Single and collective cell migration: the mechanics of adhesions

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ABSTRACT **Chemical and physical properties of the environment control cell proliferation, differentiation, or apoptosis in the long term. However, to be able to move and migrate through a complex three-dimensional environment, cells must quickly adapt in the short term to the physical properties of their surroundings. Interactions with the extracellular matrix (ECM) occur through focal adhesions or hemidesmosomes via the engagement of integrins with fibrillar ECM proteins. Cells also interact with their neighbors, and this involves various types of intercellular adhesive structures such as tight junctions, cadherin-based adherens junctions, and desmosomes. Mechanobiology studies have shown that cell–ECM and cell–cell adhesions participate in mechanosensing to transduce mechanical cues into biochemical signals and conversely are responsible for the transmission of intracellular forces to the extracellular environment. As they migrate, cells use these adhesive structures to probe their surroundings, adapt their mechanical properties, and exert the appropriate forces required for their movements. The focus of this review is to give an overview of recent developments showing the bidirectional relationship between the physical properties of the environment and the cell mechanical responses during single and collective cell migration.**

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INTRODUCTION

Cells, tissues, and organs must constantly adapt to their surroundings. A cell's interaction with its environment is crucial for physiological tissue organization and functions during development, as well as for homeostasis, regeneration, and aging. It is also involved in pathological conditions–for instance, during tumor progression or fibrosis. The cell microenvironment is composed of the extracellular matrix (ECM) neighboring cells and surrounding intercellular medium. The microenvironment varies in composition and organization, depending on the tissue or in vitro culture conditions. At the cellular level, when a cell touches a permissive surface, be it a substrate or another cell, it will form adhesive structures that allow it to sense and respond to the properties of its surrounding. Cells can sense two major types of information: chemical signals, such as small molecules and soluble factors, which are read through specific receptors, and physical properties, including substrate stiffness, topology, porosity, and elastic behavior, as well as compressive and traction forces (Figure 1). We focus here on the recent evidence pointing to substrate rigidity as a critical parameter controlling cell mechanical responses. However, it is important to keep in mind that other physical properties of the microenvironment are as likely to affect cell behavior. Each tissue has its own stiffness, which affects cell differentiation or behavior (Swift *et al.*, 2013; Swift and Discher, 2014; Ivanovska *et al.*, 2015). For example, axon elongation in *Xenopus* depends on a stiffness gradient that affects persistent growth and fasciculation of the retinal ganglion axon in the developing brain (Koser *et al.*, 2016). Variations in tissue stiffness control cell proliferation or cell fate specification (Tse and Engler, 2011; Aleksandrova *et al.*, 2015). Cardiac myocytes need a specific stiffness to become actively beating cells, and muscle cells need muscle-like stiffness to form myotubes; excessive stiffness will impede correct myofibril development and may lead to sclerosis and scars (Engler *et al.*, 2004, 2008). In the case of mesenchymal stem cells, a stiffer environment induces bone-like development, whereas a soft

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Abbreviations used: CAF, cancer-associated fibroblast; ECM, extracellular matrix; FAK, focal adhesion kinase; FRET, fluorescence resonance energy transfer; MDCK, Madin–Darby canine kidney; MEF, mouse embryonic fibroblast; MSM, monolayer stress microscopy; PIP_2, phosphatidylinositol-4,5-biphosphate; PKC, protein kinase C; RIAM, Rap-1 GTP-interacting adaptor protein; TFM, traction force microscopy; VASP, vasodilator-stimulated protein; ΔVBS, Δ vinculin–binding site; Vh, vinculin head; VH1-2-3, vinculin homology domains 1-2-3; Vt, vinculin tail; YAP, Yes-associated protein.

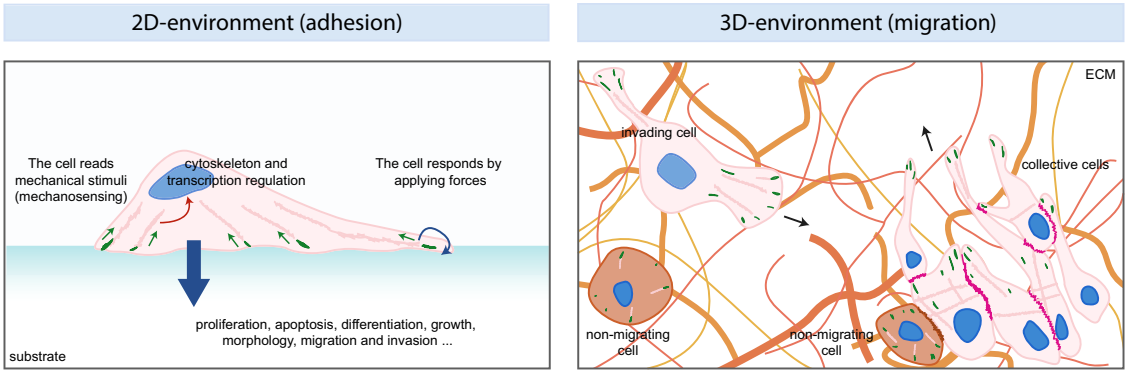

FIGURE 1: Mechanobiology and migration. Schematic of cells migrating on two-dimensional (2D) or 3D matrices. The 2D example shows the principles of mechanobiology by which a cell reads (green arrows) the mechanical properties of the ECM and converts them into a biochemical intracellular signal (red arrow) that affects the cytoskeleton, signaling, and transcription. Ultimately, the cell responds both by applying forces to the matrix itself (blue arrow) and undergoing processes such as proliferation, apoptosis, differentiation, and migration (large blue arrow). Mechanosensing occurs as the cells interact with the ECM through focal adhesions (green), which are linked to actin fibers (pink). The situation is more complicated in 3D migration, in which cells can move inside a matrix, here composed of fibers (different shades of orange) of different composition, structure, topology, and rigidity and other nonmigrating cells (pink). The drawing shows both a single invading cell (pink), moving in the direction of the arrow, and a group of migrating cells (pink) moving collectively and attached to one another by cell–cell junctions (magenta). Attached to the group of cells there can also be nonmigrating, nonpolarized cells (brown). In this complex situation, cells must integrate the signals transmitted by different types of focal adhesions and adherens junctions.

one induces neuron-like behavior, and intermediate stiffness induces a muscle-like phenotype (Engler *et al.*, 2006). Signaling cascades responsible for the control of gene expression in response to the physical properties of the environment are being deciphered. The protein Yes-associated protein (YAP) is involved, and its shuttling to the nucleus is controlled by mechanical cues (Aragona *et al.*, 2013). In the nucleus, YAP interacts with TEAD transcription factors to induce specific gene transcription, promote proliferation, and inhibit differentiation (Dupont *et al.*, 2011; Piccolo *et al.*, 2014). Of interest, optogenetic control of contractility shows that the nuclear localization of YAP is a rapid process downstream of RhoA (Valon *et al.*, 2017). The number of studies on the physics and mechanics of tumor tissues has steadily increased over the past decade, showing differences between normal and cancer cells. Most of these studies have been performed at the scale of the tumor or the tissue and shown that some tumors exhibit increased tissue stiffness (Egeblad *et al.*, 2010). In addition, the mechanical properties of tumor cells could also contribute to the physical properties of tumor tissues (Baker *et al.*, 2010). Tumor cells can also exploit stiffness to their advantage. Changes in tumor rigidity resulting from tumor cell activity or the physical remodeling of the ECM by surrounding stromal cells can promote tumor cell invasion, proliferation, and survival (Paszek *et al.*, 2005; Kostic *et al.*, 2009; Levental *et al.*, 2009).

The interaction between the cell and its environment functions both ways. On one side, cells sense the signals from the environment (Figure 1). Cells read physical stimuli through the use of mechanical sensors. This can occur by opening a channel, stretching a protein, exposing cryptic binding sites, or inducing biochemical signaling pathways. Ultimately this information is integrated so that the cell can respond appropriately. Responses can occur quickly via cytoskeletal rearrangements and changes in cell shape and motility. For instance, endothelial cells realign their cytoskeleton in the direction of the flow when subject to shear stress (Takahashi *et al.*, 1997). The reciprocal relationship between the mechanics of the cell and the physical properties of its surrounding is crucial during cell migration. During spreading and migration, cell adhesion to the substrate drives cytoskeletal rearrangements to promote membrane protrusion and cell spreading. To migrate, cells also use the adhesion sites located at the cell front as cortical anchors for the polymerizing actin meshwork that pushes against the plasma membrane and pulls on the substrate while contracting the cell body forward. As the cell forms new adhesions at the cell edge, it must test the mechanical resistance of the ECM to generate the appropriate amount of force to optimize migration. This mechanosensing process does not occur only at the single focal adhesion level: it is also integrated over the whole cell (Figure 1). After the establishment of myosin-based polarization (Raab *et al.*, 2012), cells can follow a gradient of stiffness in the ECM in a process called durotaxis (Lo *et al.*, 2000; Isenberg *et al.*, 2009; Tse and Engler, 2011). Variations in the physical properties of the ECM may also trigger a particular type of invasion (Tozluoğlu *et al.*, 2013). In cancer-associated fibroblasts (CAFs), the presence of a stiff matrix causes actomyosin contractility. This induces stress fiber formation and Src activation at focal adhesions. This in turn causes nuclear shuttling of YAP, which maintains the aggressive phenotype of CAFs, as it creates a feedback loop in which YAP transcription induces matrix stiffening (Calvo *et al.*, 2013). In the case of tumors, mechanical changes, such as increased confinement during migration, can also induce changes in DNA organization that ultimately modulate the cell's ability to migrate, participating in the invasive phenotype (Irianto *et al.*, 2017). ECM remodeling by matrix metalloprotease secretion can generate paths or tunnels in which cells can migrate more easily. It can also mechanically facilitate migration by changing the orientation and the tension of ECM fibers (Hynes, 2009; Egeblad *et al.*, 2010).

Collective migration is particularly important during development and in processes such as tissue shaping and wound healing. Collective migration corresponds to the coordinated movement of cell groups, sheets, or chains. It also plays a critical role in the progression of many tumors. Much as in the case of single-cell migration, collective cells are able to respond to mechanical cues. Different factors can affect collective migration, including crowding (cell density), cohesion (strength of adhesions), and constraints (boundary conditions

imposed by the ECM; Doxzen *et al.*, 2013). This implies that the cells must integrate information from the environment, which, in this case, also includes the neighboring migrating cells (Figure 1).

In this review, we focus first on the regulation of forces during single-cell migration and then in collectively migrating cells.

MECHANOCOUPLING BETWEEN SUBSTRATE RIGIDITY AND TRACTION FORCES DURING MIGRATION

Mechanosensing at focal adhesions

Single migrating cells must sense the physical properties of the ECM and, in response, apply the appropriate forces to generate movement. Adhesion and traction on the ECM mainly rely on integrins. Integrins are heterodimeric transmembrane receptors composed of an α and a β subunit, which bind specific ECM proteins. Their binding to ECM proteins is controlled by a conformational change that can be activated by outside-in signaling upon ECM binding and by inside-out signaling triggered by the association of partner proteins to the integrin cytoplasmic tail (Huttenlocher and Horwitz, 2011). As cells spread on the ECM, a growing number of integrins interact with the ECM proteins, which progressively form clusters, also called nascent adhesions or focal complexes. The initial steps leading to the formation of nascent adhesions occur before mechanosensing, at least during spreading, and are independent of myosin (Choi *et al.*, 2008; Changede *et al.*, 2015; Sun *et al.*, 2016a). However, forces contribute to the maturation of nascent adhesions into focal adhesions (Riveline *et al.*, 2001; Sun *et al.*, 2016a).

The formation of focal adhesions is initiated when the cluster of ECM-engaged integrins is large enough. In NIH3T3 fibroblasts on fibronectin, clusters of integrins smaller than 0.11 μm^2 are unstable and unable to exert forces because the cluster force cannot sustain the cytoskeletal force (Coyer *et al.*, 2012). By developing the tension gauge tether method, Wang and Ha (2013) demonstrated that for CHO-K1 cells, a tension of 40 pN is necessary for integrins to form adhesive structures. During migration, two tension levels can be identified, corresponding to nonclustered integrins (40 pN) and clustered integrins (54 pN). The latter level depends on actomyosin and actin stress fibers that connect focal adhesions together and represents integrins under higher tension, which are found in motile focal adhesions (Wang *et al.*, 2015).

In focal adhesions, integrin clusters can recruit up to 160 different proteins (Zaidel-Bar *et al.*, 2007; Horton *et al.*, 2015; for a review, see Li *et al.*, 2016). These proteins form a physical bridge between integrins engaged with the ECM and the cell cytoskeleton, and more particularly to actomyosin contractile fibers (Figures 2 and 3B). A key article by the Waterman group defined focal adhesions structurally by three-dimensional (3D) super-resolution. Integrins and actin are separated by a 40-nm focal adhesion core subdivided into a lower group (integrin tails, paxillin, and focal adhesion kinase [FAK]), an intermediate, force-transduction group (talin and vinculin), and a higher, actin-regulatory group (zyxin, α-actinin, and vasodilator-stimulated phosphoprotein [VASP]; Kanchanawong *et al.*, 2010). The intermediate proteins talin and vinculin are fundamental mechanosensors, as they can change conformation and signaling properties upon force-induced stretching (for a review, see Yan *et al.*, 2015; Haining *et al.*, 2016). Ultimately, talin and vinculin allow force transmission through β integrins, regulating migration and detection of stiffness (Austen *et al.*, 2016; Nordenfelt *et al.*, 2016).

Talin was one of the first proteins to be identified as an integrin partner (Horwitz *et al.*, 1986; Figure 2A). In absence of talin, as in absence of integrins, focal adhesions cannot form properly (Zhang *et al.* 2008). Talin is recruited together with FAK to nascent adhesions (Lawson *et al.*, 2012). Talin is a large protein of 270 kDa composed of an N-terminal head, a neck, and a C-terminal rod domain. It can adopt an autoinhibited, closed conformation and is activated upon release of this autoinhibition and opening into an extended form (Calderwood *et al.*, 2013). Integrin binding to the rod domain activates talin, which reinforces the interaction (Himmel *et al.*, 2009) and promotes the conformational change of the β integrin subunit. Talin binding to the integrin tail can be induced by inside-out signaling. Protein kinase Cα (PKCα), Rap1, Rap-1 GTP-interacting adaptor protein (RIAM), and phosphatidylinositol-4,5-biphosphate (PIP_2) induce talin activation and promote integrin engagement with the ECM (Das *et al.*, 2014). Talin-2 has a particularly high affinity for β integrins, which leads to higher traction forces and faster

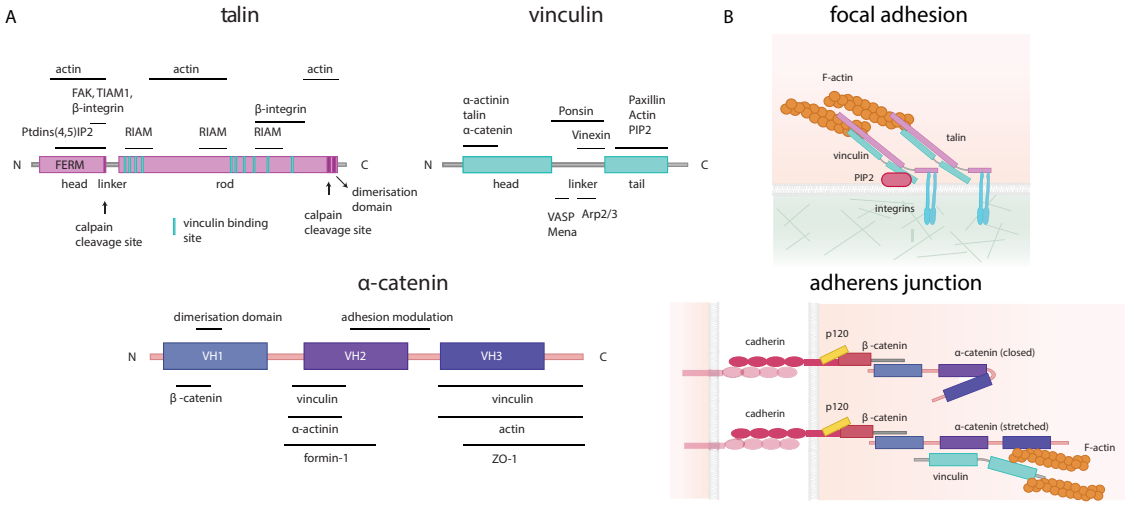

FIGURE 2: Tension-sensitive proteins are mechanical players of adhesion sites. (A) Schematic representation of the main tension-sensitive proteins involved in focal adhesions and adherens junctions: talin (purple), vinculin (light blue), and α-catenin (dark blue). The main protein interaction domains are shown, and the known interactors (with their binding sites) are indicated above or below each protein. (B) Top, components of focal adhesions and the structures of talin and vinculin when stretched (talin in pink, vinculin in light blue, PIP_2 in purple, and F-actin in orange). Bottom, components of adherens junctions and the structure of the unstretched (closed, top) or stretched (bottom) α-catenin (cadherin in purple, p120 in yellow, β-catenin in coral, α-catenin in purple, vinculin in light blue, and actin in orange).

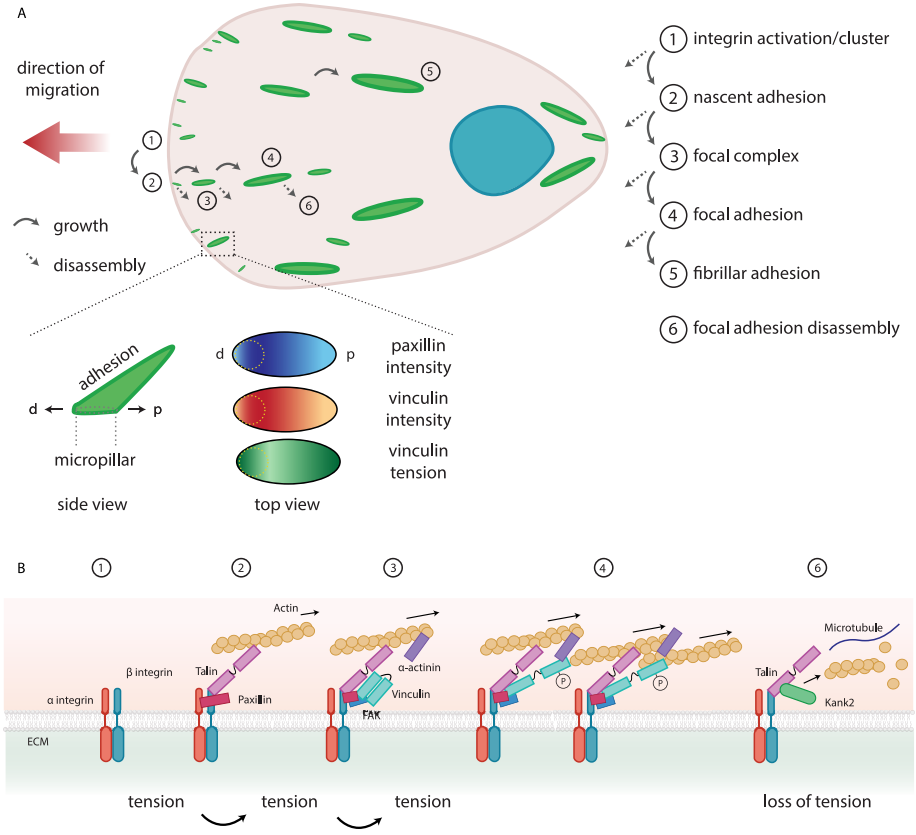

FIGURE 3: Turnover of focal adhesions. (A) Schematic representation of a migrating cell (pink; nucleus in blue; the arrow shows the direction of migration), highlighting focal adhesion (green) formation, maturation, and disassembly. Different maturation stages (labeled 1–6) can be observed, which can grow (full arrow) or disassemble (dotted arrow) at every step. Inset, summary of the work by Sarangi *et al.* (2016). The intensity of vinculin and paxillin is analyzed in parallel to vinculin tension (green, high; to white, low) on micropillars. The intensity of paxillin (blue, high; to white, low) and vinculin (red, high; to white, low) is higher in the region of the focal adhesion corresponding to the edge of the micropillar (yellow dotted lines), whereas the vinculin tension is higher at the distal (d) and proximal (p) sites in the adhesion. (B) Focal adhesions, from an integrin cluster to a mature focal adhesion that forms with tension. The disassembly occurs with loss of tension. The ECM (green), integrins (green and red), paxillin (purple), talin (pink), vinculin (light blue), FAK (blue), α-actinin (purple), actin (yellow), microtubules (blue line), and Kank2 (green).

Vinculin, a cytoplasmic 117-kDa protein, was initially identified as an actin-binding protein (Geiger *et al.*, 1980) and later found to bind a high number of partners, including talin, α-actinin, Arp2/3, paxillin, VASP, catenins, and PIP_2 (Carisey *et al.*, 2013; for a review, see Peng *et al.*, 2011; Goldmann, 2016; Figure 2A). Vinculin comprises an N-terminal globular head (Vh), which can bind talin, and a C-terminal rod tail (Vt), which can directly or indirectly interact with actin (Cavalheiro *et al.*, 2017). These two major domains are separated by a short, flexible, proline-rich linker. Similar to talin, vinculin can be found in a closed, autoinhibited state in which Vh and Vt bind each other (Johnson and Craig, 1994, 1995a). Vinculin is recruited via talin to adhesion sites. After actin binding to the Vt domain, vinculin stretching dissociates the Vh and Vt (Bakolitsa *et al.*, 2004; Izard *et al.*, 2004; Cohen *et al.*, 2005; Chen *et al.*, 2006). At this point, vinculin can induce recruitment, activation, or release of other integrins, paxillin, focal adhesion proteins, and more actin, promoting the growth of the focal adhesion in a force-dependent manner (Humphries *et al.*, 2007; Carisey *et al.*, 2013). Owing to its activity and localization, vinculin is considered an optimal candidate in mechanotransduction (Atherton *et al.*, 2016). Its loss induces small but dynamic focal adhesions and defects in locomotion (Coll *et al.*, 1995; Saunders *et al.*, 2006; Thievessen *et al.*, 2013). Loss of vinculin is associated with cancer, as well as with developmental diseases such as cardiomyopathies (Olson *et al.*, 2002; Goldmann *et al.*, 2013). Depletion of the vinculin gene in mice leads to embryonic lethality by embryonic day 10, with defects consistent with problems in adhesion, such as neural tube defects and cardiac malformations. Mouse embryonic fibroblasts (MEFs) from vinculin knockout mice are faster but less adhesive, with disrupted focal adhesions (Xu and Baribault, 1998). A recent study showed that hyperactivation of vinculin also causes lethality and muscular defects in *Drosophila* due to the formation of cytoplasmic aggregates that resemble adhesion subcomplexes, which are bound to talin tail but not to integrins or actin (Maartens *et al.*, 2016). In these complexes, vinculin can ectopically activate talin, mimicking the effect of force.

invasion (Qi *et al.*, 2016). The whole rod can be stretched by a force in the range of 5–10 pN (Yao *et al.*, 2016), allowing binding of many possible partners in response to force (Haining *et al.*, 2016). In particular, stretching of the rod domain exposes more vinculin-binding sites (del Rio *et al.*, 2009). A new tension sensor based on HP35 (a 35–amino acid–long villin head-piece peptide) flanked by two fluorophores has recently allowed the demonstration that talin experiences forces up to 7 pN, sometimes even reaching 10 pN when associated with vinculin and actin (Austen *et al.*, 2016). Focal adhesion coupling to the actin retrograde flow is responsible for the generation of pulling forces (Case and Waterman, 2015; Comrie *et al.*, 2015). However, actomyosin contraction induces even more conformational changes in both the rod and the linker domain of talin, exposing more vinculin-binding sites and promoting the formation of more stable focal adhesions (Calderwood *et al.*, 2013). A recent study demonstrated by super-resolution microscopy that vinculin binds talin in a cooperative manner (the binding is optimal when talin is stretched to 180 nm; Hu *et al.*, 2016). Multiple vinculin proteins actually bind the rod domain of talin when the latter is stretched as an antiparallel dimer.

The recruitment of talin and vinculin to focal adhesions correlates with the mechanical force applied to the focal adhesion (Golji *et al.*, 2011). The use of a vinculin fluorescence resonance energy transfer (FRET) tension sensor showed that vinculin is recruited to focal adhesions in a force-dependent manner (Grashoff *et al.*, 2010). The Vt binding to actin induces actin fiber bundling to regulate migration and tractions (Johnson and Craig, 1995a; Janssen *et al.*, 2006; Thompson *et al.*, 2014; Jannie *et al.*, 2015). Bundling is most likely mediated by the displacement of the first helix (H1) in Vt upon actin binding, partially unfolding vinculin (Ho Kim *et al.*, 2016). Vinculin–actin interaction is also necessary for transmission of forces, mediating myosin contractility, which enhances forces (Dumbauld *et al.*, 2010). The Vt

domain is necessary to generate forces (Dumbauld *et al.*, 2010), whereas the Vh domain probably enhances adhesion strength (Dumbauld *et al.*, 2013). Vinculin also plays a role in engaging and stretching talin with the actomyosin system, locking it in an open conformation and stabilizing the talin–integrin complex (Dumbauld *et al.*, 2013) and focal adhesion (Atherton *et al.*, 2016).

Front-to-rear control of mechanotransduction

During migration, cells form, use, and dissociate focal adhesions. Much stronger traction forces are applied on mature focal adhesions than on nascent adhesions (Gardel *et al.*, 2008). The newer adhesions at the cell front have a higher tension than the retracting ones at the cell rear (Grashoff *et al.*, 2010), as talin tension is higher in peripheral focal adhesions than in older ones (Kumar *et al.*, 2016). Vinculin appears incorporated in the proximal tip of new focal adhesions with minimal tension in the paxillin-rich lower layer of the focal adhesion. Vinculin then treadmills toward the distal end of the focal adhesion, binding actin and talin, opening and increasing its tension (Case and Waterman, 2015; Figure 3). Vinculin interaction with actin is necessary to regulate the actin retrograde flow, as it slows the flow and leads to higher traction forces (Humphries *et al.*, 2007; Thievessen *et al.*, 2013; Jannie *et al.*, 2015). As tension increases, vinculin progressively detaches from the lower layer and is carried inward and upward by the actin retrograde flow as an open protein but without any tension (Case and Waterman, 2015).

Mechanotransduction through talin and vinculin is continuously influenced by the cytoskeletal dynamics and molecular signaling. As forces increase on new focal adhesions, p130Cas, a protein involved in integrin signaling, is stretched. In this case, the stretching renders phosphorylation sites accessible to the Src kinase (Sawada *et al.*, 2006). The FAT domain of p130Cas appears essential in mechanosensing substrate rigidity and controlling cell speed (Bradbury *et al.*, 2017). The following p130Cas phosphorylation increases integrin signaling to the small GTPase Rap1, which in turn can activate talin via RIAM and promote further integrin engagement. As the focal adhesions mature, vinculin competes with RIAM to bind talin and stabilizes the integrin-talin-actin complex independently of Rap1 (Lee *et al.*, 2013). Vinculin phosphorylation by Src on Y100 and Y1065 promotes vinculin opening and increases adhesion and force transmission (Auernheimer *et al.*, 2015). Phosphoinositide signaling affects both talin and vinculin activities. PIP_2 activates autoinhibited talin (Ye *et al.*, 2016). Vinculin also binds PIP_2 (Johnson and Craig, 1995b; Izard and Brown, 2016), and vinculin stretching increases its binding to PIP_2 (Dwivedi and Winter, 2016). A recent model resolved the structure for a short-chain PIP_2 binding to vinculin tail and showed that vinculin dimerizes in the presence of PIP_2 (Chinthalapudi *et al.*, 2014, 2015). Vinculin mutants that cannot bind lipids are associated with altered focal adhesion turnover but are still able to reinforce cell stiffness upon mechanical deformation (Thompson *et al.*, 2017).

Disassembly or sliding of focal adhesions can result from the negative regulation of talin (Figure 3). Kank2 was recently identified as a component of focal adhesions that forms a "belt" around more mature focal adhesions. In migrating cells, Kank2 concentrates around most mature focal adhesions and binds talin. This interaction displaces actin but maintains talin active and thereby uncouples integrins from actin fibers, reducing force transmission and promoting the sliding of the focal adhesions (Sun *et al.*, 2016b). Ultimately, the loss of traction can also promote the disassembly of focal adhesions. A decrease in traction forces promotes the association of the clathrin adaptor Dab2 with integrin β_3 while excluding talin and thereby promotes clathrin-mediated endocytosis of integrins (Yu *et al.*, 2015).

Adaptation of forces to substrate rigidity

During migration, cells use focal adhesion to apply traction forces on the ECM. They respond in a linear manner to the substrate stiffness and change focal adhesion size accordingly (Pelham and Wang, 1997; Saez *et al.*, 2005; Ghibaudo *et al.*, 2008). To measure the traction exerted by the cell, different techniques have been developed over the past 25 years. Initially, cells were plated onto deformable silicon sheets, and the sheet wrinkling was an indirect measure of the cell's traction onto the substrate (Harris *et al.*, 1980). Toward the end of the 1990s, in a key article, Pelham and Wang (1997) reported that the deformation of a polyacrylamide gel could be used to infer the traction force field exerted by a cell, leading to the development of traction force microscopy (TFM; Dembo and Wang, 1999). TFM is based on the measurement of the displacement of fluorescent beads embedded into an inert hydrogel: the amplitude of displacement indicates how much traction the cell exerted. Other techniques, such as micropillars and atomic force microscopy, have also been developed to better study the cells from a mechanical point of view (Polacheck and Chen, 2016). Mechanotransduction at focal adhesions allows the cells to adapt the forces they exert to the physical properties of the substrate (Figure 1). Thus cells tend to exert higher forces on stiffer substrates and lower tractions on softer substrates (Saez *et al.*, 2005; Ghibaudo *et al.*, 2008). On soft gels, focal adhesions usually appear diffuse and dynamic; on stiffer gels (or glass), they are stabler and larger (Pelham and Wang, 1997; Ghibaudo *et al.*, 2008). During branching on soft substrate, human mesenchymal stem cells show small patches of rapidly turning over focal adhesions but longer protrusions. The vinculin head–tail interaction is necessary for this response, as the mutation (T12) of vinculin that prevent this interaction stabilizes the talin–vinculin complex in focal adhesions in amounts that are not rigidity dependent (Liu *et al.*, 2016). The size–force relationship in focal adhesions is not simple, and focal adhesions of the same size can exert different forces, depending on the substrate stiffness (Trichet *et al.*, 2012). The nature of integrins associated with the substrate also influences the mechanical responses. β_1 integrins induce Rac1 activation to assemble new small adhesions. α_V integrins are involved in rigidity sensing and accumulate in areas of high tension to reinforce adhesions and actomyosin contractility by activating a RhoA-mDia pathway and the formation of additional actin bundles (Schiller *et al.*, 2013). β_1 and α_V integrins cooperate to promote myosin II contractility and adapt the level of forces to the rigidity of the substrate.

A recent challenging study analyzed the relationship between focal adhesion internal forces and traction forces by combining micropillars of given stiffness and FRET tension sensors (Sarangi *et al.*, 2016). The authors found that the tension inside focal adhesions correlates in space and time with the force exerted on the substrate, depending on the integrity of the stress fibers (Sarangi *et al.*, 2016). Whereas a previous study found that the traction peak localizes distally a few micrometers from where paxillin is most abundant (Plotnikov *et al.*, 2012), Sarangi *et al.* (2016) demonstrated that both paxillin and vinculin are concentrated at the distal end of the focal adhesions and are less abundant behind the central area (Figure 3A). Vinculin forces are higher in the region that directly contacts the substrate, where vinculin is not at its peak concentration (Sarangi *et al.*, 2016). The coupling between integrins and actomyosin forces was initially explained in neurons by the "molecular clutch" hypothesis (Mitchison and Kirschner, 1988; Schwarz and Gardel, 2012). Actin rapidly polymerizes and pushes the lamellipodia forward, whereas its contraction through myosin II leads to net rearward flow of the actin network. When the retrograde actin flow is coupled to the ECM through integrins and focal adhesion proteins (in other

words, when the clutch is engaged), the force of the actin polymerization at the leading edge is converted into a protrusion force pushing the leading edge forward. The force is transmitted to the ECM (rearward traction), allowing the cell to move forward (Swaminathan and Waterman, 2016).

The molecular clutch model allows a better understanding of how cells sense the environment. According to the Odde model, the molecular clutch behaves differently, depending on the substrate stiffness. On stiff matrices, the retrograde flow is fast, with low traction ("frictional slippage"), because the F-actin bundle is continuously disengaged from the clutch. On soft matrices, the retrograde flow is slower, tension can build up, and the clutch remains engaged for longer time, until the load reaches such high levels that some proteins in the clutch are lost and the whole clutch fails ("load-and-fail"; Chan and Odde, 2008). One limitation of the Odde model is that it predicts a biphasic force–rigidity relationship. However, in most conditions, a monotonic increase of traction forces is observed as a function of ECM stiffness. The Roca-Cusachs group (Elosegui-Artola *et al.*, 2016) recently demonstrated that the biphasic curve can be masked by talin. Above a certain rigidity threshold, the force loading becomes fast enough to allow unfolding of talin before integrins disengage, leading to recruitment of vinculin and integrins, reinforcement of integrin binding, adhesion growth, and increase of force transmission. Moreover, when talin unfolds, YAP translocates to the nucleus, possibly through integrin clustering, signaling downstream of vinculin and talin and transmission of forces to the nucleus via actin stress fibers. Below this stiffness threshold, talin is not stretched rapidly enough, integrins disengage, and YAP is not shuttled to the nucleus (Elosegui-Artola *et al.*, 2016). Vinculin, together with FAK and paxillin, is involved in sensing rigidity. Inhibition of FAK and paxillin reduces traction and decreases the rigidity threshold that promotes tugging on softer ECM, involving vinculin recruitment in strengthening the molecular clutch (Mierke *et al.*, 2008; Plotnikov *et al.*, 2012). In line with this, vinculin tends to adopt an inactive conformation on softer ECM and an active one on stiffer ECM, which is important for stiffness-dependent migration (Yamashita *et al.*, 2014). Other proteins involved in the molecular clutch include $\alpha_5\beta_1$ integrin (Schiller *et al.*, 2013; Riaz *et al.*, 2016) and α-actinin (Meacci *et al.*, 2016), the loss of which causes aberrant rigidity sensing.

Adaptation to substrate rigidity is a very fast process (Mitrossilis *et al.*, 2010). The cell must continuously sense and respond in a feedback loop to maintain the situation in a steady state (Roca-Cusachs *et al.*, 2013). How the cell really measures rigidity is still debated; most probably the cell exerts submicrometer contractions and detects the local deformation of the substrate by "measuring" how much force/contraction it needs to generate such deformation. These contraction areas are similar to sarcomeres, as shown by the recruitment of α-actinin on the pillar tips and of myosin-II between pillars. The contraction units involve nanometer-size, myosin-dependent steps with a frequency of ~2–3 steps/s; when the force reaches a threshold of ~20 pN, a pause is triggered so that the adhesion can be reinforced by recruiting more α-actinin (Ghassemi *et al.*, 2012; Wolfenson *et al.*, 2015). A recent study on human skin fibroblasts highlighted the role of two receptor tyrosine kinases, AXL and ROR2, which regulate rigidity sensing by respectively modulating the strength or the duration of these contractions (Yang *et al.*, 2016). In the case of MEFs on micropillars, cells measure displacements of 60 nm in early steps of adhesion, until the adhesion itself can grow and couples to the actin retrograde flow (Ghassemi *et al.*, 2012). Moreover, the actin cytoskeleton responds through rheological changes, behaving like a fluid on soft substrates and a nematic solid on stiff ones (Gupta *et al.*, 2015).

Mechanotransduction beyond actin

The role of other cytoskeletal networks in the cell mechanical responses is still understudied. However, evidence is accumulating suggesting a possible role of microtubules in the generation of adapted forces. First, microtubules are involved in the regulation of adhesion sites (Akhmanova *et al.*, 2009; Etienne-Manneville, 2013), contractility (Kolodney and Elson, 1995; Rape *et al.*, 2011), and RhoA signaling (Heck *et al.*, 2012). In parallel, microtubules can modulate traction through FAK (Rape *et al.*, 2011). Second, microtubule dynamics appear to be controlled by the rigidity of the substrate. In endothelial cells, both actin and microtubules participate in cell branching, and microtubule growth depends on substrate stiffness and myosin (Myers *et al.*, 2011). Microtubules have also been shown to orient toward stiffer areas (Maiuri *et al.*, 2015; Raab and Discher, 2016) and retract from the stiff area when contraction is locally inhibited (Kaverina *et al.*, 2002). On stiff matrices, microtubules are important to regulate cell polarity, while protrusions are mainly generated by actin dynamics (Etienne-Manneville, 2013). However, in soft 3D matrices, microtubules are necessary for fibroblast dendritic-like extensions and endothelial cell migration (Rhee *et al.*, 2007; Bouchet and Akhmanova, 2017). Kank family proteins were shown to regulate talin-mediated force transmission (Sun *et al.*, 2016b). Kank1 was recently shown to bind talin, and this interaction is necessary to allow targeting of microtubules near focal adhesions (Bouchet *et al.*, 2016); it will be interesting to see whether this mediates a mechanosensory response.

Detyrosination, a posttranslational modification of microtubules associated with their stability, participates in mechanotransduction of striated muscles. Reduced tubulin detyrosination is associated with decreased cytoskeletal stiffness and faster muscle contraction and relaxation, suggesting a role in mechanotransduction (Kerr *et al.*, 2015). Oncogenes may increase tumor cell stiffness and invasion through HDAC6 (histone deacetylase 6), which inhibits microtubule acetylation and causes the reorganization of the vimentin intermediate filament network (Rathje *et al.*, 2014). In different cell types, solubility of vimentin depends on ECM stiffness and correlates with cell ruffling. On softer substrates, the soluble pool is maintained by microtubules, whereas on stiffer substrates, it depends on contractility (Murray *et al.*, 2014). Intermediate filaments have been shown to participate in and regulate cell migration (Gonzales *et al.*, 2001; Bhattacharya *et al.*, 2009; Mendez *et al.*, 2010; Dupin *et al.*, 2011; Weber *et al.*, 2011; Sakamoto *et al.*, 2013; Leduc and Etienne-Manneville, 2015; Liu *et al.*, 2015a; Vincent *et al.*, 2015). Because of this and their peculiar properties as highly elastic filaments and role in cell mechanics (Herrmann *et al.*, 2007; Block *et al.*, 2015), intermediate filaments are an ideal candidate to mediate mechanotransduction in cells.

THE MECHANICS OF COLLECTIVELY MIGRATING CELL GROUPS

Just as single cells, migrating cell groups are also clearly affected by the biochemical and physical properties of their environment (Figure 1B). However, migrating collectives cannot be simplified as a group of independent cells that happen to move at the same speed and direction. The collective behavior results in a more efficient migration and sometimes in the acquisition of specific features (Mayor and Etienne-Manneville, 2016). This relies on the communication between migrating cells, and the direction of each cell depends on its neighbors (Vicsek *et al.*, 1995; Szabo *et al.*, 2006). During collective migration, cells couple to one another mechanically and chemically through cell–cell contacts and the actin cytoskeleton (for a review, see Mayor and Etienne-Manneville, 2016). This allows the cells

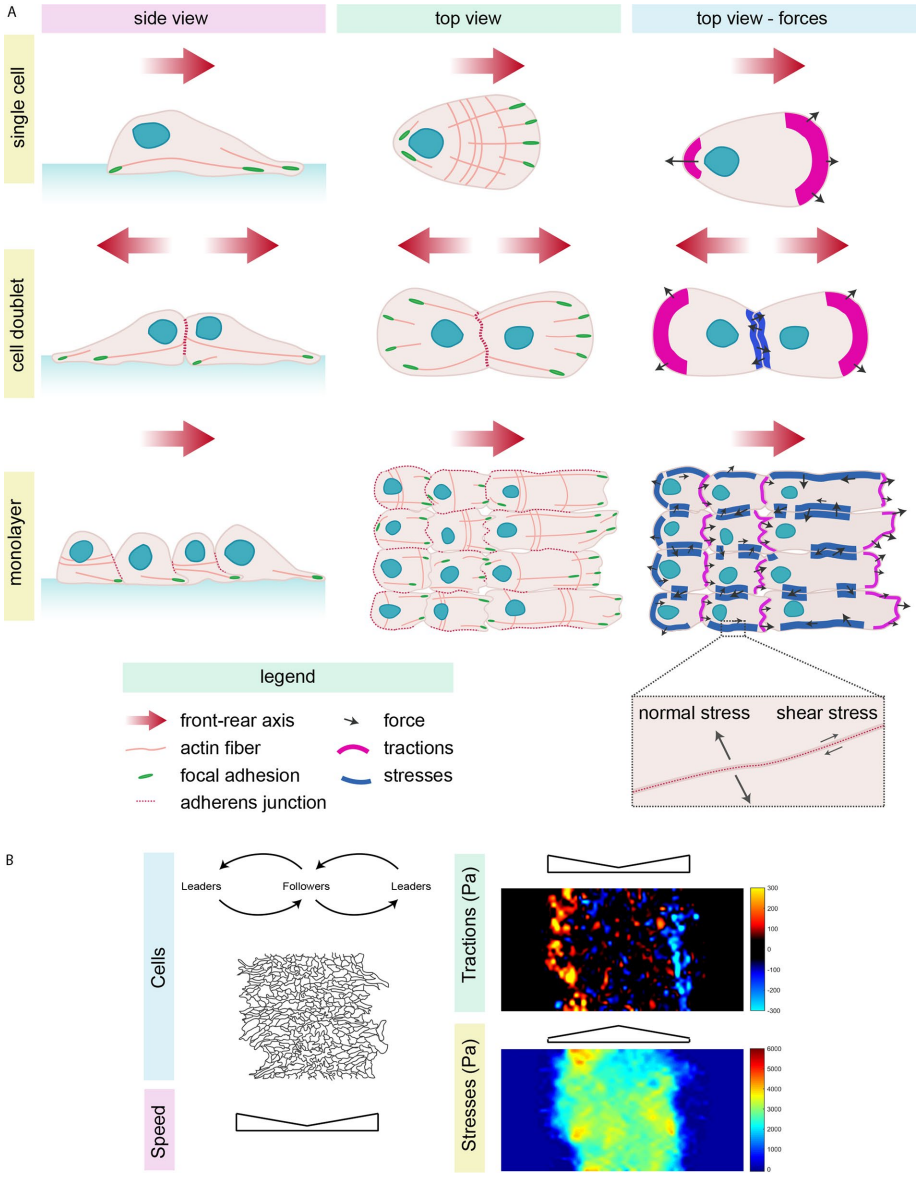

FIGURE 4: Cell migration and force transmission and their study in collective migration. (A) Single cell (top), doublets (middle), and a migrating monolayer (bottom) from the side and top views. Cells (light pink) show a polarized (red arrow, front–rear axis of migration) morphology, with the nucleus (blue) at the back, an asymmetric distribution of focal adhesions (green) and actin (pink lines), microtubule (not shown), and intermediate filament (not shown) networks. Cell–cell contacts (red dotted line) allow adhesion between cells. The third column shows representative forces (tractions on the substrate in magenta and intercellular stresses in blue); tractions are high at the cell front, whereas intercellular stresses concentrate at cell–cell contacts. The gray arrows represent possible forces and their directions. (B) Representative images of cells migrating on hydrogels (black lines show the cell edges). Collectively migrating cells are divided into leaders and followers, which influence one another. The speed of migration is higher at the edges of the monolayer, as are tractions. Tractions are calculated by TFM (bead displacements) and are higher where the color intensity is stronger—yellow and blue correspond to the maximal forces in opposite directions along the axis of migration. Stresses, calculated with MSM, are higher at the center of the migrating monolayer (strong intensity in red). TFM and MSM images were obtained on migrating astrocytes on a 9-kPa collagen-coated hydrogel by C.D.P. and C. Pérez González.

to influence the behavior of one another and modify the supracellular front–rear polarity. A hierarchy is established inside the group by selecting a population of leaders that sense the mechanical and chemical cues that induce migration. Leaders influence followers via mechanical coupling. Cells within the migrating group also influence each other. In the particular case of contact inhibition of locomotion, which will not be discussed here, cells can also repel each other as a mechanism of collective guidance (Theveneau *et al.*, 2013; Scarpa *et al.*, 2015; Zimmermann *et al.*, 2016). How cells collectively adjust their forces and how they sense and transduce the mechanical properties of their neighbors is currently under intensive investigation.

Distribution of forces in migrating collectives

The first attempts to measure forces in collectively migrating Madin–Darby canine kidney (MDCK) cells on micropillars showed that tractions are mainly localized at the cell front and perpendicular to the monolayer edge, with an average force of 5 nN. This demonstrated that migration is due to the pulling of the leader cells onto the substrate and not to the pushing of follower cells (du Roure *et al.*, 2005). The strongest tractions are applied at the leading edge, but, at least in epithelial cell monolayers, traction forces are generated up to several hundreds of micrometers inside the monolayer (Trepat *et al.*, 2009; Tambe *et al.*, 2011; Serra-Picamal *et al.*, 2012; Figure 4B). However, recent measurements obtained with a new silicone wrinkling, temperature-sensitive substrate show that tractions are limited to the first row of MDCK leader cells (Yokoyama *et al.*, 2016). In general, cells far from the leading edge exert smaller forces than leaders, but tractions in the monolayer are heterogeneous and change continuously over time, with small hot spots and fluctuations (Serra-Picamal *et al.* 2012). Although leader cells give biochemical and mechanical cues to followers, cells inside the monolayer can slow down, move in different directions (sometimes even opposite to the direction of the group), or form swirls (Petitjean *et al.*, 2010; Vedula *et al.*, 2012; Reffay *et al.*, 2014). Thus, the distribution of forces across the monolayer is dynamic and fluctuating, with variations in both the adhesion to the substrate and contractility (Ng *et al.*, 2014). These local variations are likely to induce cells to polarize and exert tractions in a direction that is not necessarily the same as that of the global movement during the entire duration of migration. Thus tractions must be regulated by velocity but also by other local parameters, such as cell polarity (Notbohm *et al.*, 2016).

Owing to unequal distribution of tractions between the leaders and the followers, the cell sheet is under global tensile stress, and forces are transmitted at large scales (Trepat *et al.*, 2009; Tambe *et al.*, 2011; Serra-Picamal *et al.*, 2012; Figure 4A). The leaders and the rest of the cells in the monolayer play a tug-of-war: the monolayer

manages to migrate forward because the leader cells are stronger. However, leaders exert forces only up to ~100 nN, which is not strong enough to pull the whole monolayer. They might nevertheless succeed because of a mechanical "X-wave" that propagates from the front to the back of the monolayer, communicating information on mechanics and polarity to the followers. This wave is continuously repeated so that the flow of information is maintained during the whole migration process (Serra-Picamal *et al.*, 2012). The coordinated behavior of the followers may be simply explained by the fact that single cells in the group align their traction forces with the general velocity of the cell group (Basan *et al.*, 2013). Development of monolayer stress microscopy (MSM) has allowed a better understanding of the distribution of stresses (σ) in the monolayer. Stresses are again heterogeneous, with large areas of tensile (positive) stresses alternating with regions of weak compressive (negative) stresses that vary over time. Stresses are defined by their components, shear stress (σ_{xy} and σ_{yx}) tangent to the surface and normal stress (σ_{xx} and σ_{yy}) perpendicular to the surface. In biological terms, these correspond respectively to the tangential and perpendicular forces exerted on cell–cell junctions by neighboring cells. During migration, cells in the monolayer migrate in the direction that maintains the shear stress minimum and the normal stress maximum (Figure 4A). The collective tendency of cells in a monolayer to migrate along the orientation of maximal principal stress is called plithotaxis (Tambe *et al.*, 2011; Trepat and Fredberg, 2011). Leader cells induce traction forces on followers and shear stress on neighbors, transforming local forces into coordinated and polarized traction forces, ensuring plithotaxis (Zaritsky *et al.*, 2015). Merlin, a tumor suppressor and regulator of the Hippo pathway, has been proposed to play a role in plithotaxis of epithelial cells through Rac1 modulation (Das *et al.*, 2015). When leader cells start to migrate, Rac1 is activated toward the cell front. Leader cells pull the followers, which in turn release merlin from junctions to promote the polarized activation of Rac1 in the followers.

The transmission of forces within the cell group is mainly mediated by adherens junctions (Tambe *et al.*, 2011; Trepat and Fredberg, 2011). To obtain direct information of the mechanical role of adherens junctions between neighboring cells migrating collectively on ECM, cells can be plated as doublets, the smallest possible group on adhesive micropatterns. Even if this is clearly not an example of collective cell migration per se, it still provides useful information. For example, a pair of endothelial cells sustains forces at cell–cell junctions of ~100–120 nN perpendicular to the cell–cell contact (Liu *et al.*, 2010; Maruthamuthu *et al.*, 2011). However, the different adherens junction proteins can differently affect the physical parameters controlling either the monolayer kinematics or forces. For example, in the case of MCF10A cells, P-cadherin and E-cadherin show different responses to mechanical stress in magnetic tweezers experiments. E-cadherin allows the cells to adapt to an extracellular force by activating a mechanotransduction pathway via vinculin, whereas P-cadherin cannot reinforce junctions. However, the two proteins seem to compete for the same mechanotransduction pathway because P-cadherin can rescue the absence of E-cadherin (Bazellières *et al.*, 2015). The specific role of each cadherin in mediating intercellular stresses during collective migration is still unclear. The expression of different levels of cadherins during epithelial-to-mesenchymal transition or tumor invasion might also help the cells migrate and invade collectively through a cadherin-dependent regulation of forces (Friedl and Mayor, 2017). In a carcinoma model, CAFs are able to pull the tumor cells to drive collective invasion. This is due to a heterophilic interaction between the N-cadherin of CAFs and the E-cadherin of the tumor cells, which actively responds to forces and allows polarization of CAFs (Labernadie *et al.*, 2017).

Sensing and adjusting forces between adjacent migrating cells

Adherens junctions are the main cell–cell adhesion structures that mediate tissue mechanical integrity. Adherens junctions are typically composed of cadherins—transmembrane proteins that interact homotypically. Cadherins bind intracellularly to catenins (p120 catenin, α-catenin, and β-catenin) and can activate different signaling pathways to influence the cytoskeleton, differentiation, and the cell cycle (Gumbiner, 2005; Leckband and de Rooij, 2014). Cadherin cytoplasmic partners also associate with actin directly or indirectly via vinculin and zyxin. Thereby, they couple cell–cell interactions to the actin cytoskeleton.

In the *Drosophila* ovary, border cells migrate as a cohesive and coordinated group through the nurse cells that compress them. Migrating border cells express E-cadherin, which on one hand contributes to their migration—E-cadherin expressed by the immobile surrounding nurse cells being used as a substrate—and on the other hand mediates the communication between the leaders to follower cells of the moving cluster. To resist compression, the migrating border cell cluster activates cycles of myosin II contraction to promote cortical tension (Aranjuez *et al.*, 2016). Moreover, the common direction of migration is controlled through E-cadherin and Rac. E-cadherin is under higher tension at the front of the border cells, where it activates Rac to increase E-cadherin tension (Cai *et al.*, 2014).

Information on the forces exerted at the level of cell–cell junctions can be obtained from assays easier to interpret than whole migrating monolayers. As for TFM or micropillar experiments, where cells are plated on ECM substrates, cells can also be plated onto cadherin patterns. These experiments demonstrated that cell spreading and force transmission on N-cadherin–coated substrate is stiffness dependent. Cadherin adhesions are larger and stronger on stiff gels, whereas cells have smaller adhesions and a disorganized actin network on softer gels (Ladoux *et al.*, 2010). Moreover, increasing forces on adherens junctions leads to a force-dependent reinforcement of their structure and of the associated actomyosin system (Lambert *et al.*, 2007; le Duc et al., 2010). These observations imply that cadherin-mediated adhesions possess a mechanosensor and serve as a major site of mechanotransduction.

Cadherins form nanoclusters that associate with the actin cytoskeleton to mediate mechanotransduction (Changede and Sheetz, 2016; Cosgrove *et al.*, 2016). The understanding of the role of cadherins in mechanical intercellular coupling has progressed significantly since the α-catenin/vinculin modulus has been involved in mechanotransduction. α-Catenin is a 102-kDa protein that possesses roles in different signaling pathways involved in proliferation and size, such as YAP, MAPK (mitogen-activated protein kinase), and Wnt (Figure 2A). It is also a key molecule in adherens junctions, where it is recruited through its association with β-catenin on one side and can bind actin filaments and vinculin on the other side to reinforce cell–cell junctions (Figure 2). Loss of α-catenin results in alterations of adherens junctions and loss of its connection to the actin cytoskeleton (Hirano *et al.*, 1992; Vasioukhin *et al.*, 2000). α-Catenin contains three main domains called vinculin homology domains (VH1, VH2, and VH3), which, as their names suggest, possess high homology with vinculin domains (27, 31, and 34%, respectively). VH1 is important for both β-catenin binding and α-catenin homodimerization. The VH2 domain contains binding sites for many of its partners, including vinculin and the actin-binding proteins α-actinin and formin-1. Part of the VH2 domain contains an adhesion modulation domain (M) of four α-helix bundles. The VH3 C-terminal domain binds actin (Kobielak and Fuchs, 2004). α-Catenin can be found in an autoinhibited conformation, where M1 and M2-3

domains interact. In a key study, Yonemura *et al*. (2010) showed that α-catenin is a mechanosensor. Stretching forces induce a change in α-catenin conformation that unmasks the vinculin-binding site. Disruption of the intramolecular inhibitory interaction requires only ~5 pN and leads to an open catenin conformation (Yao *et al*., 2014). The interaction of α-catenin with vinculin reinforces the junction in a force-dependent manner by promoting actin recruitment (Yonemura *et al*., 2010). Vinculin binding stabilizes catenin in an intermediate conformation, which allows its activity as a mechanotransducer without excessively opening it. Forces >30 pN induce vinculin dissociation and junction disassembly (Ishiyama *et al*., 2013; Yao *et al*., 2014; Maki *et al*., 2016). A recent study described the nanoscale architecture of cadherin-based cell–cell junctions (Bertocchi *et al*., 2016). Similar to the structure of focal adhesions (Kanchanawong *et al*., 2010), cell–cell junctions are divided into compartments. The cytoplasmic tails of cadherins bound by catenins are separated from the actin and actin-regulatory protein compartment by vinculin, which bridges the two compartments and separates them by ~30 nm. In this model, the conformation and position of vinculin depend on α-catenin and tension. Vinculin opening can also be induced by Abl kinase–mediated phosphorylation of Tyr-822, which can be dephosphorylated by protein tyrosine phosphatase 1B. Once open, vinculin recruits proteins such as VASP, probably promoting further actin polymerization and a feedback loop (Bertocchi *et al*., 2016; Figure 2).

Ultimately, α-catenin and vinculin cooperate to link cadherins and actin and allow a proper force response and junction reinforcement over time (le Duc *et al*., 2010; Borghi *et al*., 2012; Thomas *et al*., 2013; Figure 2). Defects in the connection to actin impair cell coordination and increase migration (Strale *et al*., 2015). This is also demonstrated by the fact that endothelial cells expressing a mutant α-catenin (ΔVBS) that cannot recruit vinculin show defects in junction reinforcement and mechanosensing (Twiss *et al*., 2012). The importance of the α-catenin–vinculin modulus in mechanotransduction has also been confirmed in vivo in *Drosophila* (Desai *et al*., 2013; Jurado *et al*., 2016) and zebrafish (Han *et al*., 2016). Although most reports focused on the α-catenin and vinculin modules in mechanotransduction, recent work in endothelial cells suggests a possible role for other proteins, such as zyxin, VASP, and testin, in the mechanical responses of adherens junctions (Oldenburg *et al*., 2015). In addition to actin, microtubules are probably involved in the strengthening of cadherin adhesions (Plestant *et al*., 2014) and could therefore influence mechanotransduction in adherens junctions. Moreover, the interaction of keratin intermediate filaments with desmosomal cadherin is also involved in mechanotransduction at cell–cell contacts (Weber *et al*., 2012). Finally, an elegant study in nontumorigenic breast epithelial cells (MCF10A) showed that many proteins involved in cell–cell junctions (not limited to adherens junctions) are important for force transmission (Bazellières *et al*., 2015). In the case of hepatocyte growth factor–stimulated MDCK cells plated on N-cadherin substrates, depletion of the cytoplasmic domain does not completely abolish tractions (Lee *et al*., 2016), suggesting that alternative mechanisms may also contribute.

Mechanical cross-talk between focal adhesions and cell–cell junctions

Focal adhesions and adherens junctions share similar structures and connection to the cytoskeleton, as well as similar mechanosensing mechanisms and mechanotransduction pathways (Han and de Rooij, 2016; Mui *et al*., 2016). It is thus tempting to speculate that these two major adhesive structures influence each other. Mui *et al*. (2016) addressed the most recent findings on adhesion cross-talk from the mechanical point of view. Several studies suggest that increasing forces in one compartment decreases them in the other; in other words, strong adhesion to the ECM decreases the strength of cell–cell junctions and vice versa (Guo *et al*., 2006; Wang *et al*., 2006). However, the relationship between the two structures is clearly more complex.

During development, mesenchymal cells have to adapt from a cell–cell adhesion-based system to one that relies more on cell–substrate interactions. A method has recently been developed to decouple the presentation of RGD (fibronectin) from that of HAVDI (N-cadherin) ligand peptides at different stiffnesses and assess mesenchymal stem cell mechanosensing (Cosgrove *et al*., 2016). On keeping RGD constant and presenting HAVDI, the cells read ECM stiffness as softer than it actually is. This is coupled to inhibition of Rac1, which reduces cell contractile forces and YAP nuclear localization and leads to errors in proliferation and differentiation (Cosgrove *et al*., 2016). A recent study showed that E-cadherin mediates force transmission by downstream activation of PI3K (phosphoinositide 3-kinase) in an epidermal growth factor receptor–dependent manner in epithelial cells, leading to integrin activation, probably by inside-out signaling, which in turn induces cell stiffening through ROCK and myosin II (Muhamed *et al*., 2016). The direct role of the cytoskeleton in the mechanical coupling between adherens junctions and focal adhesions is not entirely clear, and more complex biochemical signaling pathways are likely to be involved. In migrating astrocytes, which mainly express N-cadherin, loss of N-cadherin or alteration of its dynamics results in the faster and less-directed migration of the leader cells, which detach from their followers (Camand *et al.* 2012). Cadherin-mediated adherens junctions are necessary to regulate the lamellipodia activity, cell polarization, and the direction of migration (Borghi *et al*., 2010; Dupin *et al*., 2011). They control the position of focal adhesions and the recruitment of the β-PIX/Cdc42/Par6/aPKC pathway proteins that promote cell polarity and persistent migration (Dupin *et al*., 2009; Camand *et al*., 2012). In C2C12 myoblasts, expression of P-cadherin, but not other cadherins, induces efficient collective cell migration and polarization. In this system, activation of Cdc42 by the guanine nucleotide exchange factor β-PIX, recruited by P-cadherin, controls polarity and cadherin-dependent forces, leading to increased traction and intracellular stresses in the monolayer (Plutoni *et al*., 2016). The maintenance of adherens junctions between actively migrating cells is crucial for the collective behavior. In astrocytes, as well as in endothelial cells or fibroblasts, adherens junctions located on lateral contacts dynamically flow backward during collective migration (Peglion *et al*., 2014). This ensures that cells keep stable yet malleable interactions as they migrate through a complex environment. Given that lateral adherens junctions link the actin transverse arcs of adjacent cells, they also likely contribute to the coordination of the actin retrograde flow between cells migrating next to each other (Etienne-Manneville, 2014). It will be interesting to test whether the retrograde flow of adherens junctions is involved in the transmission of forces through the monolayer.

The cross-talk between focal adhesions and adherens junctions is bidirectional. The ECM also affects the localization and the forces exerted on cell–cell junctions. The physical proximity between ECM and junctions results in higher intercellular and intracellular forces, which control the position of the junctions (Tseng *et al*., 2012), supporting the fact that integrins and ECM regulate cell–cell adhesions (Marsden and DeSimone, 2003; De Rooij *et al*., 2005). This phenomenon may explain how durotaxis can be acquired during the collective migration of cells that do not normally durotax (Sunyer *et al*., 2016). Leader cells sense substrate rigidity and communicate mechanical information to their followers through actomyosin contractility. The efficiency of this mechanical signal decays over large distances in a stiffness-dependent manner (Ng *et al*., 2012). Changes in substrate rigidity modulate

forces at the level of cell–cell junctions, demonstrating that tension at focal adhesions correlates with tension at junctions (Maruthamuthu *et al.*, 2011). During convergent extension movements—for instance, during *Xenopus* development—β_1 integrin modulates cell–cell adhesion. Blocking fibronectin or β_1 integrins alters cadherin-mediated adhesion, aggregation, cell intercalation, and axial extension during gastrulation (Marsden and DeSimone, 2003).

CONCLUSIONS

Many open questions remain to be answered in the expanding field of mechanobiology and migration. First, reports have concentrated on proteins that act as mechanosensors by stretching and allowing the binding of other binding partners. It will be crucial to understand whether stretching of proteins can also induce enzymatic activity in addition to the unmasking of protein-binding sites. Stretching might not be limited to protein structure but could also be related to the deformation of a membrane (e.g., pulling forces, curved membranes, or protrusions), which is especially crucial during migration. A recent study describes cadherin fingers—polarized VE-cadherin–rich protrusions between leaders and followers—during endothelial migration (Hayer *et al.*, 2016). These fingers are formed by convex curved membranes that recruit curvature-sensing proteins that might induce specific signaling pathways. The primary candidates are BAR proteins, which contain domains for reading membrane curvatures and are likely to be essential players in mechanosensing (McMahon and Boucrot, 2015). Much work still needs to be done to better understand the molecular mechanisms involved in mechanotransduction and the coupling between mechanotransduction sites. More attention will have to be devoted to understanding how the cytoskeleton—not only actin, but also microtubules, intermediate filaments, and septins—regulates mechanotransduction in migration. It is crucial to decipher which GTPases affect the cytoskeleton during mechanosensing. How exactly does a cell integrate information from both junctions and focal adhesions? Mechanically it is the same type of signal (a force), but biochemically, different signaling pathways are involved. From a biological point of view, adherens junctions and focal adhesions share similar molecular organization and common mechanosensing mechanisms but differ in their downstream signaling (Han and de Rooij, 2016). Key questions are whether and when one type of adhesion site predominates over the other, although it is probable that the two systems form a feedback loop. Finally, many different physical parameters other than substrate rigidity can affect migration. These include substrate topography, porosity, elasticity, and other physical constraints (Nelson and Tien, 2006; Liu *et al.*, 2015b). There are influences of both nanoscale and microscale cues, although the microscale geometric cues tend to dominate (Nam *et al.*, 2016). How these physical properties are sensed by cells and affect mechanotransduction to control cell migration needs to be further investigated. More generally, we do not understand how cells process the multiple physical inputs in a robust and coherent manner, clearly pointing to the need for a systems-level investigation of mechanobiology.

The majority of reports have given information on in vitro conditions. With the advent of new technologies and intravital imaging, studies will focus on the in vivo situation during morphogenesis and pathological conditions. Some studies have already started to describe what happens in vivo during migration (Koser *et al.*, 2016) or fibrosis (Kai *et al.*, 2016). A key question to answer is whether mechanobiological signals and cues are druggable. For example, during fibrosis or tumor growth and invasion, modifying the mechanobiological properties of the cell or its surrounding could be a valid treatment option that has not yet been approached.

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