PERSPECTIVES

OPINION

Mechanotransduction at a distance: mechanically coupling the extracellular matrix with the nucleus

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Abstract | Research in cellular mechanotransduction often focuses on how extracellular physical forces are converted into chemical signals at the cell surface. However, mechanical forces that are exerted on surface-adhesion receptors, such as integrins and cadherins, are also channelled along cytoskeletal filaments and concentrated at distant sites in the cytoplasm and nucleus. Here, we explore the molecular mechanisms by which forces might act at a distance to induce mechanochemical conversion in the nucleus and alter gene activities.

Mechanical forces influence the growth and shape of virtually every tissue and organ in our bodies. However, little is known about the mechanisms by which individual cells sense these mechanical signals and transduce them into changes in intracellular biochemistry and gene expression — a process that is known as mechanotransduction. It is commonly known in the field that when a physical force is applied to the cell surface, it distorts the membrane cortex and then quickly dissipates into the cytoplasm[1]. Therefore, mechanochemical conversion must only occur in or near these sites on the cell surface. As expected, surface-membrane receptors — such as integrins and cadherins, which mediate cell adhesion to extracellular matrix (ECM) scaffolds and to neighbouring cells, respectively — have a central role in mechanotransduction[2].

Application of a mechanical stimulus, such as fluid shear stress, to the cell surface activates mechanosensitive ion channels, heterotrimeric G proteins, protein kinases and other membrane-associated signal-transduction molecules; these trigger downstream signalling cascades that lead to force-dependent changes in gene expression[3] (see the Review by Hahn and Schwartz[103] in this issue). But these responses are usually mediated by the distortion of specific adhesion receptors that link to the cytoskeleton, rather than by deformation of the lipid bilayer alone. For example, endothelial cells sense fluid shear through a cell–cell junctional complex that contains vascular endothelial (VE)-cadherin and platelet/endothelial cell-adhesion molecule 1 (PECAM1), in addition to integrin activation[4]. Mechanical forces that are applied directly to integrins using micromanipulation or magnetic techniques also alter ion flux through stress-activated ion channels[5,6] (see the Review by Chalfie[104] in this issue), G-protein-dependent cyclic AMP signalling[7], binding kinetics of structural molecules[8] (for example, zyxin), protein-translation-complex formation[9] and activities of protein kinases, such as p130CAS (also known as BCAR1) and Src[3,10]. Thus, surface-adhesion receptors and focal adhesion proteins have a key role in mechanical signalling in various cell types, and the field of mechanotransduction focuses mainly on the cell surface[1]. But is this the whole story?

Mechanical stresses will dissipate quickly after passing through the plasma membrane. Therefore, it makes sense to focus on surface signalling if one views the cell as an elastic membrane that surrounds a viscous or viscoelastic cytoplasm that is filled with cytoskeletal filaments that continuously depolymerize and repolymerize[11–13] (BOX 1). However, an alternative model of cell structure suggests that this dynamically remodelling cytoskeleton is also a 'hard-wired' tensegrity network that can promote coordinated changes in cell, cytoskeletal and nuclear structure in response to mechanical distortion[14] (FIG. 1a). (Herein, the term hard-wired refers to cytoskeletal structures that are stable enough as interconnected units to resist mechanical stresses and thereby maintain shape stability, even though they undergo continuous dynamic remodelling at the molecular level.) This model takes into account the observation that individual cytoskeletal filaments can bear significant tensile and compressive loads in living cells because their structural integrity is maintained for longer than the turnover time of individual protein monomers[15–17].

Key to the cellular tensegrity model is the idea that overall cell-shape stability and long-distance force transfer are governed by the level of isometric tension, or 'prestress', in the cytoskeleton that is generated through the establishment of a force balance between opposing structural elements (that is, microtubules, contractile microfilaments and extracellular adhesions) (FIG. 1a). This occurs because the cell can tense, and thereby stiffen, load-bearing cytoskeletal filaments relative to surrounding regions of the cytoplasm[14,18,19]. In this type of prestressed inhomogeneous solid structure, mechanical signals propagate through the cytoplasm much quicker than diffusion-based chemical signals (BOX 1) (see the Review by Jaalouk and Lammerding[105] in this issue). However, the viscoelastic properties of the cytosol that permeates this prestressed network can also influence stress propagation to distant cytoplasmic sites at slower timescales, and non-covalent protein–protein interactions in the cytoplasm might govern time-dependent stiffening and inelastic energy dissipation in the cell[20].

Because integrins and cadherins are physically coupled to cytoskeletal filament networks that, in turn, link to nuclear scaffolds, nucleoli, chromatin and DNA inside the nucleus, mechanical forces that are applied at the surface do more than activate membrane-signalling events — they also promote structural rearrangements deep in the cytoplasm and nucleus[21,22]. This raises the intriguing possibility that mechanical forces applied at the cell surface might act at a distance to promote mechanochemical conversion in the nucleus[23], in addition

Box 1 | **Mechanotransduction on the fast track**

Stress-wave propagation predicts rapid signal transduction in the cytoplasm
A small chemical, such as calcium (which has a diffusion coefficient of <100 μm² per s), that is moving by diffusion takes ~25 s to reach a distance of 50 μm in the cytoplasm, and a molecule that is transported by a motor-based translocation mechanism in the cytoplasm takes ~50 s (at a velocity of ~1 μm per s) to migrate the same distance. By contrast, mechanical stresses that are propagated along tensed cytoskeletal filaments move the same distance in ~2 μs (at a velocity of ~30 m per s).

Only prestressed cell models predict long-distance force propagation
The homogeneous solid (elastic or viscoelastic) model. Physiological local loads of <100 Pa, or surface local deformation of <0.5 μm, decay to insignificant magnitudes within 10 μm of the site of force application in the cell. This is because induced stress or strain decays according to the equation $1/R^2$, of which R is the distance from the site of mechanical load application.

The prestressed inhomogeneous solid (tensegrity) model. Induced deformation that is produced by physiological load application at the cell surface is approximately ten times larger than that predicted by the homogeneous solid model. Forces applied in this manner can lead to physiologically relevant distortion of molecular structures that are ~100 μm away, inside the cytoplasm and nucleus.

Intracellular stiffness differentials are required for distant force propagation
When all stress-supporting elements in a structure have the same stiffness, as in the homogeneous elastic or viscoelastic cell models, stress decays rapidly as the reciprocal of the distance squared (as according to St Venant's principle) because the input mechanical energy must be equally distributed among all elements. By contrast, in a prestressed inhomogeneous material (that is, a tensegrity cell model), the stresses are preferentially channelled over structural elements that are stiffened owing to prestress and, hence, they decay at a slower rate than forces that are transferred over soft elements in the same structure[18]. High nuclear stiffness relative to cytoplasmic stiffness[22,101], and the higher stiffness of some intranuclear structures, might also facilitate long-distance force propagation in the nucleus, as stresses tend to dissipate less in stiffer structures. The ability of the prestressed structure to concentrate and focus stresses facilitates longer distance force propagation compared with a non-prestressed homogeneous structure with the same total input mechanical energy. The higher the ratio of the prestress, and thus the higher the modulus of stiff elements (that is, tensed bundles of microfilaments or intermediate filaments) compared with the modulus of more flexible portions of the cytoplasm and softer cytoskeleton, the further the distance that the force is propagated.

to mechanochemical transduction in the cytoplasm. Such a hard-wired mechanism for direct nuclear mechanotransduction is particularly interesting because mechanical-based signal propagation is much faster than chemical-diffusion- or translocation-based signal propagation. Here, we highlight recent studies that provide direct experimental support for mechanochemical coupling between the cell surface and the nucleus and discuss potential molecular mechanisms that might mediate rapid force transmission through the cytoplasm to initiate nuclear mechanotransduction.

The hard-wired cell

Experimental studies that are designed to test predictions of the cellular tensegrity model have confirmed that when surface integrins are directly stressed by applying large forces with ligand-coated micropipettes or magnetic particles, or by physically deforming cells that are attached to flexible ECM-coated substrates, immediate force-dependent changes in internal structures, such as mitochondria and nucleoli, can be visualized deep inside the cytoskeleton and nucleus, respectively[22,24–26]. Pulling on integrins in cultured cells induces the molecular realignment of individual actin stress fibres and nucleoli, which change their positions and reorientate along the newly applied tension field lines[22] (FIG. 1b,c). Forces that are applied to integrins also induce displacements of mitochondria and nuclei up to 20 μm away from the site of force application, whereas generalized deformation of the surface bilayer — by pulling on transmembrane metabolic receptors that are not strongly connected to cytoskeletal actin bundles — only produces local effects at the cell surface[24]. Mechanical coupling between integrins and nuclei is lost when intermediate filaments are disrupted[22], and fluid shear stresses that drag endothelial cells against their fixed focal adhesions also displace intermediate filaments deep in the cytoplasm[27]. As similar mechanical coupling can be shown in membrane-permeabilized cells in the presence of ATP, which supports actomyosin-based tension generation and the maintenance of prestress in the cytoskeleton, these coordinated changes in structural elements throughout the cell, the cytoplasm and the nucleus are due to direct mechanical force transfer and not to associated chemical signalling events[28]. These findings also have physiological relevance as they can explain how mitochondria that are located far from the surface membrane on cytoplasmic microtubules can sense and respond to mechanical strain by releasing reactive oxygen species and activating signalling molecules (such as nuclear factor-κB (NF-κB) and vascular cell-adhesion molecule 1 (VCAM1)) that contribute to inflammation and atherosclerosis[29].

Recent technological developments that enable stress mapping in the cytoplasm of living cells[29,30] confirm that even small mechanical deformations of surface integrins can result in long-range force propagation, and stress concentrations can be visualized many micrometres away from sites of force application (FIG. 2a), including locations near the nucleus and at the opposite pole of the cell[30,31]. Most importantly, these mechanical signals induce rapid (<300 ms) mechano-chemical conversion, as detected by focal activation of Src kinase in regions of the cytoplasm that are distant from the site of force application (>50 μm), as well as at local sites (FIG. 2b). Strikingly, this mechanical response is 40 times faster than that induced by soluble epidermal growth factor[32], as predicted by physical models (BOX 1; FIG. 2c). Moreover, both long-range force transfer and distant mechanochemical conversion through Src can be inhibited by either disrupting the actin cytoskeleton or by dissipating cytoskeletal prestress[29–32] (FIG. 2a). Amazingly, mechanical coupling even occurs between different chromosomes (FIG. 1c; Supplementary information S1 (movie)) and between the mitotic spindle, actin microfilaments and surface integrins in dividing cells[33]; this coupling might contribute to the control of cell division orientation, as well as to the fidelity of chromosome alignment.

Physical coupling in the cytoplasm

The studies discussed above unequivocally confirm the existence of long-range force propagation in living cells. However, these studies are mostly phenomenological and the molecules that link cell-adhesion receptors to the cytoskeleton and nucleus have only recently been identified. Transmembrane integrins link the ECM to the cytoskeleton by clustering in specialized submembranous anchoring complexes (focal adhesions), in which they form molecular bridges by binding to actin-associated proteins, such as talin, vinculin, zyxin and paxillin[34] (see the Review by Geiger, Spatz and Bershasky[106]

in this issue). Certain integrin subtypes (such as α6β4 integrin) also bind directly to intermediate filaments[35]. Cadherins link to the cytoskeleton by forming junctional complexes that contain β-catenin and γ-catenin, which bind actin filaments and intermediate filaments, respectively[36]. Although highly dynamic, these molecular couplings (see below) are stable enough to function as tensed hard wires to propagate mechanical stresses from the ECM to the nucleus.

The LINC complex. Early studies revealed that the intermediate filament vimentin binds directly to the nuclear lamina protein lamin B and connects it to attachment sites on the plasma membrane of reticulocytes[37,38]. More recently, a specialized nuclear anchoring structure for cytoskeletal filaments, known as the LINC (linker of nucleoskeleton and cytoskeleton) complex, that contains nesprins, sun and lamin proteins[39–41], was identified (FIG. 3).

The largest isoforms of mammalian nesprins (nesprin 1 and nesprin 2; also known as SYNE1 and SYNE2), and the related ANC-1 in *Caenorhabditis elegans* and MSP300 in *Drosophila melanogaster*, are rod-like nuclear membrane proteins that contain an amino terminus with a conserved calponin-like actin-binding domain, a huge central spectrin-like domain, and a carboxyl-terminal KASH (klarsicht, ANC-1, SYNE1 homology) domain that mediates sun protein binding[42]. Nesprin 1 and nesprin 2 on the outer nuclear membrane connect actin microfilaments to SUN1 (also known as UNC84A) and SUN2 (also known as UNC84B) on the inner nuclear membrane; SUN1, in turn, binds to lamin A on the nuclear scaffold[39–41,43,44]. Shorter isoforms of nesprins are localized to the inner and outer nuclear membranes. These isoforms lack the actin-binding domain but might still interact with cytoskeletal components through spectrin repeats. SUN1 also connects this anchoring structure to nuclear pore complexes (NPCs) and, it might therefore mediate the mechanical coupling that has been observed between the tensed cytoskeleton and nuclear pores[45]. It is unknown, however, whether SUN1 binds nesprin 1 and 2 and the NPC simultaneously[46]. Nesprin 3, a smaller but related family member that lacks the N-terminal actin-binding domain, connects to cytoplasmic intermediate filaments by binding to plectin 1 and interacts with SUN1 and SUN2 (REFS 47,48). ANC-1 similarly tethers nuclei to the actin cytoskeleton through interactions with the sun family member UNC-84, and ANC-1 mutants have defects in nuclear positioning and nuclear anchorage[49]. ZYG-12 and UNC-83, two other proteins that only share the KASH domain with nesprins, respectively mediate tethering of centrosomes (and, hence, the microtubule cytoskeleton) to nuclei and contribute to nuclear positioning in *C. elegans* by binding to UNC-84 (REFS 50–52). Thus, the hard-wire function of these LINC proteins seems to have been conserved throughout evolution.

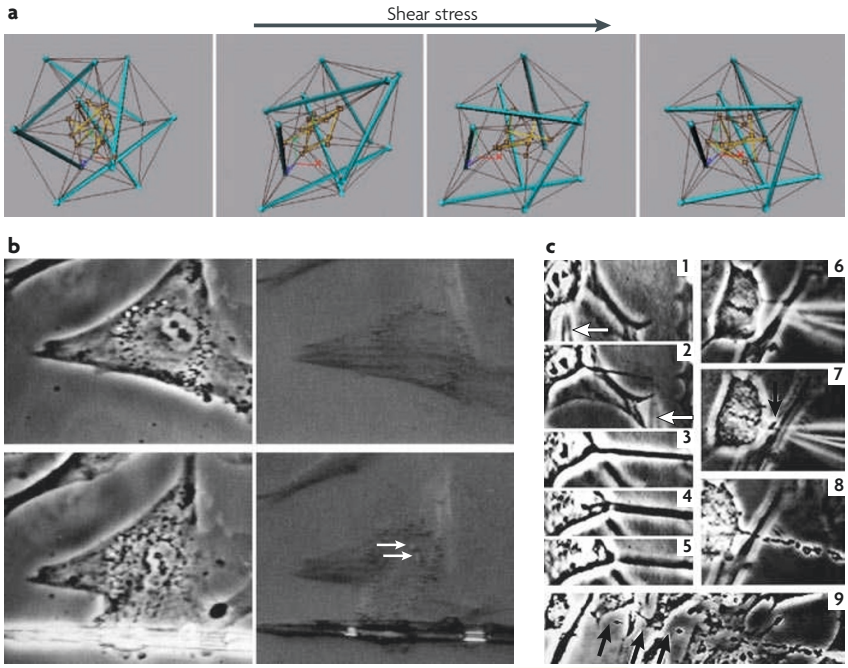

Figure 1 | **Structural connectivity and long-distance force propagation. a** | Computer simulations of a nucleated tensegrity cell model that exhibits mechanical coupling between the cell, the cytoskeleton and the nucleus. The images show the model, anchored to the bottom substrate at 2 points, before stress application (left panel), at 15 s and 37 s after stress application that is orientated to the right (middle panels) and after the stress is released (right panel). The 'cell' and 'nucleus' of the model rearrange in accordance with the stress, and recoil back to their original positions when the force is released, as observed in living cells. **b** | Phase contrast and corresponding birefringence microscopic images that show immediate molecular realignment in the cytoskeleton and nucleoli when stresses are applied to integrins. The appearance of white nucleoli in distorted cells (arrows) indicates molecular realignment in these regions. **c** | Molecular connectivity of chromosomes in interphase and mitotic cells, as revealed by inserting a microneedle tip into the nucleus and pulling out one nucleolus (panels 1–5) or chromosome (panels 6–9). This results in the progressive removal of all interphase chromatin or condensed chromosomes as if they were beads on an elastic string. White arrows indicate the needle tip and black arrows indicate the nucleolus being pulled out. Images in part **b** are reproduced, with permission, from REF. 22 © (1997) National Academy of Science. Images in part **c** are reproduced, with permission, from REF. 33 © (1997) Liss.

Lamins. Lamins A, B and C are intermediate filament-like proteins that form a molecular network or nuclear lamina on the nucleoplasmic surface of the inner nuclear membrane and are also found in the internal nuclear scaffold. Lamins have a central role in the control of nuclear organization and gene function[53]. These lamins can be divided into two subgroups: A-type lamins (lamin A and lamin C) and B-type lamins (lamin B). A- and B-type lamins have different rates of turnover in the nucleoplasm and are thought to have different structural and functional roles[53]. Cells that are deficient for A-type lamins have decreased viability, reduced expression of mechanosensitive genes and altered nuclear mechanics in response to mechanical distortion, whereas defects in lamin B1 do not produce similar effects, which suggests that the A-type lamins might have a more central role in mechanotransduction[54,55].

Lamins might connect to the genetic machinery and to DNA both directly and by binding to other nuclear proteins, including emerin and lamin B receptor (LBR)[53,56–58]. Emerin, which binds to the LINC complex through nesprins and lamins[59,60], also associates with many different regulatory proteins

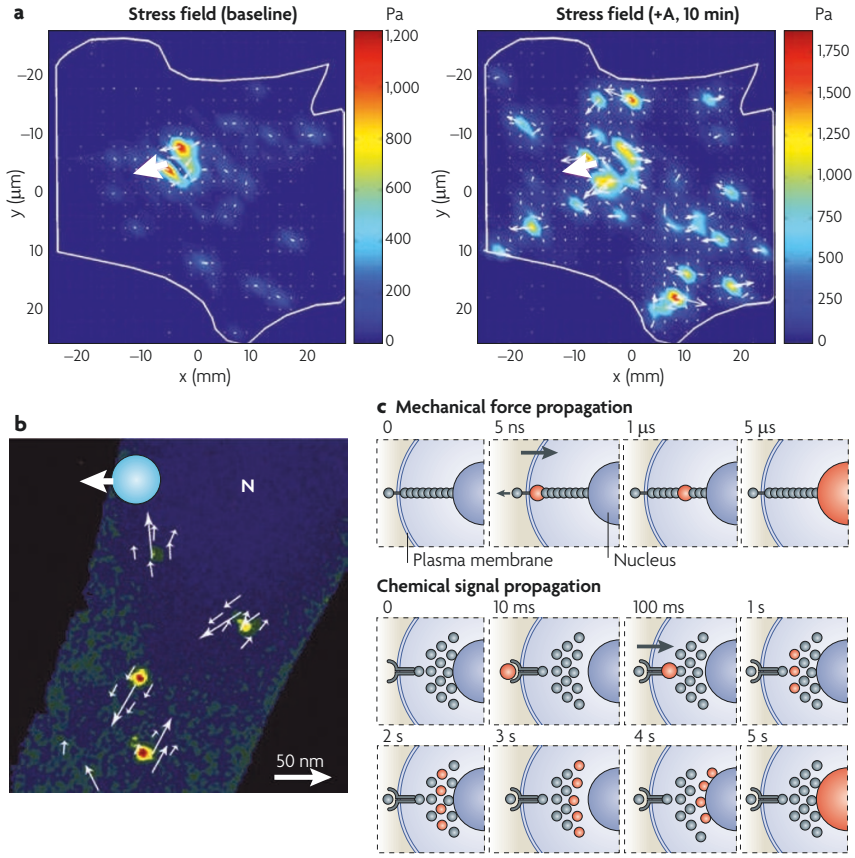

Figure 2 | **Mechanotransduction at a distance. a** | Dependence of long-distance force propagation on prestress. Two stress maps are shown of a cell that expresses a low baseline level of caldesmon (left panel), which downregulates cytoskeletal prestress without disrupting focal adhesions or stress fibres; and of the same cell after treatment with 5 μg per ml of the calcium ionophore A23187 (+A, 10 min; right panel), which inhibits caldemon and restores prestress. In these maps, applied stress is 17.5 Pa (at 0.3 Hz), the large arrow indicates the bead movement direction, small arrows indicate the relative magnitudes of stresses and red represents high stress. **b** | Rapid (<300 ms) and strong Src activation (red and yellow spots) colocalizes with regions of large microtubule deformation (small arrows). A local stress of 17.5 Pa was applied to integrins for 3 s using a 4 μm magnetic bead. The blue circle indicates the bead–cell contact area (~6 μm^2), the large arrow indicates bead movement direction and N indicates the nucleus. **c** | Comparing mechanical and chemical signal propagation. A force that is applied to cytoskeleton-linked integrins propagates into the nucleus in <5 μs (top panels). The transmitted mechanical signal is depicted as a red dot that eventually reaches the stretched nucleus. A growth-factor-triggered release of chemical signals (red dots; lower panels) propagates through receptor Tyr kinase second-messenger systems. These signals reach the nucleus in ~5 s. The small arrow indicates the direction of force application and the larger arrows indicate the direction of signal propagation across the cell membrane.

that are involved in chromatin modification, transcriptional regulation and mRNA processing, and with BAF protein (also known as BANF1), which binds directly to double-stranded DNA[56,61–63]. LBR also binds to multiple inner nuclear targets, including DNA, histone and various chromatin-associated proteins[64].

Other crucial connectors. Molecular connections between nesprin, sun and lamin proteins are crucial for the mechanical stability of the nucleus and the whole cell, as cells with impaired nesprin 1, nesprin 2 or nesprin 3 functionality exhibit decreased mechanical stiffness[65]. Moreover, stretching of rat cardiac muscle cells leads to changes in the spatial organization of the intermediate filament (desmin)–lamin network and to chromatin alterations at the nuclear envelope[66]. Again, this might have clinical relevance, as mutations of intermediate filaments (such as desmin and vimentin) that mechanically couple surface-adhesion receptors to nuclear structures through the LINC complex substantially alter cell-mechanical properties, as well as cell, tissue and organ function[67]. Conversely, mutations of lamins or emerin, as observed in patients with Emery–Dreifuss muscular dystrophy or with the premature ageing disease progeria, lead to loss of nuclear shape stability, cell structural abnormalities and eventually to death[68]. Taken together, these results suggest that physical connections between cytoskeletal filaments and the LINC complex enable the entire cell, cytoskeleton and nucleus to function as a single mechanically coupled system (FIG. 3).

Some proteins, such as lamins and matrin 3, are found in the internal nuclear scaffold or matrix that extends throughout the depth of the nucleus and orientates much of the nuclear regulatory machinery[23,69–71]. Lamins also bind a nuclear isoform of titin[72], which could potentially contribute to the nuclear structure, given that the cytoplasmic form of this large elastic protein has major effects on muscle-cell elasticity[73]. Interestingly, actin and myosin also seem to contribute to nuclear structure and nuclear functions, including chromosome movements and transcription[74–76]. Emerin and BAF connect lamins to nuclear actin[77,78], and emerin preferentially binds polymerized actin and stimulates its polymerization[77,78]. The presence of nuclear actin and myosin, and the observation that intact cytoskeletal and nucleoskeletal networks that lack membranes physically contract *in vitro* when ATP is added[28], raise the possibility that actomyosin interactions might also contribute to nuclear prestress and, hence, to the regulation of force propagation and transduction in the nucleus.

The genome itself is organized into loops (5–200 kb) and is partitioned into functional chromosome territories through the binding of nuclear matrix attachment regions (MARs), which link nuclear scaffolds to distinct DNA regions on the basis of their sequences and geometry[79]. Transcription and replication complexes might also help to tether interphase chromosomes to the nuclear matrix[80,81]. The exact composition and structure of the nuclear matrix is unknown, although in addition to lamins and matrin 3, it contains RNA and heterogeneous nuclear ribonucleoproteins that are associated with mRNA processing[79].

Genome organization and nuclear matrix composition change in response to cell and tissue differentiation and to many environmental factors[82]. Many nuclear proteins that were originally identified as DNA regulatory proteins might also have a structural role in the nucleus. For example, RUNX is both a chromatin-structure-modifying protein that is crucial for osteoblast differentiation and a

nuclear scaffolding protein that links different regions of chromosomes, thereby facilitating the combinatorial control of gene transcription[83–85]. Thus, forces that are transmitted over the LINC complex and channelled over nuclear scaffolds might be focused directly on crucial DNA regulatory enzymes and binding factors (FIG. 3).

Nuclear mechanotransduction

Because stress-induced changes in molecular shape, position or movement (for example, vibration) can alter thermodynamic and kinetic properties of load-bearing molecules[19], forces that are propagated to the nucleus over discrete cytoskeletal networks might alter molecular self-assembly events[86] and modulate nuclear biochemistry by many possible mechanisms (FIG. 4). For example, nuclear membrane distortion induced by forces that are propagated from the cell surface in spreading cells stimulates calcium entry through nuclear ion channels and induces associated gene transcription[87]. And, ion flux through nuclear membranes — as measured by a patch clamp — can be altered by modulating the actin cytoskeleton[88]. Although the molecular identity of mechanosensitive ion channels on the nuclear membrane are unknown, one can predict a mechanism by which the channel is mechanically coupled both to the mechanosensitive cytoskeleton and to nuclear scaffolds, which are approximately nine times stiffer than the cytoplasm in living cells[22]. In this scenario, pulling on the cell could distort the channel, producing channel distortion relative to the channel's stiffened nuclear attachments when the cytoskeleton is deformed; this alteration of channel conformation can then promote ion influx.

As lamin A and emerin bind transcription factors[89,90], and as emerin also interacts with splicing factors[63], forces transferred through the LINC complex to these molecules could also directly alter gene expression and protein-isoform expression through sequestration or modification of the transcription or splicing factors (FIG. 4a). As newly synthesized transcripts are processed by the pre-mRNA splicing 5′ capping and 3′ processing machinery[91], forces that are transferred to these molecules over MARs could also regulate mRNA splicing or processing[92] (FIG. 4b). For example, forces transferred to load-bearing proteins in nuclear scaffolds could potentially regulate gene activities as a result of physical unfolding of their peptide backbone, which in turn can promote binding or self-assembly of other nuclear regulatory factors. This force transfer might function analogously to the way in which stress-induced distortion of cytoskeletal titin influences the nuclear translocation of MURF2 (also known as TRIM55), which is a ligand of the transactivation domain of the serum response transcription factor SRF[93]. Additionally, stress or strain in nuclear scaffolds might change higher-order chromatin organization, thereby restricting or promoting the accessibility of transcription factors or other regulatory factors (such as DNA or RNA polymerases, topoisomerases and helicases) to specific gene sequences, which could similarly influence gene transcription[84].

As cells extend and round, nuclear pores physically expand and contract and alter their transport rates. As this occurs, nuclear pores can mediate mechanochemical conversion and control of gene activities[94]. Nuclear pores have been implicated in the control of genes that are tethered to these structures, as well as in the regulation of histone H2 ubiquitylation and mRNA transport[95]. The concentration of stresses on NPCs through transmission over the LINC complex could therefore both physically distort (for example, expand) the size of the pore (perhaps through distortion of the basket structure) and change mRNA transport, transcriptional regulation and chromatin status by deforming the shape of molecular components of the pore and altering their chemical activities (FIG. 4c). Interestingly, nuclear distortion is a prerequisite for entry into S phase during cell cycle progression, and it has been suggested that this might be due to enhanced transport of large DNA-regulatory complexes through nuclear pores[96].

Interestingly, it is possible that force transferred over nuclear scaffolds to the DNA backbone might directly alter gene function[23]. Many MARs localize to regions of destabilized DNA, in which mechanical strain can lead to melting of the double helix[79]. Stress-induced DNA melting could expose binding sites for transcriptional regulators in a similar way to which increased twisting strain in the *MYC* gene promoter induces melting of far upstream binding elements (FUSE) and thereby stimulates binding of FBP (also known as FUBP1) and FIR (also known as PUF60) transcription factors[97,98] (FIG. 4d). Intriguingly, the tissue specificity of genome

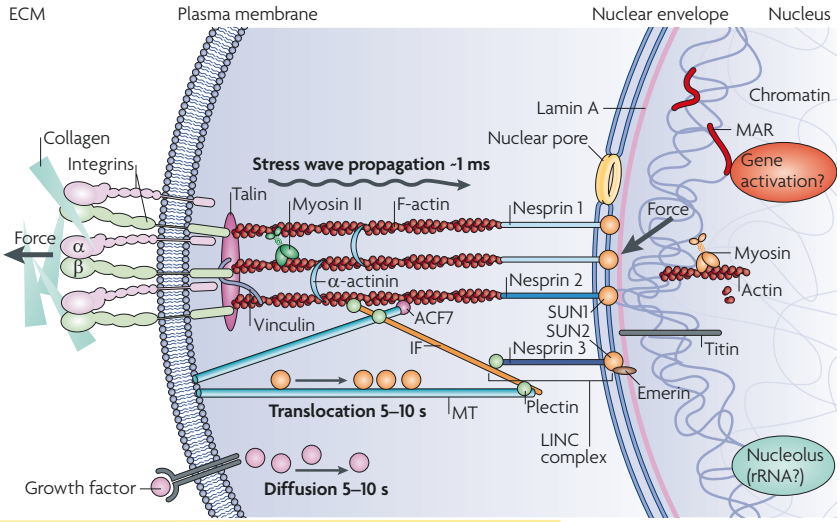

Figure 3 | **Molecular connectivity from the ECM to the nucleus.** A local force applied to integrins through the extracellular matrix (ECM) is concentrated at focal adhesions and channelled to filamentous (F)-actin, which is bundled by α-actinin and made tense by myosin II, which generates prestress. F-actins are connected to microtubules (MTs) through actin-crosslinking factor 7 (ACF7), and to intermediate filaments (IFs) through plectin 1. Plectin 1 also connects IFs with MTs and IFs with nesprin 3 on the outer nuclear membrane. Nesprin 1 and nesprin 2 connect F-actin to the inner nuclear membrane protein SUN1; nesprin 3 connects plectin 1 to SUN1 and SUN2. Owing to cytoplasmic viscoelasticity, force propagation from the ECM to the nucleus might take up to ~1 ms. The sun proteins connect to the lamins that form the lamina and nuclear scaffold, which attaches to chromatin and DNA (for example, through matrix attachment regions (MARs)). Nuclear actin and myosin[102] (and nuclear titin) might help to form the nuclear scaffold, control gene positioning and regulate nuclear prestress. The force channelled into the nuclear scaffold might directly affect gene activation within milliseconds of surface deformation. By contrast, it takes seconds for growth factors to alter nuclear functions by eliciting chemical cascades of signalling, which are mediated by motor-based translocation or chemical diffusion. LINC, linker of nucleoskeleton and cytoskeleton; rRNA, ribosomal RNA.

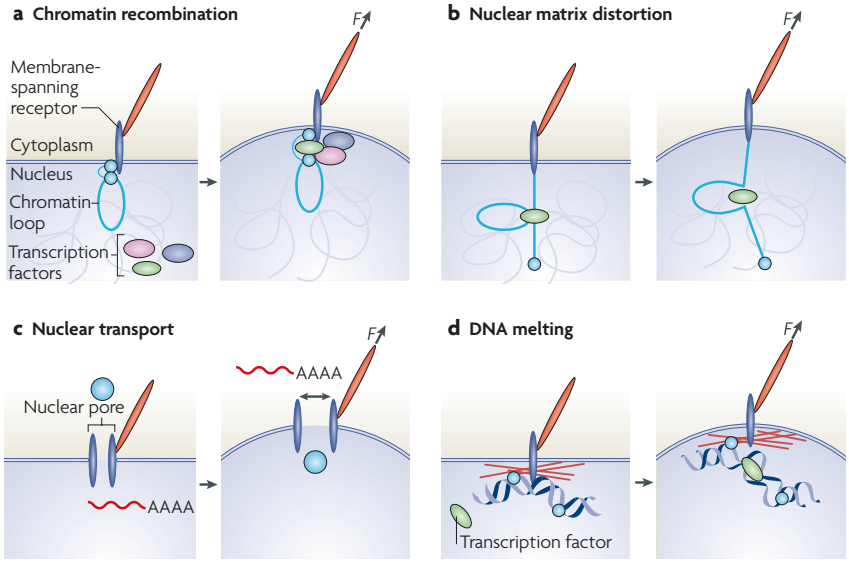

Figure 4 | **Possible nuclear mechanochemical conversion mechanisms. a** | Molecules that constitute nuclear scaffolds, and hence carry mechanical loads, might deform in response to a force (*F*, arrow), thereby altering self-assembly of regulatory complexes or other molecular structures that are important for gene regulation. Stress- or strain-induced changes in chromatin organization could lead to differential accessibility or binding of DNA regulatory factors that are involved in gene transcription, RNA splicing or chromatin modification. **b** | Forces that are focused on a specific chromatin region that is directly tethered to nuclear membrane-spanning receptors and to either the underlying lamin molecules or the internal nuclear scaffold could modulate the activities of associated transcription or splicing factors (green). **c** | Force application through the cytoskeleton to nuclear pores might increase nuclear transport and influence post-transcriptional control of gene expression (through altered mRNA transport). This would occur by either stretching the pore, opening the baskets and other components of the inner nuclear pore complex, altering its opening kinetics or modulating its molecular composition. **d** | Mechanical strain of certain regions of the nuclear scaffold relative to others could stretch specific regions of the DNA through their matrix attachment region (MAR) tethers. This strain on the DNA could lead to melting (for example, at sensitive AT-rich sites), and thereby facilitate binding of transcriptional regulators in a force-dependent manner.

organization and nuclear matrix composition suggests that different cell types could be 'primed' to react differently to the same stimulus through differential tethering of genes to load-bearing nuclear scaffolds and, hence, to key regions of stress concentration in the nucleus (for example, as shown by MARs).

Conclusions

It is now clear that mechanical action at a distance occurs in living cells[22,29–33]. This is made possible by the propagation of forces and vibrational energy through transmembrane integrins and cadherins, associated focal adhesions and junctional complexes, and cytoskeletal filaments that connect to the nucleus, its internal nuclear scaffolds and linked chromatin. Mechanical action at a distance only occurs if the input energy is concentrated or channelled across discrete load-bearing cytoskeletal filaments, and the spatial distribution and efficiency of force propagation depends on differences in stiffness between these support elements (BOX 1). It is for this reason that the fidelity and speed of this intracellular mechanical signalling response can be modulated by altering cytoskeletal prestress, which controls the stiffness of tensed cytoskeletal filaments, such as stress fibres[15,99] and intermediate filaments[100], that span long distances in the cytoplasm. Forces that act on the nucleus might promote changes in the shape, folding or kinetics of specific load-bearing molecules or might modify higher-order chromatin organization, and thereby alter nuclear protein self-assembly, gene transcription, DNA replication or RNA processing — all of which are crucial for cell behaviour. This unique form of mechanical signalling provides a more rapid and efficient way to convey information over long distances in living cells than diffusion-based chemical signalling. It also helps to explain how mechanical forces simultaneously alter the activities of multiple molecules at various sites in the cytoplasm and nucleus, a response that is crucial for control of cell physiology and tissue development[19].

Future work is needed to fully understand the molecular and biophysical basis for this direct form of nuclear mechanotransduction and to understand how these processes are integrated with chemical diffusion-based signalling mechanisms. This will require entirely new methods for probing and analysing structure–function responses in living cells, and will probably require integration of molecular cell biology methods with novel approaches from engineering, physics and nanotechnology.

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DATABASES

Entrez Gene: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
MYC
Interpro: http://www.ebi.ac.uk/interpro
KASH
OMIM: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM
Emery–Dreifuss muscular dystrophy
UniProtKB: http://www.uniprot.org
ANC-1 | BANF1 | BCAR1 | emerin | LBR | matrin 3 | MSP300 | nesprin 1 | nesprin 2 | PECAM1 | titin | TRIM55 | UNC84A | UNC84B | VCAM1
FURTHER INFORMATION
Ning Wang's homepage: http://www.mechse.uiuc.edu/content/directory/faculty/profile.php?user_id=1498
The Ingber laboratory: http://www.childrenshospital.org/research/ingber

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