Evidence of a large-scale mechanosensing mechanism for cellular adaptation to substrate stiffness

Léa Trichet1, Jimmy Le Digabel1, Rhoda J. Hawkins3,4, Sri Ram Krishna Vedula4, Mukund Gupta4, Claire Ribault4, Pascal Hersen1,6, Raphaël Voituriez5, and Benoît Ladoux1,6,2

1Laboratoire Matière et Systèmes Complexes, Centre National de la Recherche Scientifique Unité Mixte de Recherche, 7057, Université Paris Diderot, 75205 Paris Cedex 13, France; 2Centre National de la Recherche Scientifique Unité Mixte de Recherche, 7600, Université Pierre et Marie Curie, 75252 Paris Cedex 05, France; 3Department of Physics and Astronomy, University of Sheffield, Sheffield S3 7RH, United Kingdom; and 4Mechanobiology Institute, National University of Singapore, Singapore 117411

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Cell migration plays a major role in many fundamental biological processes, such as morphogenesis, tumor metastasis, and wound healing. As they anchor and pull on their surroundings, adhering cells actively probe the stiffness of their environment. Current understanding is that traction forces exerted by cells arise mainly at mechanotransduction sites, called focal adhesions, whose size seems to be correlated to the force exerted by cells on their underlying substrate, at least during their initial stages. In fact, our data show by direct measurements that the buildup of traction forces is faster for larger substrate stiffness, and that the stress measured at adhesion sites depends on substrate rigidity. Our results, backed by a phenomenological model based on active gel theory, suggest that rigidity-sensing is mediated by a large-scale mechanism originating in the cytoskeleton instead of a local one. We show that large-scale mechanosensing leads to an adaptive response of cell migration to stiffness gradients. In response to a step boundary in rigidity, we observe not only that cells migrate preferentially toward stiffer substrates, but also that this response is optimal in a narrow range of rigidities. Taken together, these findings lead to unique insights into the regulation of cell response to external mechanical cues and provide evidence for a cytoskeleton-based rigidity-sensing mechanism.

Cell migration is not only sensitive to the biochemical composition of the environment, but also to its mechanical properties. Cells directly probe the physical properties of their environment, such as substrate stiffness, by pulling on it. Increasing evidence show that matrix or tissue elasticity has a key role in regulating numerous cell functions, such as adhesion (1), migration (2) and differentiation (3). Such functions are affected by cell-generated actomyosin forces that depend on substrate stiffness through a feedback mechanism (4). The sensitivity of cells to mechanical properties of the extracellular matrix (ECM) arises from the mechanosensitive nature of cell adhesion. Numerous plausible candidates for the transduction of mechanochanical signals have been tested (5). Among them, focal adhesions (FAs) appear to be the most prominent, as shown by the reported correlation between their area and sustained force exhibiting a constant stress (6–9). This mechanosensitivity was usually accounted for by a generic local mechanism in which a force applied to an FA induces an elastic deformation of the contact that triggers conformational and organizational changes of some of its constitutive proteins, which in turn can enhance binding with new proteins enabling growth of the contact (10–12). However, how this local mechanosensitivity can result in the ability of cells to sense and respond to the rigidity of their surroundings (2, 3, 13, 14) at a large scale remains largely unknown (5, 15). Much conflicting evidence has emerged from a variety of studies, leading to important questions. Not only FAs but also the opening of calcium ion channels (2, 16, 17) could participate in the build-up of cell tension in response to mechanical cues. Moreover, recent modeling (18) as well as indirect observations (19, 20) suggest that the contractile actomyosin apparatus can act as a global rigidity sensor (21). From a physical point of view, the deformation of the surrounding matrix in response to cell contractility is poorly understood; plausible mechanisms of cell mechanosensitivity imply that the regulation could be either mediated by the stress exerted by cells, or by the strain in the ECM (7, 22–24). These intriguing questions are currently intensively debated, because the detailed mechanisms of force transduction in response to ECM might explain the observed discrepancies in adhesion (1, 25), migration (2, 26), and differentiation (3, 27) of cells in environments of different rigidities and over different time scales.

Results and Discussion

Dynamics of Focal Adhesions and Traction Force Measurements on Substrates of Various Stiffnesses. Here we report real-time measurements of explicit correlations between traction forces and the formation of FAs as a function of substrate stiffness. We used microforce sensor arrays (μFSA) (28) together with epifluorescence microscopy of REFS2 fibroblast cells expressing a fluorescently tagged FA protein (YFP-paxillin) (Fig. 1 A and B). We seeded REFS2 cells stably expressing YFP-paxillin on pillars of various diameters and heights coated with fibronectin (13, 29, 30). These different-shaped pillars result in substrates with various spring constants, k, from 3 to 80 nN/μm (Fig.1 C, Movie S1) without altering the molecular scale properties of its surface. After allowing cells to adhere on the substrate for at least approximately 5 h, cells developed traction forces oriented toward their center that caused a deflection of the micropillars (Fig. 1B). We simultaneously analyzed the dynamics of the traction forces and FA patches over time. As a control experiment, we compared the size distributions of FAs on μFSA of different rigidities to those on a flat polydimethylsiloxane (PDMS) surface (Fig. S1). As expected from previous studies (23, 25, 31), these distributions were skewed toward larger values for substrates of increased stiffness. The topography of 2-μm pillar substrates did not significantly affect the size of FAs, as shown by the similar size distributions of FAs on μFAS and flat PDMS substrates (Fig. S1).

We analyzed traction forces in the proximity of the cell edge where the highest forces as well as the largest FAs were observed. In most cases, force generation and FA assembly over time were


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1L.T. and J.L.D. contributed equally to this work.
2To whom correspondence should be addressed. E-mail: benoit.ladoux@univ-paris-diderot.fr.
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tightly correlated (Fig. 1 D and E): An increase of both forces and FA sizes followed by a saturation phase occurred within a timescale of minutes (see an example on a substrate of 34 nN/μm, Fig. 1E). To characterize the dependence of such dynamics on substrate stiffness, we performed the measurements over a broad range of rigidities (from around 4 to 80 nN/μm). For each time point, we averaged the force, F, over different FAs present at the cell edge of different cells (n ≥ 5). Average forces, \( \langle F_k \rangle \), exerted at paxillin sites, grew more rapidly and reached higher saturation values on substrates with higher rigidities (Fig. 2A). In contrast to the force, the dependency of FA growth (area) was less obvious although the saturation size depended on the stiffness of the pillars (Fig. 2B).

In addition, the saturation force \( F_s \) was found to be proportional to the stiffness of the substrate within our range of rigidities (Fig. 2C). This result implied that saturation forces correspond to a constant deformation of the substrate of around 0.84 ± 0.03 μm, in agreement with previous studies on other cell types (13, 23). Interestingly, the initial rate of force increase over time, \( dF/dt \), also varied linearly with substrate rigidity, giving a speed of micropillar displacement equal to 1.3 nm/s independent of the stiffness. All together, these data suggest the existence of a mechanosensitivity mechanism that is regulated by substrate deformation.

**Relationship Between Focal Adhesion Area, Force, and Stress.** To further assess the nature of force transmission, we investigated the relationship between force and focal adhesion area as a function of substrate stiffness. The relationship between force and area for all focal adhesions at all time points is plotted in Fig. 3A for substrate rigidities from 4 to 80 nN/μm (each point represents an average over at least 15 FAs of approximately equal area). This range of stiffnesses corresponds to an equivalent Young’s modulus, \( E_{eff} \), of the micropillar substrate varying from 2.8 up to 60 kPa (13). We clearly obtained a linear dependence between traction force and FA area at a given rigidity. This dependence, however, is not the same for each stiffness; surprisingly, it appears that different force values could be reached for the same FA area. For instance, an FA area of approximately 2 μm² leads to forces that vary from 3 up to 42 nN within a stiffness range from 4.7 up to 80 nN/μm (Fig. 3A). The fact that FAs of similar areas can sustain different forces, illustrated in Fig. 3A, is compatible with the results of ref. 24 where a variability of the stress between FAs at different positions was found, but only for a given substrate rigidity. These results overall contrast with the commonly accepted understanding of FA mechanosensitivity by a local force-dependent mechanism, which usually assumes a constant stress (6–8). Interestingly, the extrapolation of this linear dependence to zero gave rise to nonzero forces. This

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**Fig. 1.** Cell adhesion and traction forces developed by REFS2 fibroblasts expressing YFP-paxillin on micropillar substrates. (A) Scanning electron micrograph image of a typical REFS2 cell on a micropillar substrate. (Scale bar, 15 μm.) (B) Epifluorescent image of a single cell deforming the micropillar substrate (here of spring constant \( k = 34 \text{ nN} / \mu \text{m} \)). Micropillars are labeled by Cy3-fibronectin (red), and YFP-paxillin-rich patches are in green. (Scale bar, 15 μm.) (C) Sequential images of the insert area of B showing the dynamics of FA growth and micropillar displacements. (Scale bar, 10 μm.) (D) Schematic representation of the experimental setup showing the formation of FAs on the top of a PDMS micropillar. (E) Typical example of the formation of an FA area (red) and the buildup of force (blue) as a function of time (on a substrate of 34 nN/μm).

**Fig. 2.** Traction forces and focal adhesion dynamics. (A) Average traction forces as a function of time for different substrate stiffnesses. Data were pooled from \( n \geq 5 \) different cells and \( n \geq 15 \) different pillars. Each curve exhibits an initial regime of fast force increase followed by a saturation regime. (B) Average focal adhesion area for different stiffnesses as a function of time. (C) Saturation force as a function of substrate stiffness. A linear relationship was observed between the maximal force and the substrate stiffness up to 80 nN/μm, showing that cells maintained a constant deformation. The fit corresponds to the theoretical model based on the active stress exerted by cytoskeleton remodeling (see SI Text). (D) Rate of increase of force with time, \( dF/dt \), as a function of stiffness; \( dF/dt \) was obtained by fitting the slope of the initial linear regime of the force curve as a function of time (A). The rate of force with time, \( dF/dt \), was proportional to the stiffness in the range of stiffnesses used in our study (up to 80 nN/μm).
contact at the molecular scale that triggers conformational and organizational changes (such as unfolding) of some of its constitutive proteins, which in turn can enhance binding of new proteins enabling growth of the contact (11). Such a mechanism should therefore depend on the local stiffness of the adhesive substrate at the submicrometer scale (33) which corresponds to the surface of the top of the micropillar in our case, characterized by the elasticity of the PDMS, i.e., its Young’s modulus, \( E_y \) (SI Text for more details on our phenomenological model).

Consequently, if the mechanical feedback was mediated by the FA itself, then the stress applied by FAs would depend on \( E_y \) only and not on \( k \), which can be varied independently of \( E_y \) in our set-up through the geometrical parameters of the pillars (SI Text). However, we show here that the stress, \( \sigma \), depends on the spring constant of the pillars \( k \) (for the same \( E_y \)). Such a dependency provides direct evidence that an extra feedback involving structures other than FAs must be involved. We suggest that this feedback could be mediated on a larger scale by the cytoskeleton, and in particular by the stress fibers pulling on FAs. We argue that a deformation of the cytoskeleton, such as a shortening, \( x \), of the length of a stress fiber, has an impact on the active stress exerted by the cytoskeleton. Generally, this mechanical activation can be justified within the framework of the theory of viscoelastic active gels (35, 36). This phenomenological theory states that in nematic (or polar) media driven out of equilibrium such as the cytoskeleton, there exists an active stress \( \sigma^{act}_{ij} \) (here due to actin/myosin contractility) proportional to the nematic order parameter tensor \( Q_{ij} = (n_i n_j - \delta_{ij})/3 \) where the vector \( n \) denotes the local orientation of actin filaments. The coupling of \( Q_{ij} \) to the strain \( U_{ij} \), which is standard in nematic gels (37), then implies that the stress \( \sigma^{act}_{ij} \) depends on \( U_{ij} \) and therefore on the deformation \( x \). In other words, a deformation \( x \) induces a strain \( U_{ij} \) in the cytoskeleton and therefore a reorganization of the orientation \( Q_{ij} \) of the filaments, which in turn yields an active stress.

For this coupling of \( Q_{ij} \) to the strain \( U_{ij} \) to be valid, the relaxation time of \( Q_{ij} \) has to be long, implying an elastic like rheology of the cytoskeleton. In fact, the rheology of the cytoskeleton is very complex and fluidization has been observed, but only in response to a transient stretch (38, 39). Our case is more like that of a sustained constraint, in which strain stiffening and long relaxation times have been reported (40–42), justifying our assumption.

**Actin Organization Depends on Substrate Stiffness.** To evaluate \( Q_{ij} \) for substrates of various stiffnesses, we performed experiments to image actin stress fibers on fixed cells spread on soft and stiff \( \mu \)FSAs. The polarization of the cell was then quantified by the scalar order parameter \( S \) defined by \( S = Q_{ijkl} n_i n_j n_k n_l \), where \( n_i \) is the average direction of stress fibers. We found that in a soft case (\( \approx 4 \) nN/\( \mu \)m), the stress fibers were fully disoriented, leading to \( S \approx 0.19 \pm 0.13 \), whereas they appeared fully polarized in a stiff case (\( \approx 100 \) nN/\( \mu \)m) leading to \( S \approx 0.80 \pm 0.09 \) (SI Text). At intermediate stiffness (\( \approx 40 \) nN/\( \mu \)m), we obtained \( S \approx 0.56 \pm 0.21 \). This result shows a relationship between force generation by cells and actin stress fiber alignment, yielding a semi-quantitative support of the coupling between \( Q_{ij} \) and \( U_{ij} \) (Fig. 4). This active stress is a deformation-dependent (and therefore stiffness-dependent) contribution, enhancing the stress exerted by the FA. The existence of such coupling shows that actomyosin forces are sufficient to explain the cellular response to matrix rigidity according to a stress-dependent relationship to substrate stiffness, as recently shown for the response of stem cells to matrix stiffness (43). By assuming a linear coupling between \( Q_{ij} \) and \( U_{ij} \), the model could be made explicit for the case of a single stress fiber, for which the stress, \( \sigma^{act}_{ij} \), at each extremity was given by the deformation of the corresponding pillar and the adhesion area, \( S_{FA} \). Based on this assumption, we made explicit the dependence of the stress, therefore the force, on the pillar rigidity and showed that this theoretical prediction, compatible with ref. 43 (SI Text), was in good agreement with our experimental data.

**Modeling of a Large-Scale Mechanosensing Process.** The mechanism usually invoked to account for a local mechanosensitivity is that a force applied to an FA induces an elastic deformation of the contact at the molecular scale that triggers conformational and...
explain the linear relationship that we obtained between the sa-
regulation by the contractility of actin-myosin fibers could also
45), can sustain contractions of 10
-0 nN/μm) (C). The scalar order parameter, S, is given here
by $S = \cos(2(\theta - \theta_0))$, where $\theta$ denotes the angle of a stress fiber with a refer-
ence axis and $\theta_0$ its average. Cells on stiffer substrate exhibit a more pro-
nounced polarization of the actin stress fibers leading to an increase of $S$
with the rigidity: $S = 0.1$, 0.47, and 0.95, respectively. (Scale bar, 15 μm.)
(D) Average order parameter for cells plated on substrates of three different
stiffnesses as a function of the pillar spring constant and the effective rigidity,
$E_{\text{eff}}$, of the substrate. Data were pooled from $n \geq 15$ cells.

(Fig. 2C, Fig. 3B). Additionally, this large-scale mechanosensitive
regulation by the contractility of actin-myosin fibers could also
explain the linear relationship that we obtained between the sa-
ture force and stiffness (Fig. 2C): The constant deformation of
around 840 nm could be attributed to the simultaneous short-
ening of several micron-sized sarcomeric substructures within
actomyosin stress fibers that, according to previous studies (44,
45), can sustain contractions of 10–25%.

Substrate Stiffness Governs the Directionality of Cell Movements.
Such a large-scale mechanism driven by cell cytoskeleton polarization
could also provide a plausible explanation for cell durotaxis.
The combination of our observations—a faster force increase and
higher saturated force values on stiffer substrates and an increasing
stress with respect to substrate stiffness—led us naturally to the
following prediction: polarized cells coming from a softer substrate
will suddenly exert large traction forces as they touch the stiff side,
and thus rotate to migrate perpendicularly to the stiff substrate.
On the other hand, cells coming from the stiff side will stay along
the boundary. These predictions guided the design of a durotaxis
assay (2): Areas of different stiffnesses on which cells can freely
move from soft to stiff and vice versa were created within the same
micropillar substrate. Such substrates were composed of consecu-
tive arrays of micropillars of diameters 1 and 2 μm (creating soft, $k_1$, and stiff, $k_2$, substrates, respectively) inducing a stiffness ratio of
around ten between both sides ($K_2/k_1 \approx 10$) while the surface
density of the micropillars was kept constant (Fig. 5A). Cells com-
ing from the soft part or from the stiff part were considered inde-
pendently. As shown in Fig. 5D and in Movie S2 for $k_2 = 3$ nN/μm
and $K_2 = 34$ nN/μm, cells indeed move toward the stiffness of
the substrate aligning perpendicularly to the boundary.

We then used this assay to analyze the migration paths of
individual cells on micropillar substrates of different stiffnesses.
Our durotaxis analysis was performed by counting the preferen-
tial orientation of the cells after they touched the border between
the two different parts of the substrate. We measured the number of
events that corresponded to cells coming from the soft sub-
straates and arriving at the boundary (40 < $n_{\text{cells}}$ < 80, where
$n_{\text{cells}}$ is the total number of cells analyzed). By changing the
rigidity of the soft micropillars from 3–134 nN/μm, we obtained
an optimal durotaxis efficiency for stiffness values around
3–10 nN/μm with around 70% of cells moving toward the stiffer
side (Fig. 5B). For $k \gg 10$ nN/μm, no preferential direction was
observed (only 35–50% of cells migrate toward the stiffer sub-
strate). On the contrary, most of the cells located on the stiffer
side did not migrate toward the soft one within the tested range of
stiffnesses represented by the rigidity of the stiff pillars (His-
togram, Fig. 5C; Movie S3). In addition, as a control experiment
to test whether cells were actually reacting to the substrate rigidity
and not the adhesion geometry, we fabricated adhesive surfaces
with the same geometry on glass coverslips coated with fluores-
cently labeled fibronectin (SI Text, Fig. S2). To limit cell adhesion
to the transferred pattern, the substrates were then treated with
polyethylene glycol to passivate the rest of the surface (26), ren-
dering it nonstick. In these conditions, we obtained an array of
fibronectin patches printed on glass with the same adhesive
surface and sizes as the tops of the pillars. On such surfaces
presenting the same geometry but no rigidity dependency, we
observed that geometry could not explain our previous results on
pillar substrates. Indeed, only 37% of the cells migrated from the
area of 1 μm patches to the area of 2 μm ones and 53% in the
opposite direction when first placed on the 2 μm patches area.

When both sides of the substrate presented a stiffness larger
than around 50 nN/μm, we observed that the migration of cells
toward the stiffer part was reduced, as if cells could not sense any
difference between sides (Fig. 5B). In other words, an optimal
response to a step difference in matrix stiffness appeared within
a narrow range of rigidities. These results could be related to the
ability of cells to adapt their own stiffness to that of the substrate
(27, 43, 46). Moreover, the range of stiffness that promoted
migration toward the stiffer side was correlated to that of the
initial regime of the stress-stiffness relationship (that of fast stress
increase before reaching saturation, see Fig. 3B). By analyzing
crossing events with the deformation of micropillars at the
boundary between soft and stiff substrates (Fig. 5), we showed
that as a cell coming from the soft part was probing the interface,
the force quickly increased up to 50 nN (Fig. 5F) and peaked in
the direction $n$ normal to the border, leading to the migration of
the cell body toward the stiffest region (Fig. 5E, Movie S4). In
agreement with our previous observations, this behavior can be
attributed to cell polarization along this axis, which in turn
favored the migration from soft to stiff.

It appears that migration toward the stiffer part was enhanced
when the step in stiffness corresponded to a large increase in
stress between both sides of the substrate. According to Fig. 3B,
the range of rigidities between 1 and 50 nN/μm corresponds to
the regime of the highest cell sensitivity to substrate rigidity.
However, if both sides of the substrate corresponded to similar
values of stress exerted by the adherent cell, cells did not migrate
from one side to the other, no matter what the rigidity step
between them. Consequently, the stress-stiffness relationship
that we established appeared as an interesting indicator for the
durotactic behavior. As cells sense the stiff side, they exert larger
forces which in turn could induce a polarization of the actin
cytoskeleton toward the stiff side and thus promote durotaxis.
Interestingly, qualitatively similar behavior has been observed
for the durotaxis of vascular cells on defined stiffness gradients
within a range of rigidities up to 80 kPa (47). The study observed
a higher polarized behavior on gradient gels than on uniform
substrates and a durotactic behavior enhanced by increasing the
magnitude of gradients. However, they did detect an upper limit of
stiffness that a cell is capable of sensing. Here we show that
such a limit could be determined by the relative variations of the
stress that the cell could exert on both sides.
mechanism we have presented here could be relevant to understanding the matrix stiffness dependence of stem cell differentiation (3, 43) and also tumor formation in vivo (49) in terms of actin reorganization and cell contractility.

Materials and Methods

Cell Culture. REFS2 cells were maintained at 37 °C in a humidified atmosphere of 5% CO₂ and 95% air in DMEM containing 10% bovine calf serum, 100 U/mL penicillin, 100 μg/mL streptomycin, and 100 μg/mL glutamine. The cells were deposited on μSA 3 to 6 h before microscopy experiments (SI Text for details).

Preparation and Calibration of Microstructured PDMS Substrates. PDMS micro-pillar arrays were prepared and calibrated according to du Roure et al. (28). The SI Text provides additional details on the experimental methods.

Image Analysis. To calculate the order parameter, the images were analyzed using ImageJ software. First the images were convolved and thresholded.

Fig. 5. Durotaxis revisited with micropillar substrates. (A) Scanning electron micrograph of a cell spread between two micropillar surfaces exhibiting different stiffnesses. The diameter of the pillars vary between 1 μm (top region) and 2 μm (bottom region), but the surface density of the micropillar substrate (fraction of surface are covered by pillars) has been kept constant. (Scale bar, 10 μm.) (B) Statistics of cells migrating from the soft substrate toward the stiff one as a function of the spring constant of the soft pillars. The spring constant, \( k_s \), of the pillar was varied between 3 and 134 nN/μm. A high percentage of migration events toward the stiff substrate was observed for values between 3 and 11 nN/μm, in correlation with the range of stiffnesses where a high increase of the stress is observed. For larger values of \( k_s \), no preferential direction was observed. In red, percentage of cells that come from the soft part and cross the boundary. In blue, percentage of cells that do not migrate. In gray, cells with undefined movement. (C) Statistics of cells migrating from the stiff part of the substrate as a function of the spring constant of the stiff pillars. Cells prefer to stay on the stiffer substrate over a wide-range of rigidity. In red, percentage of cells that come from the stiff part and prefer to stay on it instead of crossing the boundary. In blue, percentage of cells that migrate toward the soft substrate. In gray, cells with undefined movement. (D) Brightfield images of the movement of REFS2 cell at the border between stiff (\( k_s = 34 \) nN/μm) and soft (\( k_s = 3 \) nN/μm) substrates. The dashed line represents the cell boundary. Time = 0 is here taken arbitrarily. (Scale bar, 20 μm.) (E) Force distribution during a typical crossing event of an REFS2 cell from soft to stiff substrate. Micropillars are labeled by Cy3-fibronectin (red) and the cell appears in green. (Scale bar, 5 μm.) Cell spread at the boundary between soft and stiff substrates (1-μm pillars versus 2-μm pillars) exhibits a roughly homogeneous distribution of the forces on the soft part (\( k_s = 3 \) nN/μm and \( K_s = 34 \) nN/μm). As the cell is probing a stiff pillar, a large deformation (i.e., high force) is peaked in the direction normal to the border inducing a polarized shape of the cell in this direction. (F) Variation of the force on the stiff pillar (designated by an asterisk in E, i) as a function of time.
Then we used the Analyze Particle tool to detect the actin filaments. Each filament was fitted with an ellipse. We then calculated the medium orientation of the filaments and the order parameter along this angle $S = \langle \cos(2(\phi - \theta)) \rangle$, where the average weighting was given by the length of the filaments. (SI Text).

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