane tension should be seen as a master regulator of cell functions, as it can be rapidly transmitted across the cell [54–60••]. As membrane tension is closely linked to actin cytoskeleton dynamics [53,61], it was postulated through mathematical modeling that adhesion dynamics could be influenced by fluctuations in membrane tension [62]. Indeed, older observations clearly linked membrane tension to cell protrusions [63], a key feature of motile cells dependent on both cytoskeletal and adhesion dynamics. From several recent studies, it emerges that membrane mechanics can influence adhesion mechanosensing at three different levels. First, it can influence adhesion formation [60••] by controlling protrusion rate and actin behavior [60••,64•]. Second, it can potentially influence adhesion clustering [30,65]. Finally, it can directly [30,66] and more surprisingly, indirectly [67,68•] induce integrin activation, although its role here is less clear.

By combining evidence from membrane tension changes in spreading and migrating fibroblasts [60••] and migrating keratocytes [64•], a consensus model for the influence of membrane tension in actin dynamics and adhesion positioning can be built (Figure 3a). At low membrane tension, a fast protruding lamellipodia is observed [60••,64•] with unbranched actin filaments perpendicular to the cell edge [64•]. At this stage, adhesions are at the back of lamellipodial actin, sustaining the leading edge structure by forming and disassembling in a staggered manner [60••]. As the cell runs out of membrane area, rising membrane tension induces an increased load on actin, resulting in a slower lamellipodia with a more branched and less

perpendicular actin network [64•]. Adhesions at the back react to this increasing load by growing and progressively organizing as a single row [60••]. At very high membrane tension, actin polymerization is potentially pushed upward due to buckling [60••]. This leads to the force-induced maturation of a single adhesion row at the back of this buckled region, as well as the creation of a preferential nucleation site for new adhesions at the front region [60••]. This explains how cells can form adhesions along the leading edge in a synchronous manner, in response to force generated by actin polymerization rather than myosin-based contractility [60••]. While the buckling was not investigated in the keratocyte-based study [64•], older reports showed potential evidence of it [69] pointing to a potentially universal mechanism.

As for adhesion positioning during motility, the influence of membrane mechanics for integrin clustering was first proposed through mathematical modeling [65], then supported experimentally [30]. The basic principle of this mechanism is a competition between relatively short molecules, integrins (about 25 nm in the non-extended configuration), and long and bulky glycoproteins in the glycocalyx (up to >100 nm). While not directly proven, the influence of membrane mechanics and potentially membrane tension is easy to explain. As both the glycocalyx and integrins are supported by the plasma membrane, the long glycocalyx hinders the accessibility of integrins to the matrix, strongly reducing binding rates (Figure 3b). Once an integrin binds, however, it bends the membrane to overcome the glycocalyx barrier, generating a region where diffusing integrins and the ECM are in close proximity, forming a 'kinetic trap' where binding rates are increased. This leads to larger and highly activated adhesions. Interestingly, a long glycocalyx is a hallmark of cancer cells, pointing to a central role of mechanical forces originated from the membrane in cancer progression [30].

The third mechanism where membrane mechanics is implicated is the potential activation of integrins by non-integrin ECM ligands, such as the urokinase-type plasminogen activator (uPAR), independently of integrin–ECM engagement [67,68•]. The mechanism proposed is based on the fact that the binding between uPAR and the ECM protein vitronectin was sufficient to trigger integrin signaling. Fascinatingly, this effect seems to require membrane tension, but not integrin–ECM binding. The working model for this cross activation could be close to the glycocalyx 'kinetic trap' [30] in the sense that uPAR binding to the substrate will induce an out of plane membrane deformation, dragging nearby integrins away from actin and adaptor proteins (Figure 3c). If integrins are bound to adaptor proteins such as talin (even if not to the ECM), this would then generate a force that would increase with membrane tension, favoring the activation of mechanochemical switches. This mechanism, while still unclear, points towards a central role for membrane-mediated

Figure 3
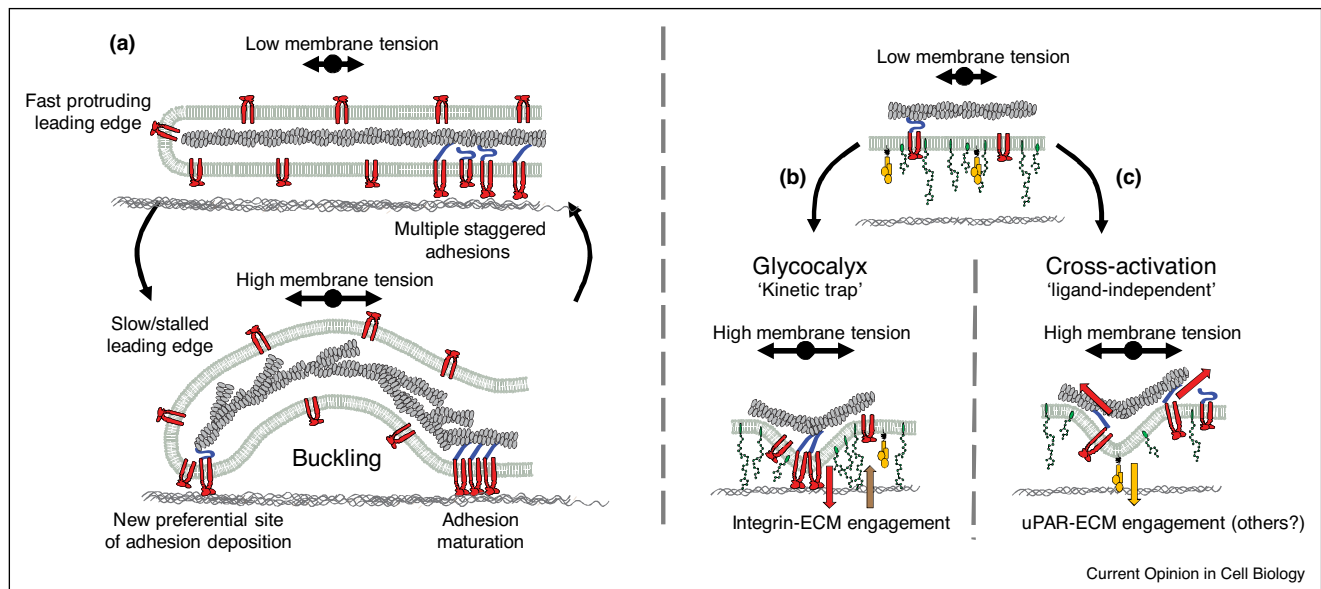
Integration of mechanosensing through membrane tension. **(a)** Membrane tension promotes adhesion positioning and lamellipodium buckling at the cell leading edge. The leading edge during cell migration constantly cycles between the two situations depicted, promoting the deposition of multiple adhesion rows. Those adhesion rows will later either disassemble or mature to focal adhesions upon myosin mediated contractility. **(b)** The length of the glycocalyx impairs integrin binding. However, at the few sites where integrins are bound, the counteracting forces between the glycocalyx (brown arrow) and integrins (red arrow) generate membrane deformation and a 'kinetic trap' favoring clustering and activation. **(c)** ECM binding of non-integrins ligands such as uPAR can increase membrane tension and potentially deform the membrane, inducing 'ligand-independent' integrin activation and triggering downstream signals.

mechanotransduction in integrin activation, as previously suggested [66].

Conclusion

At the molecular level, cell–matrix adhesion mechano-sensitivity is enabled by mechanisms which are reasonably clear, such as force regulation of binding dynamics and protein conformation. However, such mechanisms are coupled to each other, and to both cellular and extracellular parameters such as myosin contractility, ECM properties, and membrane tension. This leads to integrated mechanisms providing fine-tuned sensitivity to the cell physical environment. Even though some mechanisms are now understood, how mechanosensing is integrated across scales remains largely unexplored. Future work should resolve, for instance, how mechanosensing is regulated in complex, three-dimensional multi-cellular environments, or why adhesion mechanosensing fails to operate in certain conditions [70].

Acknowledgements

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Abercrombie M, Heaysman JE, Pegrum SM: **The locomotion of fibroblasts in culture. IV. Electron microscopy of the leading lamella**. *Exp Cell Res* 1971, **67**:359-367.

2. Charras G, Sahai E: **Physical influences of the extracellular environment on cell migration**. *Nat Rev Mol Cell Biol* 2014, **15**:813-824.

3. Winograd-Katz SE, Fassler R, Geiger B, Legate KR: **The integrin adhesome: from genes and proteins to human disease**. *Nat Rev Mol Cell Biol* 2014, **15**:273-288.

4. Pickup MW, Mouw JK, Weaver VM: **The extracellular matrix modulates the hallmarks of cancer**. *EMBO Rep* 2014, **15**:1243-1253.

5. Zaidel-Bar R, Itzkovitz S, Ma'ayan A, Iyengar R, Geiger B: **Functional atlas of the integrin adhesome**. *Nat Cell Biol* 2007, **9**:858-868.

6. Riveline D, Zamir E, Balaban NQ, Schwarz US, Ishizaki T, Narumiya S, Kam Z, Geiger B, Bershadsky AD: **Focal contacts as mechanosensors: externally applied local mechanical force induces growth of focal contacts by an mDia1-dependent and ROCK-independent mechanism**. *J Cell Biol* 2001, **153**:1175-1186.

7. Elosegui-Artola A, Oria R, Chen Y, Kosmalska A, Perez-Gonzalez C, Castro N, Zhu C, Trepat X, Roca-Cusachs P:
•• **Mechanical regulation of a molecular clutch defines force transmission and transduction in response to matrix rigidity**. *Nat Cell Biol* 2016, **18**:540-548.
This article shows that the different properties under force of integrin–fibronectin bonds (which operate as catch bonds) and talin unfolding (slip

bond) allow focal adhesions to sense matrix rigidity. The process can be understood by coupling talin and integrin dynamics to a computational clutch model.

8. Nakazawa N, Sathe AR, Shivashankar GV, Sheetz MP: **Matrix mechanics controls FHL2 movement to the nucleus to activate p21 expression**. *Proc Natl Acad Sci U S A* 2016, **113**:E6813-E6822.

9. Miralles F, Posern G, Zaromytidou AI, Treisman R: **Actin dynamics control SRF activity by regulation of its coactivator MAL**. *Cell* 2003, **113**:329-342.

10. Elosegui-Artola A, Andreu I, Beedle AEM, Lezamiz A, Uroz M,
•• Kosmalska AJ, Oria R, Kechagia JZ, Rico-Lastres P, Le Roux A-L *et al.*: **Force triggers YAP nuclear entry by regulating transport across nuclear pores**. *Cell* 2017, **171**:1397-1410.
This article shows that growth of focal adhesions and stress fibers trigger the nuclear entry of the transcriptional regulator YAP by transmitting force to the nucleus. Nuclear force then deforms nuclear pores and increases YAP import rates.

11. Sun Z, Guo SS, Fassler R: **Integrin-mediated mechanotransduction**. *J Cell Biol* 2016, **215**:445-456.

12. Hirata H, Sokabe M, Lim CT: **Molecular mechanisms underlying the force-dependent regulation of actin-to-ECM linkage at the focal adhesions**. *Prog Mol Biol Transl Sci* 2014, **126**:135-154.

13. Kong F, Garcia AJ, Mould AP, Humphries MJ, Zhu C: **Demonstration of catch bonds between an integrin and its ligand**. *J Cell Biol* 2009, **185**:1275-1284.

14. Chen Y, Lee H, Tong H, Schwartz M, Zhu C: **Force regulated conformational change of integrin αVβ3**. *Matrix Biol* 2016, **60–61**:70-85.

15. Huang DL, Bax NA, Buckley CD, Weis WI, Dunn AR: **Vinculin**
•• **forms a directionally asymmetric catch bond with F-actin**. *Science* 2017, **357**:703-706.
This article shows that the vinculin–actin bond responds to force as a catch bond, which is highly sensitive not only to the magnitude but also to the direction of force application.

16. Strohmeyer N, Bharadwaj M, Costell M, Fassler R, Muller DJ:
• **Fibronectin-bound alpha5beta1 integrins sense load and signal to reinforce adhesion in less than a second**. *Nat Mater* 2017, **16**:1262-1270.
This article employs an elegant force spectroscopy assay based on atomic force microscopy to show that force-induced signalling mediated by integrins is triggered within a second of force application.

17. Miroshnikova YA, Rozenberg GI, Cassereau L, Pickup M, Mouw JK, Ou G, Templeman KL, Hannachi EI, Gooch KJ, Sarang-Sieminski AL *et al.*: **alpha5beta1-Integrin promotes tension-dependent mammary epithelial cell invasion by engaging the fibronectin synergy site**. *Mol Biol Cell* 2017, **28**:2958-2977.

18. Chan CE, Odde DJ: **Traction dynamics of filopodia on compliant substrates**. *Science* 2008, **322**:1687-1691.

19. Sunyer R, Conte V, Escribano J, Elosegui-Artola A, Labernadie A, Valon L, Navajas D, Garcia-Aznar JM, Munoz JJ, Roca-Cusachs P *et al.*: **Collective cell durotaxis emerges from long-range intercellular force transmission**. *Science* 2016, **353**:1157-1161.

20. Bangasser BL, Shamsan GA, Chan CE, Opoku KN, Tuzel E, Schlichtmann BW, Kasim JA, Fuller BJ, McCullough BR, Rosenfeld SS *et al.*: **Shifting the optimal stiffness for cell migration**. *Nat Commun* 2017, **8**:15313.

21. Elosegui-Artola A, Bazellières E, Allen MD, Andreu I, Oria R, Sunyer R, Gomm JJ, Marshall JF, Jones JL, Trepat X *et al.*: **Rigidity sensing and adaptation through regulation of integrin types**. *Nat Mater* 2014, **13**:631-637.

22. Bharadwaj M, Strohmeyer N, Colo GP, Helenius J, Beerenwinkel N, Schiller HB, Fassler R, Muller DJ: **alphaV-class integrins exert dual roles on alpha5beta1 integrins to strengthen adhesion to fibronectin**. *Nat Commun* 2017, **8**:14348.

23. Bouaouina M, Lad Y, Calderwood DA: **The N-terminal domains of talin cooperate with the phosphotyrosine binding-like domain to activate beta 1 and beta 3 integrins**. *J Biol Chem* 2008, **283**:6118-6125.

24. Rantala JK, Pouwels J, Pellinen T, Veltel S, Laasola P, Mattila E, Potter CS, Duffy T, Sundberg JP, Kallioniemi O *et al.*: **SHARPIN is an endogenous inhibitor of beta1-integrin activation**. *Nat Cell Biol* 2011, **13**:1315-1324.

25. Lilja J, Zacharchenko T, Georgiadou M, Jacquemet G, De Franceschi N, Peuhu E, Hamidi H, Pouwels J, Martens V, Nia FH *et al.*: **SHANK proteins limit integrin activation by directly interacting with Rap1 and R-Ras**. *Nat Cell Biol* 2017, **19**:292-305.

26. Sun Z, Tseng HY, Tan S, Senger F, Kurzawa L, Dedden D,
•• Mizuno N, Wasik AA, Thery M, Dunn AR *et al.*: **Kank2 activates talin, reduces force transduction across integrins and induces central adhesion formation**. *Nat Cell Biol* 2016, **18**:941-953.
This article shows that kank2 interacts with talin to induce both integrin activation and reduced ability of integrin–fibronectin bonds to withstand forces. This strongly affects the binding/unbinding dynamics of integrins, modulating their mechanosensitivity.

27. Theodosiou M, Widmaier M, Bottcher RT, Rognoni E, Veelders M, Bharadwaj M, Lambacher A, Austen K, Muller DJ, Zent R *et al.*: **Kindlin-2 cooperates with talin to activate integrins and induces cell spreading by directly binding paxillin**. *Elife* 2016, **5**: e10130.

28. Bouin AP, Kyumurkov A, Regent-Kloeckner M, Ribba AS, Faurobert E, Fournier HN, Bourrin-Reynard I, Manet-Dupe S, Oddou C, Balland M *et al.*: **ICAP-1 monoubiquitylation coordinates matrix density and rigidity sensing for cell migration through ROCK2-MRCKalpha balance**. *J Cell Sci* 2017, **130**:626-636.

29. González-Tarragó V, Elosegui-Artola A, Bazellières E, Oria R, Pérez-González C, Roca-Cusachs P: **Binding of ZO-1 to α5β1 integrins regulates the mechanical properties of α5β1–fibronectin links**. *Mol Biol Cell* 2017, **28**:1847-1852.

30. Paszek MJ, DuFort CC, Rossier O, Bainer R, Mouw JK, Godula K, Hudak JE, Lakins JN, Wijekoon AC, Cassereau L *et al.*: **The cancer glycocalyx mechanically primes integrin-mediated growth and survival**. *Nature* 2014, **511**:319-325.

31. Austen K, Ringer P, Mehlich A, Chrostek-Grashoff A, Kluger C, Klingner C, Sabass B, Zent R, Rief M, Grashoff C: **Extracellular rigidity sensing by talin isoform-specific mechanical linkages**. *Nat Cell Biol* 2015, **17**:1597-1606.

32. Kumar A, Ouyang M, Van den Dries K, McGhee EJ, Tanaka K, Anderson MD, Groisman A, Goult BT, Anderson KI, Schwartz MA: **Talin tension sensor reveals novel features of focal adhesion force transmission and mechanosensitivity**. *J Cell Biol* 2016, **213**:371-383.

33. Yao M, Goult BT, Klapholz B, Hu X, Toseland CP, Guo Y, Cong P, Sheetz MP, Yan J: **The mechanical response of talin**. *Nat Commun* 2016, **7**.

34. Yao M, Goult BT, Chen H, Cong P, Sheetz MP, Yan J: **Mechanical activation of vinculin binding to talin locks talin in an unfolded conformation**. *Sci Rep* 2014, **4**:4610.

35. Dumbauld DW, Lee TT, Singh A, Scrimgeour J, Gersbach CA, Zamir EA, Fu J, Chen CS, Curtis JE, Craig SW *et al.*: **How vinculin regulates force transmission**. *Proc Natl Acad Sci U S A* 2013, **110**:9788-9793.

36. Ehrlicher AJ, Nakamura F, Hartwig JH, Weitz DA, Stossel TP: **Mechanical strain in actin networks regulates FilGAP and integrin binding to filamin A**. *Nature* 2011, **478**:260-263.

37. Sawada Y, Tamada M, Dubin-Thaler BJ, Cherniavskaya O, Sakai R, Tanaka S, Sheetz MP: **Force sensing by mechanical extension of the Src family kinase substrate p130Cas**. *Cell* 2006, **127**:1015-1026.

38. Zhou J, Aponte-Santamaria C, Sturm S, Bullerjahn JT, Bronowska A, Grater F: **Mechanism of focal adhesion kinase mechanosensing**. *PLoS Comput Biol* 2015, **11**:e1004593.

39. Saxena M, Changede R, Hone J, Wolfenson H, Sheetz MP: **Force-**
•• **induced calpain cleavage of talin is critical for growth, adhesion development, and rigidity sensing**. *Nano Lett* 2017, **17**:7242-7251.
This article shows that force does not only promote the unfolding of talin, but also the cleavage of its rod domain. This constitutes a novel

mechano-chemical switch mediated by talin which may be coupled to talin unfolding to enable differential mechanosensing.

40. Ortiz Franyuti D, Mitsi M, Vogel V: **Mechanical stretching of**
 • **fibronectin fibers upregulates binding of interleukin-7**. *Nano Lett* 2017, **18**:15-25.
This article shows that mechanical stretch increases the affinity of fibronectin for interleukin-7, providing an interesting example of how extracellular proteins can also operate as mechano-chemical switches.

41. Schwarz US, Gardel ML: **United we stand: integrating the actin cytoskeleton and cell–matrix adhesions in cellular mechanotransduction**. *J Cell Sci* 2012, **125**:3051-3060.

42. Oakes PW, Wagner E, Brand CA, Probst D, Linke M, Schwarz US,
 • Glotzer M, Gardel ML: **Optogenetic control of RhoA reveals zyxin-mediated elasticity of stress fibres**. *Nat Commun* 2017, **8**:15817.
This work shows zyxin binding changes the behavior of stress fibers from fluid-like to elastic, affecting force transmission through them and thereby regulating mechanosensing events.

43. Swaminathan V, Kalappurakkal JM, Mehta SB, Nordenfelt P,
 • Moore TI, Koga N, Baker DA, Oldenbourg R, Tani T, Mayor S *et al.*: **Actin retrograde flow actively aligns and orients ligand-engaged integrins in focal adhesions**. *Proc Natl Acad Sci U S A* 2017, **114**:10648-10653.
In this article, the authors develop a sensor of molecular orientation to show that force is able to sculpt both the alignment and orientation of integrins within focal adhesions, potentially enabling cells to sense directional cues.

44. Gupta M, Sarangi BR, Deschamps J, Nematbakhsh Y, Callan-Jones A, Margadant F, Mege RM, Lim CT, Voituriez R, Ladoux B: **Adaptive rheology and ordering of cell cytoskeleton govern matrix rigidity sensing**. *Nat Commun* 2015, **6**:7525.

45. Schwarz US, Erdmann T, Bischofs IB: **Focal adhesions as mechanosensors: the two-spring model**. *Biosystems* 2006, **83**:225-232.

46. Plotnikov SV, Pasapera AM, Sabass B, Waterman CM: **Force fluctuations within focal adhesions mediate ECM-rigidity sensing to guide directed cell migration**. *Cell* 2012, **151**:1513-1527.

47. Wu Z, Plotnikov SV, Moalim AY, Waterman CM, Liu J: **Two distinct actin networks mediate traction oscillations to confer focal adhesion mechanosensing**. *Biophys J* 2017, **112**:780-794.

48. Meacci G, Wolfenson H, Liu S, Stachowiak MR, Iskratsch T, Mathur A, Ghassemi S, Gauthier N, Tabdanov E, Lohner J *et al.*: **alpha-Actinin links ECM rigidity sensing contractile units with periodic cell edge retractions**. *Mol Biol Cell* 2016, **27**:3471-3479.

49. Wolfenson H, Meacci G, Liu S, Stachowiak MR, Iskratsch T, Ghassemi S, Roca-Cusachs P, O'Shaughnessy B, Hone J, Sheetz MP: **Tropomyosin controls sarcomere-like contractions for rigidity sensing and suppressing growth on soft matrices**. *Nat Cell Biol* 2016, **18**:33-42.

50. Yang B, Lieu ZZ, Wolfenson H, Hameed FM, Bershadsky AD, Sheetz MP: **Mechanosensing controlled directly by tyrosine kinases**. *Nano Lett* 2016, **16**:5951-5961.

51. Oria R, Wiegand T, Escribano J, Elosegui-Artola A, Uriarte JJ,
 •• Moreno-Pulido C, Platzman I, Delcanale P, Albertazzi L, Navajas D *et al.*: **Force loading explains spatial sensing of ligands by cells**. *Nature* 2017, **552**:219-224.
This article shows that the density and spatial organization of matrix ligands determines cell response by affecting how cell contractility is distributed among bound integrins. Thus, cells employ mechanosensing to respond not only to mechanical but also to spatial cues.

52. Ju L, Chen Y, Xue L, Du X, Zhu C: **Cooperative unfolding of**
 • **distinctive mechanoreceptor domains transduces force into signals**. *Elife* 2016, **5**.
The platelet receptor glycoprotein Ib contains two force-sensitive domains that unfold under force. This work shows that their activation results in different effects that interact with each other, providing a potential differential mechanosensor.

53. Pontes B, Monzo P, Gauthier NC: **Membrane tension: a challenging but universal physical parameter in cell biology**. *Semin Cell Dev Biol* 2017, **71**:30-41.

54. Diz-Munoz A, Thurley K, Chintamen S, Altschuler SJ, Wu LF, Fletcher DA, Weiner OD: **Membrane tension acts through PLD2 and mTORC2 to limit actin network assembly during neutrophil migration**. *PLoS Biol* 2016, **14**:e1002474.

55. Gauthier NC, Fardin MA, Roca-Cusachs P, Sheetz MP: **Temporary increase in plasma membrane tension coordinates the activation of exocytosis and contraction during cell spreading**. *Proc Natl Acad Sci U S A* 2011, **108**:14467-14472.

56. Gerard A, Patino-Lopez G, Beemiller P, Nambiar R, Ben-Aissa K, Liu Y, Totah FJ, Tyska MJ, Shaw S, Krummel MF: **Detection of rare antigen-presenting cells through T cell-intrinsic meandering motility, mediated by Myo1g**. *Cell* 2014, **158**:492-505.

57. Houk AR, Jilkine A, Mejean CO, Boltyanskiy R, Dufresne ER, Angenent SB, Altschuler SJ, Wu LF, Weiner OD: **Membrane tension maintains cell polarity by confining signals to the leading edge during neutrophil migration**. *Cell* 2012, **148**:175-188.

58. Lieber AD, Yehudai-Resheff S, Barnhart EL, Theriot JA, Keren K: **Membrane tension in rapidly moving cells is determined by cytoskeletal forces**. *Curr Biol* 2013, **23**:1409-1417.

59. Masters TA, Pontes B, Viasnoff V, Li Y, Gauthier NC: **Plasma membrane tension orchestrates membrane trafficking, cytoskeletal remodeling, and biochemical signaling during phagocytosis**. *Proc Natl Acad Sci U S A* 2013, **110**:11875-11880.

60. Pontes B, Monzo P, Gole L, Le Roux AL, Kosmalska AJ, Tam ZY,
 •• Luo WW, Kan S, Viasnoff V, Roca-Cusachs P *et al.*: **Membrane tension controls adhesion positioning at the leading edge of cells**. *J Cell Biol* 2017, **216**:2959-2977.
This article shows that membrane tension exerts an upstream control to mechanotransduction by resisting edge advancement. This generates a force that gets transmitted through actin to adhesions, inducing both deposition at the lamellipodial font and maturation at the back.

61. Keren K: **Cell motility: the integrating role of the plasma membrane**. *Eur Biophys J* 2011, **40**:1013-1027.

62. Shemesh T, Bershadsky AD, Kozlov MM: **Physical model for self-organization of actin cytoskeleton and adhesion complexes at the cell front**. *Biophys J* 2012, **102**:1746-1756.

63. Raucher D, Sheetz MP: **Cell spreading and lamellipodial extension rate is regulated by membrane tension**. *J Cell Biol* 2000, **148**:127-136.

64. Mueller J, Szep G, Nemethova M, de Vries I, Lieber AD, Winkler C,
 • Kruse K, Small JV, Schmeiser C, Keren K *et al.*: **Load adaptation of lamellipodial actin networks**. *Cell* 2017, **171** 188–200.e116.
This article elegantly demonstrates the direct effect of membrane tension fluctuations on dynamic actin organisation, through events such as polymerization or branching, at the cell leading edge.

65. Paszek MJ, Boettiger D, Weaver VM, Hammer DA: **Integrin clustering is driven by mechanical resistance from the glycocalyx and the substrate**. *PLoS Comput Biol* 2009, **5**: e1000604.

66. Wang X, Ha T: **Defining single molecular forces required to activate integrin and notch signaling**. *Science* 2013, **340**:991-994.

67. Ferraris GM, Schulte C, Buttiglione V, De Lorenzi V, Piontini A, Galluzzi M, Podesta A, Madsen CD, Sidenius N: **The interaction between uPAR and vitronectin triggers ligand-independent adhesion signalling by integrins**. *EMBO J* 2014, **33**:2458-2472.

68. Schulte C, Ferraris GM, Oldani A, Galluzzi M, Podesta A, Puricelli L,
 • de Lorenzi V, Lenardi C, Milani P, Sidenius N: **Lamellipodial tension, not integrin/ligand binding, is the crucial factor to realise integrin activation and cell migration**. *Eur J Cell Biol* 2016, **95**:1-14.
This article is a nice addition to previous work of the same group. It shows the ligand-independent activation of integrins caused by tension in lamellipodia, with a clear link to membrane tension.

69. Gabella C, Bertseva E, Bottier C, Piacentini N, Bornert A, Jeney S, Forro L, Sbalzarini IF, Meister JJ, Verkhovsky AB: **Contact angle at the leading edge controls cell protrusion rate**. *Curr Biol* 2014, **24**:1126-1132.

70. Oakes PW, Gardel ML: **Stressing the limits of focal adhesion mechanosensitivity**. *Curr Opin Cell Biol* 2014, **30**:68-73.