Minireview

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Integrins in Mechanotransduction*

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Mechanical forces are crucial to the regulation of cell and tissue morphology and function. At the cellular level, forces influence cytoskeletal organization, gene expression, proliferation, and survival. Integrin-mediated adhesions are intrinsically mechanosensitive and a large body of data implicates integrins in sensing mechanical forces. We review the relationship between integrins and mechanical forces, the role of integrins in cellular responses to stretch and fluid flow, and propose that some of these events are mechanistically related.

Mechanical forces are important regulators of cell and organism physiology. Control by physical forces is most apparent in blood pressure regulation, vascular responses to fluid shear stress, remodeling of bone, maintenance of muscle, and perception of touch and sound (1–3). Responses of cells to mechanical forces may also contribute to pathological states such as cardiac hypertrophy (4) and atherosclerosis (5). However, cell growth, migration, and gene expression are strongly influenced by mechanical variables in most if not all cell types (6), indicating that mechanosensitivity is broadly expressed.

Integrins, as the main receptors that connect the cytoskeleton to the extracellular matrix (ECM),[1] have an intimate relationship to force. Integrins transmit mechanical stresses across the plasma membrane; thus, tractional forces developed in the cytoskeleton are conveyed to the ECM through the integrins, as are stresses applied to cells from the ECM (6). Because integrins also regulate signaling pathways (7), they are positioned to transduce physical forces into chemical signals as well.

Current evidence makes a strong case for a bidirectional relationship between integrin-mediated adhesion and mechanical forces. Cells exert tractional forces on the substratum to which they are attached through adhesive structures such as focal adhesions (FA) and focal complexes (FC) (8, 9). Conversely, formation of these structures requires tension generated by actomyosin within the cell and resisted by a substratum of sufficient stiffness (10, 11). These regulatory arrows, pointed in opposite directions, create opportunities for regulatory loops that may guide migration, matrix assembly, and tissue organization.

Our goal is to review what is known about integrins in mechanotransduction. We will consider formation of normal adhesions as a mechanically sensitive system, the responses of cells to externally applied strains, and the responses of cell to fluid flow. Integrins are strongly implicated in all three; thus, possible connections between these systems will be explored and a unifying hypothesis offered.

Force and Adhesion Formation

The earliest interactions between integrins and their matrix ligands occur irrespective of force (12), but following initial ligation, integrins attach to the actin cytoskeleton, inducing a 2-pN talin-dependent increase in adhesion strength (13). These early adhesions initiate signals that include activation of Rac and Cdc42, which then induce the formation of lamellipodia and filopodia, respectively, and progression of early adhesions into FC (14). Transition from early adhesions to FC is marked by the recruitment of paxillin, phosphoproteins, and vinculin (12, 15). Vinculin levels within adhesions correlate linearly with tractional force (16). FC exert forces between 1 and 3 nN/μm^2, which are comparable to the 0.8–0.9 nN/μm^2 tractional force exerted by the lamellipodia (12). Somewhat at odds with these results, FC were reported to generate stronger traction forces in the leading edge of migrating cells than did large FA generate elsewhere (17). The reasons for this discrepancy are unknown, but all studies agree that FC exert significant forces on the substratum. Importantly, laser trapping studies using beads coated with fibronectin fragments showed that recruitment of vinculin required development of tension between the bead and the cell, which is linked to adhesion strengthening or adhesion reinforcement (12). Furthermore, loss of cytoskeletal tension results in a rapid dissociation of vinculin from FC, suggesting that force is required for both FC development and maintenance (12, 16, 18). Thus, FC both exert and require tension for their formation and stabilization.

FC are precursors to FA (18), which are larger, elongated structures that form in response to Rho activation. They require increases in cellular contractility (10) mediated by the Rho effector Rho kinase, which induces increased phosphorylation of myosin light chain. The increase in force at adhesion sites results in an increase in the density of integrins, the recruitment of adhesion structural proteins, and the elongation of the adhesion site in the direction of force (16, 19, 20). Rho activation and increased contractility also induces assembly of fibrillar adhesions and fibronectin matrix (21–23). Matrix assembly in response to force may therefore contribute to increased integrin density and signaling. Indeed, a ligand density of 1 fmol of RGD ligands/cm^2 supported cell spreading, but FA formation required 10-fold more (24), suggesting that tension-dependent matrix assembly may be important. FA produce forces in the neighborhood of a few nanonewtons/μm^2 (16, 25) and require surfaces that are sufficiently stiff to support this tension (11). Thus, FA as well as FC both transmit and require tension. Importantly, outcomes are similar whether forces are generated by the cell or applied externally (12, 20).

FA remodeling also occurs in a tension-dependent manner (19, 23, 26, 27). Under some conditions, FA proteins labeled with green fluorescent protein appear to "slide" centripetally, in the direction of tension. This effect is due to increased assembly at the front and increased disassembly at the rear of each adhesion and appears to be tension-dependent because it is prevented by inhibitors of contraction (19). FA are generally linked by actin stress fibers that are in a state of balanced isometric contraction; thus, tension pulls FA toward the center of the cell. In stationary cells, all adhesions consequently move toward the cell center. However, in polarized, migrating cells, adhesions at the front of the cell remain fixed, whereas adhesions at the rear of the cell tend to slide (26), indicating the existence of additional mechanisms that modulate this process.

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[1] The abbreviations used are: ECM, extracellular matrix; FA, focal adhesion(s); FAK, focal adhesion kinase; FC, focal complex(es); N, newton; MAP, mitogen-activated protein; ERK, extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinase; EC, endothelial cell.

Cell proliferation has long been recognized to require cell spreading and exertion of force on the ECM, but the mechanisms that mediate effects on growth have been poorly understood (6, 28). Recent work has shown that integrin clustering in FA in response to force generation is required for sustained MAP kinase activation in response to growth factors (29). Artificially clustering integrins with antibodies relieves the requirement for actomyosin-dependent tension, which strongly suggests that the FA itself is the key site of mechanotransduction.

Because migration requires that cells exert directional forces on their surroundings, it is not surprising that mechanical forces also regulate cell migration. Cells grown on flexible substrates show enhanced rates of cell migration compared with rigid substrates (11). On matrices that have boundaries between regions of different elasticities, cells migrate toward areas of higher substrate rigidity, a process termed durotaxis (30). This effect requires expression of focal adhesion kinase (FAK) suggesting that this molecule is involved in sensing forces (31). FAK is well known to respond to integrin clustering and FA formation by autophosphorylation and activation (32). Interestingly, FAK phosphorylation on a specific site, tyrosine 397, is sensitive to the tethering of integrins to a rigid substratum, whereas clustering alone regulates phosphorylation of other sites (33). As FAK is implicated in the regulation of both Rho (34) and Rac (35), FAK activity might control cell movement in durotaxis. When binding of proteins from cell lysates to isolated, detergent-insoluble cytoskeletons was assayed, stretching of the cytoskeletons increased binding of FAK, paxillin, and p130^{cas} (36). Thus, FAK appears to be a key component of the mechanotransduction apparatus, and both FAK and its interacting proteins are candidate transducers. However, the functional importance of FAK tyrosine 397 phosphorylation in durotaxis is unclear as durotaxis was seen in FAK$^{-/-}$ cells reconstituted with nonphosphorylatable Y397F FAK (31).

Tyrosine phosphatases have also been implicated in force-dependent adhesion reinforcement. Adhesion reinforcement in response to a restraining force applied to fibronectin-coated beads was inhibited by the tyrosine phosphatase inhibitor phenyl arsine oxide (37). Adhesion reinforcement through integrin $\alpha_v\beta_3$ involves the sequential activation of receptor protein phosphatase α and Fyn (38). The phosphatase activity of SHP-2 enhances the focal complex strengthening by inhibiting FAK-induced phosphorylation and inactivation of the cytoskeletal linker α-actinin (38).

Taken together, the above discussion suggests two likely mechanisms for mechanotransduction within focal adhesions. One is that force applied to integrins results in increased clustering, perhaps as a result of increased actin and myosin recruitment and cytoskeletal assembly (10). Increased fibronectin fibril assembly in response to tension could increase the density of integrin binding sites and therefore contribute to increased receptor density. This mechanism would give rise to increased integrin signaling and is also consistent with the key role of integrin clustering in growth control (29). A second possibility is that tension alters the conformation of certain force-sensitive components of the FA to induce new binding interactions or direct modulation of enzymatic activity. A comparable effect has been demonstrated for fibronectin, providing one mechanism for force-dependent matrix assembly (21). These conformation changes would result in phosphatase-dependent activation of tyrosine kinases such as FAK to mediate mechanotransduction. Identification of such force-dependent interactions is therefore an important goal. These two mechanisms are not mutually exclusive and could function cooperatively.

Responses of Cells to Externally Applied Strain

Analyses of mechanotransduction *in vitro* are generally performed by subjecting cells adhered to elastic substrata to either a single round of increased strain, so-called static stretch, or repeated cycles of positive and negative strain, so-called cyclic stretch. These stimuli are used as models for pressure-induced cardiac hypertrophy and vascular hypertension. Classical studies of cellular responses to mechanical forces have demonstrated that fibroblasts, smooth muscle cells, and cardiac myocytes orient in response to cyclic stretch, although the direction of alignment can be either parallel or perpendicular to the direction of stretch depending on the cell type (3, 4). Externally applied strain also influences cell growth and survival (4, 39, 40). In all of the *in vitro* systems, forces are by definition transmitted through cell contacts with the substratum, thereby implicating integrins in mechanotransduction.

Further evidence for the involvement of integrins comes from effects of strain on focal adhesion signaling. Cyclic strain induces tyrosine phosphorylation of the focal adhesion proteins FAK, paxillin, and p130^{cas} (41, 42), events that appear to be mediated by stretch-induced activation of c-Src (42). The phosphorylation of FAK is critical to stretch-induced extracellular signal-regulated kinase (ERK) and p38 activation (43, 44). Thus, an important subset of mechanotransduction events occurs within focal adhesions.

Some responses to strain depend on the specific ECM to which cells are adhered (Table I). Static biaxial stretch of cardiac fibroblasts activated the MAP kinase pathways, ERK2 and c-Jun N-terminal kinase (JNK1) in an ECM-specific manner (45). ERK2 was stimulated only in cells plated on fibronectin; JNK1 was activated on fibronectin, vitronectin, or laminin; and cells on collagen did not activate any of these MAP kinases. In cardiac myocytes, mechanical stretch also activated p38 MAP kinase (39), and this effect is mediated by a pathway involving integrins, FAK, Src, and Ras (44). In vascular smooth muscle cells, cyclic strain stimulated mitogenesis through integrin $\alpha_v\beta_3$-dependent release of platelet-derived growth factor (46). Cyclic stretch of vascular smooth muscle cells increased apoptosis of cells on collagen I, but not on other matrixes, and this effect was mediated by a pathway involving Rac, p38 MAP kinase, and p53 (40). Smooth muscle contraction was inhibited by brief pretreatment with RGD peptides that bind $\alpha_v\beta_3$ and $\alpha_5\beta_1$ integrins (47). Whether these peptides disrupt existing integrin-ligand bonds in the short time of treatment, act as positive stimulators of integrin signals, or interfere with integrin dynamics is unclear. In many cases, these effects are consistent with known specific signaling properties of individual integrins (7). The ECM/integrin specificity of these responses provides some of the best evidence that integrins participate in mechanotransduction.

Tension transmitted through integrins can also inhibit signaling. Stretching cells resulted in deactivation of Rac, whereas Rho activity was unaffected (48). Another study demonstrated strain inhibition of membrane association of Rho and Rac, which was dependent on microtubule polymerization (49). Although the effects on Rac in these two studies were consistent, the divergent effects on Rho remain to be explained. Uniaxial stretch suppressed Rac activity only in the regions of the membrane that experienced tangential strain, *i.e.* along cell edges that are lengthened (48). Endogenous tension induced by Rho and myosin similarly inhibited Rac activity in a vectorial manner, an effect that appears to contribute to cytoskeletal alignment and polarity during migration (50). Thus, Rac could play an essential role in mechanotransduction in moving cells.

The simplest explanation for the involvement of integrins in cellular responses to strain is that externally applied deformations modify the balance of forces within focal adhesions and the cytoskeleton. Thus, mechanisms of transduction involving changes in integrin clustering or opening of cryptic sites in FA molecules are similar to events during normal cell adhesion, spreading, and migration. This hypothesis may explain the wide distribution of mechanical sensitivity among many cell types. For instance, the effects of tension on directional FA remodeling (19, 26) may contribute to the alignment of cells in response to strain. It is likely, however, that additional, perhaps cell type-specific mechanisms mediate some responses.

Responses to Fluid Shear Stress

Fluid shear stress, the frictional force of flowing blood upon the endothelium, is an important regulator of vascular tone, arterial remodeling, development of atherosclerosis (2), and cardiac embryogenesis (51). Endothelial cell responses to shear include activation of ion currents, many intracellular signaling pathways, alignment of the cells and cytoskeleton in the direction of flow, and changes in gene expression and cell function (Table II). Cells must be anchored to the underlying subendothelial ECM to resist being dislodged by flow, implying a necessary role in maintaining the physical integrity of the tissue and a possible role for integrins in mechanotransduction.

TABLE I
Integrin-dependent responses to strain

We list only those events induced by externally applied strain in which integrins or known integrin-dependent pathways have been implicated. We do not mean to exclude other responses to strain for which there is no clear evidence regarding integrin dependence. In no case has a mechanism of signal transduction been elucidated at the level of the integrins.

Cell type	Proximal event	Downstream events
Vascular smooth muscle	$\alpha_v\beta_3$-dependent PDGF[a] secretion (46)	Proliferation
	Collagen-specific activation of p38 (40)	Apoptosis
Cardiac myocytes	Unknown (3)	Alignment (parallel)
	Src-dependent activation of FAK (44)	Activation of p38 and ERK; hypertrophy
Endothelial cells	Src-dependent phosphorylation of FAK and paxillin (41)	Alignment (perpendicular) cytoskeletal organization
Fibroblasts	Src-dependent activation of FAK, paxillin, and p130^{cas} (42)	Alignment (perpendicular)
	ECM-specific activation of ERK and JNK (45)	Not determined but ECM remodeling suggested

[a] Platelet-derived growth factor.

TABLE II
Integrin-dependent responses to fluid shear stress

We list only those events induced by shear stress in which integrins or known integrin-dependent pathways have been implicated.

Mechanism	Signaling pathway	Downstream events
Activation of integrins induces their binding to subendothelial ECM	Rho (57)	Transient actin stress fiber disassembly
	Rac (68)	Directionality of actin, activation of NFκB
	Cdc42 (67)	MTOC orientation
	Shc (66)	Unknown
Not determined	FAK (58)	Cytoskeleton, cell migration
	p130^{cas} (60)	Cytoskeleton, cell migration
	SREBP[a] (63)	Cholesterol transport and metabolism

[a] Sterol regulatory element-binding protein.

One model for the role of integrins in shear stress signaling is that tension is transmitted from the apical surface through the cytoskeleton to the integrins, which then experience changes in tension (2). The main observation supporting this model is that flow induces rapid remodeling of FA (52). Other data implicating integrins in shear stress signaling include the observation that RGD peptides that inhibit the binding of integrins $\alpha_v\beta_3$ and $\alpha_5\beta_1$ to their ligands block the shear-induced vasodilation of coronary arteries *in vivo* (53). One appealing aspect of this model is that it avoids difficulties posed by the endothelial glycocalyx. The endothelium has an apical glycocalyx a few hundred microns thick that forms a barrier to fluid flow (54, 55). Thus, the apical surface *per se* experiences negligible shear stress. The proteins that anchor the carbohydrate chains experience shear and therefore could conceivably be mechanosensors, although there are no data to support this idea. Alternatively, surface glycoproteins could transmit forces through the cytoskeleton to integrins or cell-cell adhesion receptors that serve as anchorage points that resist the flow. Thus, the notion that integrins or junctional receptors are shear stress sensors is consistent with the properties of the glycocalyx.

Shear stress stimulates many of the pathways that are regulated by integrin binding to ECM. Both β_1-activating antibody and shear stress elicit similar endothelial cell activation of MAP kinase (56) and similar changes in Rho activity (57). Shear stress triggers activation of FAK and c-Src (58, 59), tyrosine phosphorylation of p130^{cas}, and its association with Crk (60), all of which are characteristic of integrin signaling. In several cases, integrin antagonists block shear stress signaling. Antibody to $\alpha_v\beta_3$ blocked shear stress activation of ERK, JNK, and NFκB (61, 62), whereas an anti-β_1-blocking antibody prevented activation of sterol regulatory element-binding proteins by shear stress (63). Blocking integrins with an RGD peptide abolishes the antiapoptotic effect of shear stress (64) and the shear stress-induced secretion of basic fibroblast growth factor (65). Shear stress triggered association of integrins with Shc, and this interaction was ECM-specific in that only those integrins that could bind to the available matrix interacted with Shc (66).

Brief treatment of endothelial monolayers with antibodies to the relevant ECM proteins that inhibited new integrin binding to the matrix without disrupting existing adhesions prevented Shc association with integrins (66). This result suggested that dynamic interactions between integrins and the ECM contribute to shear stress signaling and that changes in integrin activation or ligand binding could be involved. Increased binding of the monovalent Fab fragment, WOW-1, that reacts selectively with activated $\alpha_v\beta_3$, directly demonstrated a rapid increase in integrin affinity following shear (57). At later times, endothelial monolayers showed increased staining with antibodies that recognize the ligand-occupied conformations of β_1 and β_3 integrins. Blocking this *de novo* occupancy inhibited several downstream responses, including regulation of Rho, Rac, and Cdc42 (57, 67, 68) and the above mentioned interaction of integrins with Shc (66). The Rho family GTPases in turn mediated alignment of the actin and tubulin cytoskeletons and activation of NFκB and its target genes. Integrin activation and downstream signaling is therefore central to the endothelial-specific shear stress response.

Although the apical membrane of ECs is directly exposed to flow, WOW-1 immunostaining was seen only at the basal side of the sheared ECs (57), indicating selective activation of integrins on the abluminal membrane. The restriction of activation to the basal surface may be a general feature of EC behavior rather than a specific consequence of shear stress signaling, as active integrins on the luminal surface of endothelia would be potentially thrombogenic. It is noteworthy, however, that neither $\alpha_v\beta_3$ activation nor the initial increase in integrin occupancy seen by antibody staining showed indications of directionality. By contrast, remodeling of FA by shear is biased for assembly toward the downstream side relative to the direction of flow (52). Activation of Rac and Cdc42 downstream of integrins also shows polarization toward the downstream edge of the cell (67, 68). Flow may therefore affect FA remodeling in a directional manner that is distinct from the overall increases in affinity and ligand binding.

The actual forces exerted on cells by fluid flow in these experiments are low compared with the FA traction forces. If forces were distributed evenly, typical experimental shear stresses of 10 dynes/cm^2 (or 1 pN/μm^2) are 1000–5000 times lower than typical traction forces (1–5 nN/μm^2). Cell-matrix adhesions occupy only a fraction (typically on the order of 10%) of the total ventral surface, so if forces are efficiently transmitted, FA would feel ~10× larger stresses. Additionally, deformations of the cytoskeleton due to fluid flow are not distributed evenly throughout the cell; small regions show higher than average displacement, indicating the existence of "strain focusing" in which certain regions absorb more of the applied force (69). But even taking these factors into account, flow would exert at most a few percent of the tractional tension from actomyosin. These considerations make it less likely that FA themselves are the sites where shear forces that trigger activation of integrins are initially transduced.

Hypothesis and Conclusions

We hypothesize that the intrinsic mechanosensitivity of integrin-mediated adhesions mediates a subset of cellular responses to externally applied mechanical forces. Indeed, many of the signals triggered by stretch are consistent with known effects on FA. Increased tension within adhesions can trigger increased integrin clustering and FAK phosphorylation, which could mediate effects of strain on ERK and JNK. In some cases, these responses to strain are ECM-specific in a manner that is consistent with the known signaling properties of the relevant integrins. We must keep in mind that there are also cell type-specific responses to forces, such as neuronal responses to touch and sound, and growth and gene expression in smooth muscle and cardiac muscle. In some cases, such as release of growth factors by smooth muscle cells in response to stretch or endothelial cells in response to shear (46, 65), these cell type-restricted mechanisms may also involve integrins. However, in many cases, integrin-independent pathways such as specific stretch-activated channels appear to be involved (3).

For fluid shear stress, we hypothesize that integrins may be involved in two distinct ways. Integrins in endothelial cells appear to be activated by fluid flow, resulting in a spatially uniform increase in cell-ECM adhesion (57, 66). By contrast, FA dynamics in endothelial cells under shear are directional, preferentially remodeling in the downstream direction (52). As discussed above, FA show tension-dependent remodeling in which they appear to slide toward the center of the cell. Mogilner and colleagues[2] hypothesize that even though the total force of shear may be relatively low, this force would add vectorially to the centripetal tension from the actin stress fibers. Thus shear stress would decrease tension at the downstream side of the cell and increase it on the upstream side. Shear may therefore create a significant bias, altering net force balance between upstream and downstream, resulting in directional remodeling of FA through the normal tension-dependent mechanisms. This effect would be distinct from but superimposed on the activation-ligation sequence described above.

Fundamental questions about mechanotransduction within integrin-mediated adhesions remain unresolved. The detailed mechanisms by which forces are converted to chemical signals and cytoskeletal rearrangements are subjects of intense interest. Whatever the answers, we suggest that continued study of integrin dynamics and force-dependent effects are likely to shed light on diverse phenomena such as endothelial responses to shear stress, regulation of vascular tone, cardiac hypertrophy and failure, and regulation of growth and gene expression in many tissues.

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