Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Cell Biology

The nucleus feels the force, LINCed in or not!

Zeinab Jahed[1] and Mohammad RK Mofrad[1,2]

Mechanical signals affect many aspects of biological processes. Physical forces from the extracellular microenvironment are ultimately transmitted to the nucleus and elicit a response that result in the deformation and remodeling of the nucleus. Recent studies have shown that nuclear deformation has several consequences such as reorganization of chromatin, changes in gene expression, and nuclear envelope rupture. It is widely believed that a direct coupling between the cytoskeleton and nucleoskeleton is required for nuclear deformation; however, some studies have proposed alternative mechanisms for nuclear deformation and the transmission of mechanical signals and stresses from the cytoskeleton to the nucleus. Herein, we review the processes, in which the cell nucleus experiences stresses and discuss the evidence of involvement of a direct link between the cytoskeleton and nucleoskeleton in nuclear deformation.

Addresses
[1] Molecular Cell Biomechanics Laboratory, Departments of Bioengineering and Mechanical Engineering, University of California, Berkeley, CA 94720, United States
[2] Molecular Biophysics and Integrated Bioimaging Division, Lawrence Berkeley National Laboratory, Berkeley, CA 94720, United States

Corresponding author: Mofrad, Mohammad RK (mofrad@berkeley.edu)

Current Opinion in Cell Biology 2019, **58**:114–119

This review comes from a themed issue on **Cell nucleus**

Edited by **Naoko Imamoto** and **Daniel Larson**

For a complete overview see the Issue and the Editorial

Available online 16th April 2019

https://doi.org/10.1016/j.ceb.2019.02.012

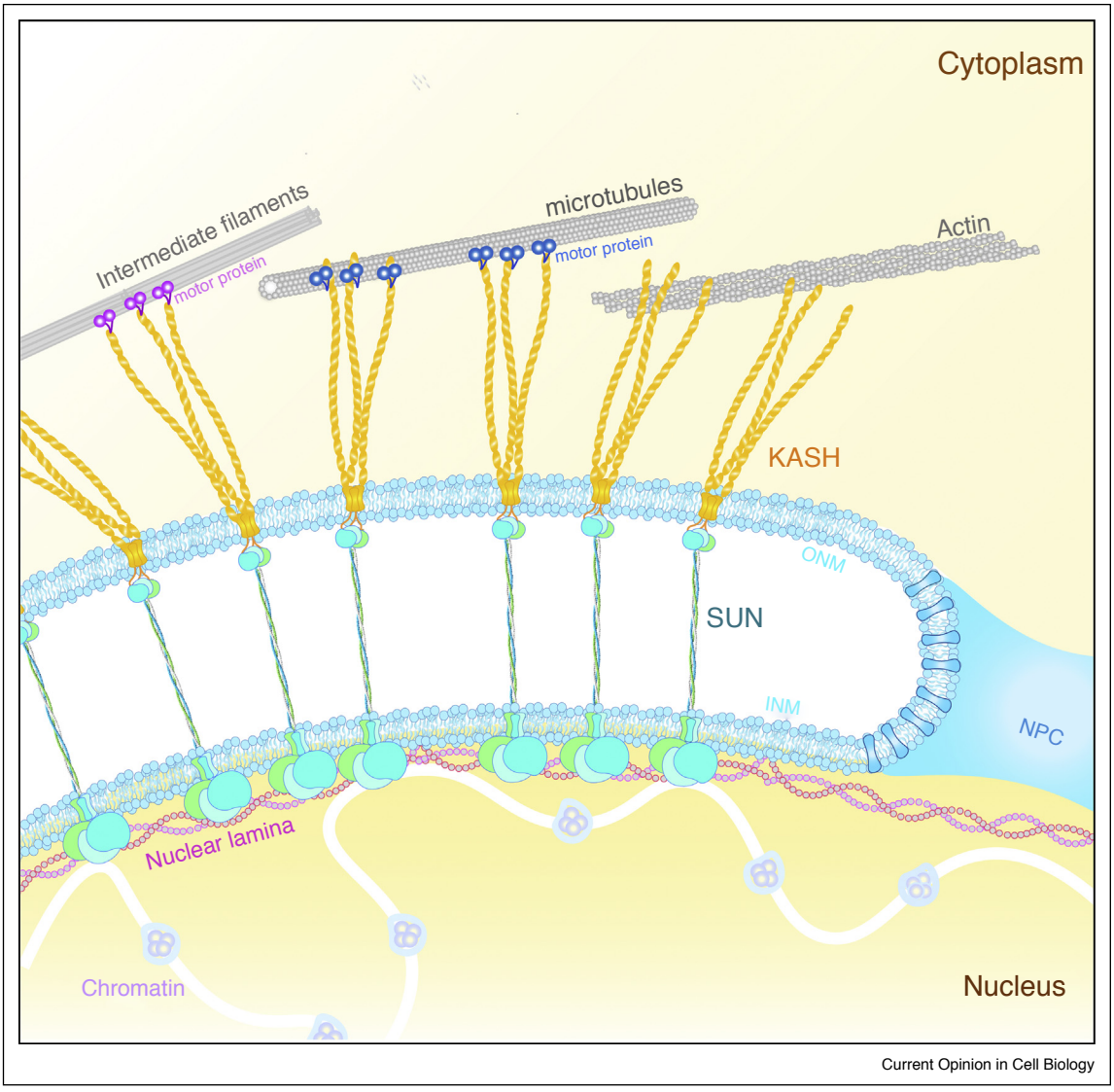
Introduction

More than a decade ago, the concept of nuclear mechanotransduction was proposed suggesting that the sensation and transduction of extracellular mechanical cues are not limited to the cell surface, and that forces acting on the cell are 'felt at a distance' inside the nucleus [1,2]. The transfer of physical forces to the nucleus is of great interest as it could potentially regulate genome organization and gene expression [3,4]. The chief candidates for force transmission to the nucleus are believed to be the protein machinery called the LINC complex (linker of the nucleoskeleton and cytoskeleton) [5]. This is not surprising since the LINC complex spans the nuclear envelope and provides a direct physical connection between primary components of the cytoskeleton, and nucleoskeletal elements such as lamins and chromatin (Figure 1). Hence, nuclear mechanotransduction research in the past decade has often focused on the LINC complex as the main mediator of nuclear mechanotransduction. Although there is some evidence for the direct involvement of LINC complex in nuclear mechanotransduction [6,7,8••,9], some recent studies have suggested that there are several LINC-independent mechanisms, by which the nucleus experiences and responds to physical forces [10,11,12•,13,14,15•,16••,17••]. Physical forces translated to the nucleus induce a mechanical stress that can deform the nucleus, resulting in local or global changes in nuclear shape. Herein, we provide a review of the different ways by which the nucleus experiences mechanical stress during various mammalian cellular processes. We also discuss the evidence or lack thereof for the significance of direct nucleo-cytoskeletal coupling in force transmission to the nucleus during these processes.

The LINC complex at the nuclear envelope

The contents of the nucleus are enclosed within a double-layered nuclear envelope consisting of an inner nuclear membrane (INM) and an outer nuclear membrane (ONM). Just as the cell plasma membrane separates the contents of the cytoplasm from the extracellular environment, the nuclear membranes separate the contents of the nucleus from the cytoplasm. Crosstalk between the interior of the nucleus, and the cytoplasm is then regulated by two macromolecular complexes namely the nuclear pore complex (NPC) and the LINC complex (Figure 1). While NPCs control the bidirectional transport of molecules across the nuclear envelope and may play a role in nuclear and cellular mechanotransduction as was originally proposed a decade ago [18,19], the LINC complexes allow the transfer of physical forces between the cytoskeleton and nucleoskeleton. The two main protein families that comprise the LINC complex are INM-anchored Sad1/UNC-84 (SUN), and ONM-anchored Klarsicht/ANC-1/SYNE homology (KASH) proteins (Figure 1). The conserved luminal KASH domain of KASH proteins binds to the conserved SUN domain of SUN proteins in the nuclear envelope. On the other hand, the cytoplasmic domains of KASH proteins can bind to various elements of the cytoskeleton (i.e. actin, microtubules and intermediate filaments), whereas the nucleoplasmic domains of SUN proteins bind to various elements of the nucleoskeleton (i.e. nuclear lamina and chromatin) (Figure 1). Through these interactions, the LINC complex provides a direct physical linkage

Figure 1



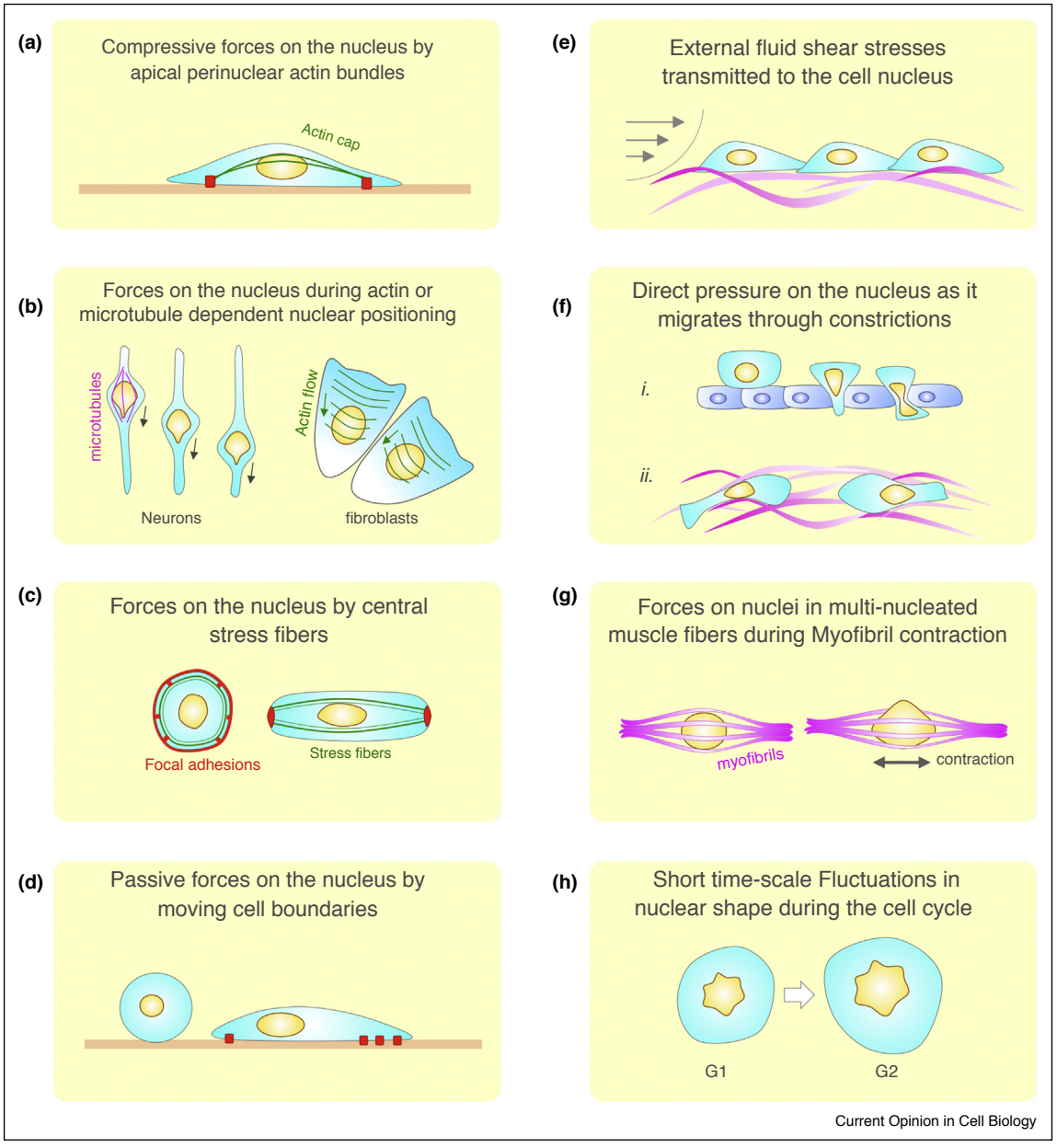
LINC complexes at the nuclear envelope.
The LINC complex is formed by the interaction of conserved domains of Sad1/UNC-84 (SUN) and Klarsicht/ANC-1/SYNE homology (KASH) proteins in the nuclear envelope. KASH domain proteins are anchored to the outer nuclear membrane (ONM) and most KASH proteins contain large cytoplasmic domains that bind to various elements of the cytoskeleton. KASH proteins can bind directly to the actin cytoskeleton, and indirectly to microtubules and intermediate filaments through motor proteins. The luminal conserved KASH domain is 10–30 amino acids in length and binds to the SUN domain of SUN proteins. SUN proteins are anchored to the inner nuclear membrane (INM) and can associate with nuclear lamina and chromatin through their nucleoplasmic domains. Various members of SUN and KASH domain proteins can pair up to perform distinct functions in the cell [20–22].

between the nucleoskeleton and cytoskeleton. Moreover, various members of the SUN and KASH domain protein families can pair up to perform distinct functions in the cell ([20–22]).

Compressive forces on the nucleus by apical perinuclear actin bundles

Several studies have shown that highly contractile acto-myosin filament bundles form a dome-like structure on top of the interphase nucleus in 2D adherent cells known as the actin cap [23–25] (Figure 2a). These actin bundles are physically tethered to the nucleus via LINC complex proteins on the apical surface of the nucleus, and form focal adhesions at the basal surface of the cell. Since its discovery, the actin cap has been characterized extensively and shown to be a highly contractile and dynamic [26]. Through these contractions, the actin cap is vastly involved in deforming the nucleus and can induce deep

Figure 2



Physical forces on the nucleus of mammalian cells by external environments or internal structures.

indentations on the apical surface of the nucleus deforming nuclear contents such as lamina and chromatin [27].

Forces on the nucleus during actin or microtubule dependent nuclear positioning

The position of the cell nucleus changes during various cellular processes and nuclear positioning plays a significant role in cellular function. As the nucleus is moved to its particular position inside the cell, it undergoes significant deformations and shape changes. Although the mechanisms of nuclear positioning in various cellular processes are still under investigation [28], there is great evidence that the LINC complex is at least partially involved in both actin and microtubule dependent nuclear positioning. For example, fibroblasts that are polarizing for migration position their nuclei rearward of the cell centroid [28] (Figure 2b). Actin cables above the nucleus that are anchored to the nucleus via LINC complex protein Nesprin-2 are responsible for the translocation of the nucleus to the rear of the cell during

retrograde actin flow [29,30•]. In a mechanism distinct from actin dependent fibroblast nuclear positioning, in newly born neurons, Nesprins bind to microtubules through kinesin-1 motor proteins and exert point forces on the nuclei [31••]. These point forces result in the rotation and deformation of the nucleus (Figure 2b).

Forces on the nucleus by central stress fibers

Some studies have suggested a model, in which lateral compressive forces from central stress fibers can change both the shape and volume of the nucleus [10] (Figure 2c). These changes can ultimately induce chromatin condensation and even affect cell proliferation [10]. Unlike the apical actin cap, central stress fibers are not known to be physically tethered to the nucleus through the LINC complex; however, studies suggest that they may contribute more to nuclear shape changes than does the apical actin. According to this model, the nuclear shape is tightly coupled with the cell shape and more elongated cells induce higher tensile stresses in central acto-myosin cables which can significantly deform the nucleus [10,27].

Passive forces on the nucleus by moving cell boundaries

Li *et al.* proposed another model of nuclear deformation of 2D cultured cells where the moving cell boundaries exert compressive forces that flatten the nucleus in early stages of cells spreading (Figure 2d). They also showed that a direct compressive force by LINC anchored apical actin cables is not required for nuclear flattening [12•]. Other studies have also shown that there is a direct correlation between the extent of cell spreading and the shape of the nucleus, and suggested that the LINC complex is not involved in nuclear compressions during cell spreading [7,15•,32]). According to this model, the passive forces generated within the cytoskeleton is sufficient for compressing the nucleus during cell spreading [33].

External fluid shear stresses transmitted to the cell nucleus

Although the effect of external fluid shears stress has been extensively studied in the context of cellular mechanotransduction, surprisingly, very few studies have looked into its effect on nuclear shape and nuclear mechanotransduction [34,35]. There is great evidence that the organization of the nuclear lamina, nuclear shape, and hence the overall mechanical properties of the nucleus can change in response to external fluid shear stresses (Figure 2e) but the mechanisms remain largely unknown [35,36]. Specifically, it is unclear whether the LINC complex has any involvement in the response of the nucleus to external fluid shear stresses.

Direct pressure on the nucleus as it migrates through constrictions

Most abovementioned nuclear deformations are observed in 2D adherent cells. However, recent studies have revealed the drastic deformations of the nucleus as cells migrate through extracellular constrictions [13,37]. For example, cancerous cells encounter and pass through confined microenvironments as they penetrate neighboring tissue during metastasis (Figure 2f-*i*) [13]. Leukocytes also experience a high degree of deformation as they create micron-wide openings to migrate through endothelial barriers (Figure 2f-*ii*) [16••]. The translocation of the nucleus through these tight constrictions is not known to be dependent on the LINC complex [4,16••,33]. Although the mechanisms are not completely understood, the LINC complex is not known to be involved, and myosin II-mediated contractility is believed to be responsible for pushing the nucleus through constricted barriers [16••,37].

Forces on nuclei in multi-nucleated muscle fibers during Myofibril contraction

During skeletal muscle differentiation the nuclei in multi-nucleated muscle fibers (myofibers) experience extensive deformations as they are moved to specific locations in the cell [38••]. The contractile units of skeletal muscle are linked by groups of longitudinal filaments (myofibrils) that are cross-linked by desmin. Very recently, studies using *in vitro* myofiber systems revealed that before nuclear movement, cross-linked myofibril bundles surround the nucleus and deform it inducing wrinkles and protrusions in the nuclei (Figure 2g) [38••]. The forces on the nucleus are exerted by actomyosin myofibril contractions and the LINC complex has shown to be dispensable for the deformation of the nucleus during this process [38••]. However, other studies have shown essential roles for the LINC complex protein Nesprin-1 in the positioning of the nuclei in myofibers [39]. Nevertheless, Nesprin-1 has multiple isoforms including ones that do not bind to the actin cytoskeleton. A recent study showed that the actin binding domain of Nesprin-1 is not required for nuclear movement or skeletal muscle function [40]. Therefore, although members of LINC complex proteins play partial roles in nuclear movement during skeletal muscle development, it remains unclear whether a direct physical nucleo-cytoskeletal connection is actually required for this process [40].

Short time-scale fluctuations in nuclear shape during the cell cycle

Finally, a less explored mechanism of nuclear deformation is short time scale shape changes of the nucleus. Early studies have shown that the size of the nucleus increases during the cell cycle. Intriguingly, a recent study showed that the nuclear shape also fluctuates at time scales of seconds, and that the amplitude of these fluctuations changes at various cell cycle stages (Figure 2h) [17••]. Further studies are required to unravel the reason and mechanisms of such shape fluctuations. Chu *et al.* hypothesize that a balance between forces from

chromatin and the cytoskeleton cause the shape fluctuations; however, the role of nucleo-cytoskeletal coupling has not yet been studied [17••].

Conclusions and perspectives

More than a decade of work has shown that cells can form a direct physical connection between their cytoskeleton and the interior of their nuclei providing a direct transmission of mechanical signals to the enclosed genetic material. Consequences of this force transmission to the nucleus, and changes in chromatin organization are exciting and emerging areas of research [3,4]; But it remains unclear whether direct physical linkages are required for force transmission to the nucleus and the initiation of nuclear mechanotransduction. In accordance with recent research presented in this review, forces can also effectively be transmitted to the nucleus independent of direct nucleo-cytoskeletal coupling through LINC complexes.

There is now some evidence that LINC complex associated proteins SUN and KASH may have several functional roles independent of their incorporation into the LINC complex [21,40,41]. To study the direct involvement of nucleo-cytoskeletal coupling through SUN and KASH in nuclear deformation, future studies should consider these alternative functions. To test the importance of SUN and KASH proteins in direct force transmission to the nucleus, their LINC related functions could be decoupled by only inhibiting their cytoskeletal or nucleoskeletal binding domains. The molecular details of the SUN–KASH interactions revealed in the past few years could be used to mutate specific sites on SUN or KASH known to be essential for force transmission through LINC complexes [42]. For example, specific mutations in SUN proteins allow the recruitment of KASH to the nuclear envelope, but inhibit efficient force transmission across the complex [30•,43,44,45••]. It would be interesting to use such mutations to study the force transfer function of the LINC complex, and elucidate its role in nuclear mechanotransduction.

Furthermore, we know that various SUN proteins can bind to distinct KASH domain proteins to mediate various cellular functions. As opposed to a holistic view of LINC, it is important to distinguish between functions of various SUN–KASH pairs and determine which ones are important in direct force transmission, nuclear deformation and nuclear mechanotransduction [41,42,46].

Conflict of interest statement

Nothing declared.

Acknowledgement

This work was supported by the National Science Foundation through grant CMMI-1538707.

References and recommended reading

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

- • of special interest
- •• of outstanding interest

1. Wang N, Tytell JD, Ingber DE: **Mechanotransduction at a distance: mechanically coupling the extracellular matrix with the nucleus**. *Nat Rev Mol Cell Biol* 2009, **10**:75-82.
2. Mofrad MRK, Kamm RD (Eds): *Cellular Mechanotransduction: Diverse Perspectives From Molecules to Tissues*. New York, NY: Cambridge University Press; 2009.
3. Uhler C, Shivashankar GV: **Regulation of genome organization and gene expression by nuclear mechanotransduction**. *Nat Rev Mol Cell Biol* 2017, **18**:717-727.
4. Kirby TJ, Lammerding J: **Emerging views of the nucleus as a cellular mechanosensor**. *Nat Cell Biol* 2018, **20**:373-381.
5. Crisp M, Liu Q, Roux K, Rattner JB, Shanahan C, Burke B, Stahl PD, Hodzic D: **Coupling of the nucleus and cytoplasm: role of the LINC complex**. *J Cell Biol* 2006, **172**:41-53.
6. Guilluy C, Osborne LD, Van Landeghem L, Sharek L, Superfine R, Garcia-Mata R, Burridge K: **Isolated nuclei adapt to force and reveal a mechanotransduction pathway in the nucleus**. *Nat Cell Biol* 2014, **16**:376-381.
7. Alam SG *et al.*: **The mammalian LINC complex regulates genome transcriptional responses to substrate rigidity**. *Sci Rep* 2016:38063 http://dx.doi.org/10.1038/srep38063.
8. •• Tajik A, Zhang Y, Wei F, Sun J, Jia Q, Zhou W, Singh R, Khanna N, Belmont AS, Wang N: **Transcription upregulation via force-induced direct stretching of chromatin**. *Nat Mater* 2016, **15**:1287-1296.

Evidence was presented of direct force transmission from integrins to the nucleus through the LINC complex resulting in the stretching of chromatin and the upregulation of transcription.

9. Wang S, Stoops E, Unnikannan CP, Markus B, Reuveny A, Ordan E, Volk T: **Mechanotransduction via the LINC complex regulates DNA replication in myonuclei**. *J Cell Biol* 2018, **217**:2005-2018.
10. Versaevel M, Grevesse T, Gabriele S: **Spatial coordination between cell and nuclear shape within micropatterned endothelial cells**. *Nat Commun* 2012, **3**:671.
11. LoVEtt D, Shekhar N, Nickerson J, Roux K, Lele T: **Modulation of nuclear shape by substrate rigidity**. *Cell Mol Bioeng* 2013, **6**:230-238.
12. • Li Y, Lovett D, Zhang Q, Neelam S, Kuchibhotla RA, Zhu R, Gundersen GG, Lele TP, Dickinson RB: **Moving cell boundaries drive nuclear shaping during cell spreading**. *Biophys J* 2015, **109**:670-686.

A simple model was presented suggesting that cell boundaries alone can shape the nucleus and that direct nucleo-cytoskeletal coupling is not required for nuclear flattening on rigid substrates.

13. Denais CM, Gilbert RM, Isermann P, McGregor AL, te Lindert M, Weigelin B, Davidson PM, Friedl P, Wolf K, Lammerding J: **Nuclear envelope rupture and repair during cancer cell migration**. *Science (80-)* 2016, **352**:353-358.
14. Lammerding J, Wolf K: **Nuclear envelope rupture : actin fibers are putting the squeeze on the nucleus**. *J Cell Biol* 2016:1-4.
15. • Makhija E, Jokhun DS, Shivashankar GV: **Nuclear deformability and telomere dynamics are regulated by cell geometric constraints**. *Proc Natl Acad Sci U S A* 2016, **113**:E32-E40.

This study provides direct evidence that changes in nuclear shape can influence the regulation of gene expression.

16. •• Thiam H-R *et al.*: **Perinuclear Arp2/3-driven actin polymerization enables nuclear deformation to facilitate cell migration through complex environments**. *Nat Commun* 2016, **7**:10997.

Mechanisms of nuclear deformation while migrating through tight constrictions were presented, and the LINC complex was shown to be dispensable for this process.

17. •• Chu F-Y, Haley SC, Zidovska A: **On the origin of shape fluctuations of the cell nucleus**. *Proc Natl Acad Sci U S A* 2017, **2017** 201702226.
Previously unidentified shape fluctuations were observed in the nucleus of human cells. These fluctuations are on the time scale of seconds and their amplitude decreases during the cell cycle.

18. Wolf CB, Mofrad MRK: **Mechanotransduction: role of nuclear pore mechanics and nucleocytoplasmic transport**.. Chapter 18 In *Cellular Mechanotransduction: Diverse Perspectives from Molecules to Tissues.* Edited by Mofrad, Kamm. New York, NY: Cambridge University Press; 2009.

19. Soheilypour M, Mofrad MRK: **Quality control of mRNAs at the entry of the nuclear pore: cooperation in a complex molecular system**. *Nucleus* 2018, **9**:202-211.

20. McGee MD, Rillo RS, Anderson A, Starr DA: **UNC-83 is a KASH protein required for nuclear migration and is recruited to the outer nuclear membrane by a physical interaction with the SUN protein UNC-84**. *Mol Biol Cell* 2006, **17**:1790-1801.

21. Jahed Z, Soheilypour M, Peyro M, Mofrad MRK: **The LINC and NPC relationship – it's complicated!** *J Cell Sci* 2016, **129**.

22. Kim DI, Birendra K, Roux KJ: **Making the LINC: SUN and KASH protein interactions**. *Biol Chem* 2015, **396**:295-310.

23. Khatau SB, Hale CM, Stewart-Hutchinson PJ, Patel MS, Stewart CL, Searson PC, Hodzic D, Wirtz D: **A perinuclear actin cap regulates nuclear shape**. *Proc Natl Acad Sci U S A* 2009, **106**:19017-19022.

24. Kim D-H, Khatau SB, Feng Y, Walcott S, Sun SX, Longmore GD, Wirtz D: **Actin cap associated focal adhesions and their distinct role in cellular mechanosensing**. *Sci Rep* 2012, **2**:555.

25. Chambliss AB, Khatau SB, Erdenberger N, Robinson DK, Hodzic D, Longmore GD, Wirtz D: **The LINC-anchored actin cap connects the extracellular milieu to the nucleus for ultrafast mechanotransduction**. *Sci Rep* 2013, **3**:1087.

26. Kim D-H, Chambliss AB, Wirtz D: **The multi-faceted role of the actin cap in cellular mechanosensation and mechanotransduction**. *Soft Matter* 2013, **9**:5516-5523.

27. Versaevel M, Braquenier J-B, Riaz M, Grevesse T, Lantoine J, Gabriele S: **Super-resolution microscopy reveals LINC complex recruitment at nuclear indentation sites**. *Sci Rep* 2014:1-8.

28. Gundersen GG, Worman HJ: **Nuclear positioning**. *Cell* 2013, **152**:1376-1389.

29. Luxton GWG, Gomes ER, Folker ES, Vintinner E, Gundersen GG: **Linear arrays of nuclear envelope proteins harness retrograde actin flow for nuclear movement**. *Science* 2010, **329**:956-959.

30. • Cain NE *et al.*: **Conserved SUN-KASH interfaces mediate LINC complex-dependent nuclear movement and positioning**. *Curr Biol* 2018, **28**:3086-3097.e4.
Mutations in conserved residues of SUN and KASH can disrupt force transmission along the LINC complex. A disulfide bridge between SUN and KASH maximizes force transfer along the complex.

31. •• Wu YK, Umeshima H, Kurisu J, Kengaku M: **Nesprins and opposing microtubule motors generate a point force that drives directional nuclear motion in migrating neurons**. *Development* 2018, **145** dev158782.
Direct point forces on the nucleus were observed which significantly deformed the nucleus in migrating neurons. This process was mediated by the interaction of KASH domain protein Nesprin-1 with micro.

32. Driscoll TP, Cosgrove BD, Heo S, Shurden ZE, Mauck RL: **Cytoskeletal to nuclear strain transfer regulates YAP signaling in mesenchymal stem cells**. *Biophysj* 2015, **108**:2783-2793.

33. Szczesny SE, Mauck RL: **The nuclear option: evidence implicating the cell nucleus in mechanotransduction**. *J Biomech Eng* 2017, **139**:021006.

34. Deguchi S, Maeda K, Ohashi T, Sato M: **Flow-induced hardening of endothelial nucleus as an intracellular stress-bearing organelle**. *J Biomech* 2005, **38**:1751-1759.

35. Dahl KN, Kalinowski A, Pekkan K: **Mechanobiology and the microcirculation: cellular, nuclear and fluid mechanics**. *Microcirculation* 2010, **17**:179-191.

36. Philip JT, Dahl KN: **Nuclear mechanotransduction: response of the lamina to extracellular stress with implications in aging**. *J Biomech* 2008, **41**:3164-3170.

37. Barzilai S *et al.*: **Leukocytes breach endothelial barriers by insertion of nuclear lobes and disassembly of endothelial actin filaments**. *Cell Rep* 2017, **18**:685-699.

38. •• Roman W, Martins JP, Carvalho FA, Voituriez R, Abella JVG, Santos NC, Cadot B, Way M, Gomes ER: **Myofibril contraction and crosslinking drive nuclear movement to the periphery of skeletal muscle**. *Nat Cell Biol* 2017, **19**:1189-1201.
It was shown that myofibrils can exert centripetal forces on the nucleus moving them to the periphery of myofibres. These forces can cause significant shape deformations of the nuclei.

39. Cadot B, Gache V, Gomes ER: **Moving and positioning the nucleus in skeletal muscle - one step at a time**. *Nucleus* 2015, **6**:373-381.

40. Stroud MJ, Feng W, Zhang J, Veevers J, Fang X, Gerace L, Chen J: **Nesprin 1α2 is essential for mouse postnatal viability and nuclear positioning in skeletal muscle**. *J Cell Biol* 2017, **216**:1915-1924.

41. May CK, Carroll CW: **Differential incorporation of SUN-domain proteins into LINC complexes is coupled to gene expression**. *PLoS One* 2018, **13**:1-14.

42. Jahed Z, Mofrad MRK: **Mechanical LINCs of the nuclear envelope: where SUN meets KASH**. *Extrem Mech Lett* 2018, **20**:99-103.

43. Jahed Z, Shams H, Mofrad MRK: **A disulfide bond is required for the transmission of forces through SUN-KASH complexes**. *Biophys J* 2015, **109**:501-509.

44. Jahed Z, Vu UT, Fadavi D, Ke H, Rathish A, Kim SCJ, Feng W, Mofrad MRK: **A molecular model for LINC complex regulation: activation of SUN2 for KASH binding**. *Mol. Biol. Cell* 2018, **29**:2012-2023.

45. •• Jahed Z, Hao H, Thakkar V, Vu UT, Valdez VA, Rathish A, Tolentino C, Kim SCJ, Fadavi D, Starr DA, Mofrad MRK: **Role of KASH domain lengths in the regulation of LINC complexes**. *Mol Biol Cell* 2019 http://dx.doi.org/10.1091/mbc.E19-02-0079. [Epub ahead of print].
Molecular dynamics simulations show that KASH domains of various lengths can transfer different magnitudes of forces to the nucleus. Additionally, swapping KASH domains of various KASH proteins which are only a few residues different can disrupt their function in vivo.

46. Jahed Z, Fadavi D, Vu UT, Asgari E, Luxton GWG, Mofrad MRK: **Molecular insights into the mechanisms of SUN1 oligomerization in the nuclear envelope**. *Biophys J* 2018, **114**.