Nucleus 6:5, 360–365; September/October 2015; © 2015 Taylor & Francis Group, LLC

Dynamic, mechanical integration between nucleus and cell- where physics meets biology

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Nuclear motions like rotation, translation and deformation suggest that the nucleus is acted upon by mechanical forces. Molecular linkages with the cytoskeleton are thought to transfer forces to the nuclear surface. We developed an approach to apply reproducible, known mechanical forces to the nucleus in spread adherent cells and quantified the elastic response of the mechanically integrated nucleus-cell. The method is sensitive to molecular perturbations and revealed new insight into the function of the LINC complex. While these experiments revealed elastic behaviors, turnover of the cytoskeleton by assembly/disassembly and binding/unbinding of linkages are expected to dissipate any stored mechanical energy in the nucleus or the cytoskeleton. Experiments investigating nuclear forces over longer time scales demonstrated the mechanical principle that expansive/compressive stresses on the nuclear surface arise from the movement of the cell boundaries to shape and position the nucleus. Such forces can shape the nucleus to conform to cell shapes during cell movements with or without myosin activity.

Introduction

It has been known for decades that the nucleus is acted upon by mechanical forces. Early observations of nuclear rotations in different cell types[1,2] revealed a mechanism for generating torque on the cell nucleus due to microtubules.[3] Yen and Pardee[4] showed that quiescent Swiss 3T3 cells varied nearly two-fold in nuclear volume despite having the same amount of DNA, and that the time of entry of these cells into S-phase upon serum stimulation correlated with nuclear volume. Similar results were found in other cell types including correlations between nuclear area and the degree of cell spreading.[5,6] Such studies led to the postulation of mechanical models in which the nucleus was a tensed structure that was continuous with the cellular cytoskeleton.[7] Mechanical integration between the nucleus and the cytoskeleton was hypothesized to enable the nucleus to respond to changes in cell shape[8] and was suggested as a mechanism for cell-shape mediated control of nuclear structure and function.

In recent years, the discovery of LINC (linker of nucleoskeleton to cytoskeleton) complex proteins[9,10] has revealed that the nucleus and the cytoskeleton are molecularly continuous.[11] The nesprin family of proteins in the outer nuclear envelope connect the nucleus to the cytoskeleton by binding to F-actin, intermediate filaments and microtubule motors.[12] Observations of moving nuclei in concert with nesprin 2G- associated actomyosin bundles on the apex of the nucleus in wounded fibroblasts and abrogation of motion on LINC disruption suggest that the LINC transfers mechanical forces from the cytoskeleton to the nuclear surface.[13,14] Experiments have revealed a requirement for the LINC complex for nuclear motion in cells in 3-D matrices[15] and for nuclear migration in *Caenorhabditis elegans*.[16,17] Given such literature that is building up on LINC complex function in the context of nucleo-cytoskeletal coupling (see review by Starr[11]), there is a need for methods to quantify the degree of mechanical integration between the nucleus and the cytoskeleton.

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Submitted: 07/29/2015

Revised: 08/20/2015

Accepted: 08/28/2015

http://dx.doi.org/10.1080/19491034.2015.1090074

Mechanically Probing the Nucleus in the Cell

Methods to aspirate whole nuclei or cells containing whole nuclei have been used to characterize nuclear mechanical properties,[18-21] but because cytoskeletal structures and tension on the nucleus are absent in isolated and trypsinized cells respectively, these methods are not suited for probing nuclear-cytoskeletal coupling in spread adherent cells. Many years ago, Maniotis et al developed an approach to pull on the membrane of adherent cells with a micropipette tip, and recorded deformation and motion of the nucleus in response.[22] A similar method was used by Lombardi et al[23] to study the LINC complex in force transmission to the nuclear surface. Other methods to apply forces to the nucleus include strain applied to cells adherent to flexible substrates.[24,25]

While these methods demonstrate mechanical coupling of the cell surface to the nuclear surface, the magnitude of the force transmitted to the nuclear surface is unknown. This limitation can create difficulties in the interpretation of the nuclear response. Consider a hypothetical experiment in which the LINC complex is disrupted and force is applied to the cell surface (whether at adhesions with the substrate or to the cell membrane). If changes in nuclear deformation/motion are observed, it cannot clearly be distinguished whether the changes are due to altered force transmission from the cytoskeleton to the nucleus, changes in the properties of the nucleus (lamina/chromatin), or altered organization of the cytoskeleton and/or cell contents. As the magnitude of the force transmitted to the nuclear surface is unknown, comparisons of nuclear deformation between normal and perturbed cells can be problematic, and potentially misleading. A related issue is that when strain is applied to the cell membrane or adhesions, the force applied is unknown and likely varying from one cell to the next for a given strain.

To address this limitation, we recently developed an approach[26] to apply force directly to the nuclear surface in living, adherent cells. The method is simple to implement on a commercially available Eppendorf system. We insert a ½ micron diameter pipette tip into the cytoplasm, and suction-seal it with the nuclear surface. The pressure at the tip is specified and the cross-sectional area of the tip is known, therefore the suction force applied at the pipette tip on the nuclear surface (pressure x area) is known. The pipette is then moved away from the nucleus at a known speed. The resulting nuclear translation and deformation depends on the suction force. At low suction pressure, the pipette detaches from the nucleus without any noticeable effect on the nucleus (**Fig. 1A**; quantitative strain-force curves are available elsewhere [26,27]). At higher suction pressure, the nucleus translates and deforms in the direction of the pipette. As the pipette moves, the nucleus eventually detaches from the pipette tip. On detachment, the nucleus relaxes back close to its original shape, and also recovers its position to a large extent. The relaxation dynamics are fast (less than a second for shape and a few seconds for position), suggesting that nuclear shape relaxation is primarily elastic. At still higher suction pressures, the nucleus does not detach from the tip, but rather is completely pulled out of the cell (**Fig. 1B**).

The sensitivity of nuclear response to the suction pressure – no response at low pressure and complete removal of the nucleus from the cell at high pressure – suggests that the suction pressure is the source of the applied force when the micropipette is translated, and adhesion forces

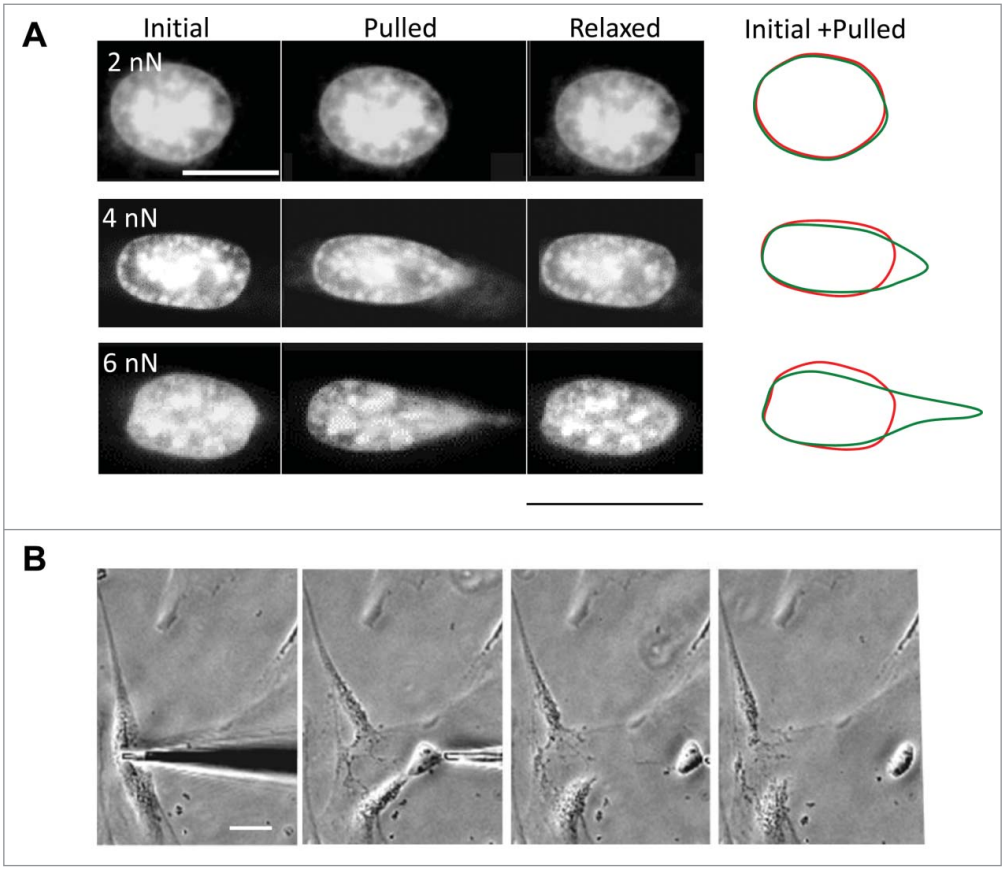

Figure 1. Nuclear response depends on the magnitude of force. (**A**) Shown are the images of nuclei labeled with SYTO 59 dye in the initial, pulled and relaxed state under pulling forces in NIH 3T3 fibroblasts. At 2 nN, there is little effect on the nuclear shape, as the force is increased (4nN and 6 nN) the nucleus deforms proportionately more. (**B**) At high enough force, 20 nN in this example, the nucleus is completely removed from the cell.

between the tip and the nuclear surface are negligible. Release of the nucleus from the pipette tip occurs at the point when the resistance to further deformation and translation balances the suction force applied to the nuclear surface. Thus, this technique provides a quantitative direct force probe for studying nuclear mechanics in the living cell.

If the nucleus were completely free to translate, no change would be expected in the nuclear shape. Therefore, the observation that the nucleus translates far less than it deforms directly demonstrates the extent of mechanical integration between the nucleus and the cytoplasm. It is remarkable that the nucleus is so tightly integrated, because the nucleus freely rotates in NIH 3T3 fibroblasts[28] and also translates during cell migration.[29] Over the short time scales (few seconds) that the pulling force is applied, the nucleus-cell integration appears primarily elastic as evident in the response to pulling.

The micropipette technique above allows direct probing of the mechanical integration between the nucleus and the cell. Importantly, because the same force is applied in each experiment, comparisons between nuclear deformations are unambiguous and reliable. **Figure 2** shows comparisons of deformation across different cell types under the same 6 nN force; the response is similar in different cell types except in breast epithelial cells where the nucleus deforms much less (**Fig. 2**).

There are some caveats that need to be considered. Flow of fluid into the micropipette from inside the nucleus can occur through nuclear pores, which means that the actual pressure on the nuclear surface will be smaller than the suction pressure in the micropipette. However, a simple calculation shows that the resistance across the nuclear envelope to flow is 10^5 times greater than resistance to the flow in the pipette.[26] Therefore, it is a safe assumption that all the pressure drop occurs across the nuclear envelope and the actual pressure on the envelope is equal to suction pressure in the micropipette tip. Other potential caveats with the method are discussed elsewhere.[26,27]

The LINC Complex- not just a Simple Mechanical Linker

The approach above is sensitive to molecular perturbations. Lamin A/C and vimentin knockdown resulted in increased nuclear deformation and translation, while F-actin and MT disruption had no effect.[26] This suggests that cytoplasmic intermediate filaments are the key structures that resist nuclear motion under applied force. However, although not required to resist translation, F-actin and MT were found to be required for complete recovery of nuclear position.

The use of the micropipette probe provided new and unexpected insight into the effects of LINC perturbation on the mechanical integration between the nucleus and the cell. If the sole effect of LINC disruption is to mechanically disconnect the nucleus from the surrounding cytoskeleton, then the predicted response is increased translation of the 'free' nucleus and concomitant decreased deformation. Surprisingly, over-expression of KASH4 (*Klarsicht, Anc-1, Syne homology*) which competitively inhibits endogenous KASH4 linkages with Sun1/2 (*Sad1p, UNC-8*) to disrupt the LINC complex had no discernible effect on nuclear deformation nor nuclear translation in NIH 3T3 fibroblasts. Following detachment, recovery of the nuclear shape was unaffected by LINC complex disruption, but the position recovered to a lesser extent than the control. Conversely, KASH4 expression in mouse embryonic fibroblasts (MEFs) resulted in decreased nuclear translation and no effect on deformation. Similarly surprising was the observation that the expression of SUN1L-KDEL, a dominant negative protein which also inhibits the LINC complex by disrupting connections between endogenous KASH and SUN-domain proteins, caused a dramatic increase in nuclear deformation but with no effects on nuclear translation or recovery of shape and position.

That the nucleus continues to resist deformation and translation under applied force in LINC disrupted cells suggests that the nucleus may be mechanically integrated with the cell in other ways. The unexpected results upon disrupting the LINC complex and differences in the response depending on the type of perturbation and cell type highlight the complex effects of disrupting the LINC complex. Presumably, LINC disruption with dominant negative constructs like KASH4 or Sun1L-KDEL impacts the cytoskeleton and the nucleus in unknown ways, making it difficult to interpret these (and past) experiments solely in terms of mechanical integration and force transfer.

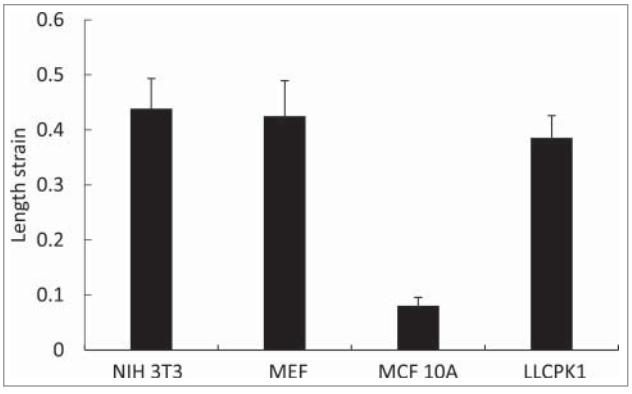

Figure 2. Nuclear deformation in different cell types. Bar plot shows length strain of the nucleus at 6 nN in NIH 3T3 fibroblasts, mouse embryonic fibroblasts (MEFs), human breast epithelial cells (MCF10A) and LLCPK1 pig kidney epithelial cells. NIH 3T3: n = 15, MEF: n = 8, MCF10A: n = 7, LLCPK1: n = 10. Values are the mean ± SEM.

Mechanical Integration between Cell and Nucleus Over Longer Time Scales

Owing to the rapid deformations and relaxations (time scales of a few seconds), the micropipette technique above essentially probes the elastic response of the nucleus under forces that disturb its homeostatic position and shape in the cell. Similarly, other methods apply forces on short time scales to cell-substrate adhesions[24,25] or cell membranes[22,23] and therefore probe an elastic response to applied forces. However, nuclear motion[15,17,29,30] and/or deformation in normal cell functions[31] are slower processes that occur over time scales of minutes. At this longer time scale, turnover of the cytoskeleton by assembly/disassembly and binding/unbinding of linkages will dissipate any stored mechanical energy in the nuclear shape or the cytoskeleton. This dissipation of energy by unbinding of strained molecules can yield a viscous rather than elastic response through a phenomenon known as "protein friction."

For example, reversible binding between nuclear dynein and microtubules is needed for nuclear rotations to occur. The time scale of unbinding scaled with the stiffness of dynein linkages – the friction coefficient – is a key parameter in determining the dynamics of rotation[28] and for centering of the centrosomal array of microtubules.[32] Dynamic assembly/disassembly of the cytoskeleton under mechanical load can dissipate its stored mechanical energy yielding a viscous response to shear and compression/expansion deformations.[33,34] Our recent studies with NIH 3T3 fibroblasts indicate a surprisingly simple, unifying mechanical principle that explains how the cell translates and shapes the nucleus - moving boundaries of the cell transmit stresses to the nuclear surface through viscous resistance of the intervening cytoskeleton to expansion/compression, thereby causing nuclear motion and deformation.[29,33]

We have recently reported that in migrating NIH 3T3 fibroblasts, protrusions that develop proximal to the nuclear surface are followed by a clearly visible deformation in the nucleus in the direction of the protrusion.[29] Upon retraction of the protrusion, the nucleus shape relaxes back to its original shape. This is in agreement with our previous observations[35] of nuclear motion toward lamellipodia engineered by photoactivation of Rac1. It is striking that there is mechanical stress transfer from the membrane to the nuclear surface over time scales much slower than near instant deformations of the nucleus in response to tugs on the cell membrane.[22] Traction force microscopy measurements confirmed that protrusions generated substantial traction stresses directed away from the nucleus, consistent with an outward pull on the nucleus.[29] Stress fibers were not affected by the local lateral protrusions, and laser severing of stress fibers proximal to the nucleus did not produce nuclear deformations. Thus, newly formed protrusions likely transmit a pull on the nuclear surface which results in its deformation and motion. Importantly, LINC disruption eliminates the deformation of the nucleus in response to protrusions.

If the moving cell membrane transmits tensile stress to the nuclear surface, then the nucleus position should be determined by a balance of tensile forces from the leading and trailing edge of the migrating cell. The prediction of such a model is that nuclear position coincides with the point of maximum tension in the cell. Using traction force microscopy to measure the point of maximum tension (PMT) (described in[27, 29]), we confirmed this prediction- the nuclear centroid tracks the PMT dynamically in the migrating cell as it forms new protrusions and re-establishes its coincidence with the shifted PMT after tail detachment. Consistent with this observation, the persistence of cell migration was significantly decreased upon LINC disruption.[35] We also found that LINC disruption significantly reduces the drop in traction at the leading edge caused by spontaneous or forced detachment of the trailing edge. Thus, the LINC complex enables the nucleus to transmit stresses from the front to the back of the cell.

The mechanical principle of stress transmission from the moving cell membrane to the nuclear surface through viscous resistance to expansion of the intervening cytomatrix also operates during nuclear shaping.[33] In spreading NIH 3T3 fibroblasts on flat substrates, the apical surface of the nucleus collapses during early cell spreading resulting in a flattened nucleus. Nuclear flattening typically preceded actomyosin bundle formation and was not due to the apical cell membrane compressing the apical nuclear surface because there is a significant gap between the two surfaces. The degree of nuclear flattening strongly correlated with the degree of cell spreading. Surprisingly, actomyosin activity was not required for nuclear flattening, nor microtubules and intermediate filaments, and flattening proceeded in the near absence of stress fibers on the apical or basal surface of the nucleus. LINC disruption slowed down the process of spreading and flattening but did not prevent it. These results are in contrast with the requirement for intermediate filaments and the LINC complex in force transmission and nuclear response during rapid pulling on the nucleus,[22,23,26] and highlight the importance of time scales in probing nuclear integration with the cell.

We proposed a mathematical model that showed how movements of the cell membrane and flow of cytoskeletal network from the membrane exerts a stress on the nuclear surface during initial cell spreading. In response to this stress, excess nuclear surface area reflected in folds in the lamina of the initially rounded nucleus get smoothed out as the nucleus flattens during spreading. Once the folds in the lamina are completely removed, then the stretched lamina resists further pulling owing to a high extensional modulus[20] and further flattening requires nuclear volume compression. This balance of pulling forces on the nuclear surface and the resistance force from the lamina helps determine the steady state height and overall shape of the flat nucleus. The model explains the close correlation between cell and nuclear shapes observed in several studies over the past decades.[5,8, 36-39]

Summary

Here we reviewed recent work that sought to probe nucleus-cell mechanical integration by applying controlled forces directly to the nuclear surface and measuring the nuclear response. The advantage of this approach is that the forces are known on the nuclear surface which allows meaningful interpretations and comparisons of measurements. While these measurements yield valuable information on short time scales of a few seconds, physiological forces on the nucleus act to move and shape the nucleus on time scales of minutes. We reviewed our recent work on how moving cell boundaries shape and position the nucleus. Mechanical integration between the nucleus and the cell is elastic to forces on time scales of seconds, while over longer time scales, the integration is labile which enables physiological motions like nuclear rotations, translations and deformations. These prior studies highlight the mechanical principle that expansive/compressive stresses on the nuclear surface arising from the movement of the cell boundaries shape and position the nucleus; such forces can shape the nucleus to conform to cell shapes during cell movements. These forces are observed to shape the nucleus with or without myosin activity, although myosin contractility and actomyosin bundles may play a secondary or separate role in nuclear shaping. Nuclear force generation is required for normal cell functions,[40] and mutations in LINC components are linked to a variety of human diseases.[13] Understanding how nuclear forces impact cell function is a key challenge for the future that will necessarily involve a convergence of thinking from the fields of physics and biology.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Funding

This work was supported by research grants NIH RO1 GM102486 (TPL and RBD) and NIH RO1 EB014869 (TPL).

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