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A new function for nuclear lamins: Providing surface tension to the nuclear drop

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Abstract

The nuclear lamina, a conserved structure in metazoans, provides mechanical rigidity to the nuclear envelope. A decrease in lamin levels and/or lamin mutations are associated with a host of human diseases. Despite being only about 15 nm thick, the perturbation of components of the nuclear lamina dramatically impacts the deformation response of the entire nucleus through mechanisms that are not well understood. Here, we discuss evidence for the recently proposed "nuclear drop" model that explains the role of A-type lamins in nuclear deformation in migrating cells. In this model, the nuclear lamina acts as an inextensible surface, supporting a surface tension when fully unfolded, that balances nuclear interior pressure. Much like a liquid drop surface where the molecularly thin interface governs surface tension and drop shape under external forces, the thin nuclear lamina imparts a surface tension on the nuclear drop to resist nuclear deformation as well as to establish nuclear shape. We discuss implications of the nuclear drop model for the function of this crucially important eukaryotic organelle.

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Introduction

Nuclear lamins are members of the intermediate family of proteins that form filamentous networks that underlie the nuclear envelope. The networks are collectively called the nuclear lamina and are a conserved structure in metazoans. The nuclear lamina has diverse functions in metazoan cells ranging from anchoring chromatin domains [1] and nuclear pore complexes [2] to providing mechanical rigidity to the nuclear envelope [3]. Mutations in lamins result in laminopathies which include Hutchinson-Gilford progeria syndrome and atypical Werner syndrome (reviewed in [4]). Lamin expression is also substantially altered in a host of cancers (reviewed in [5]).

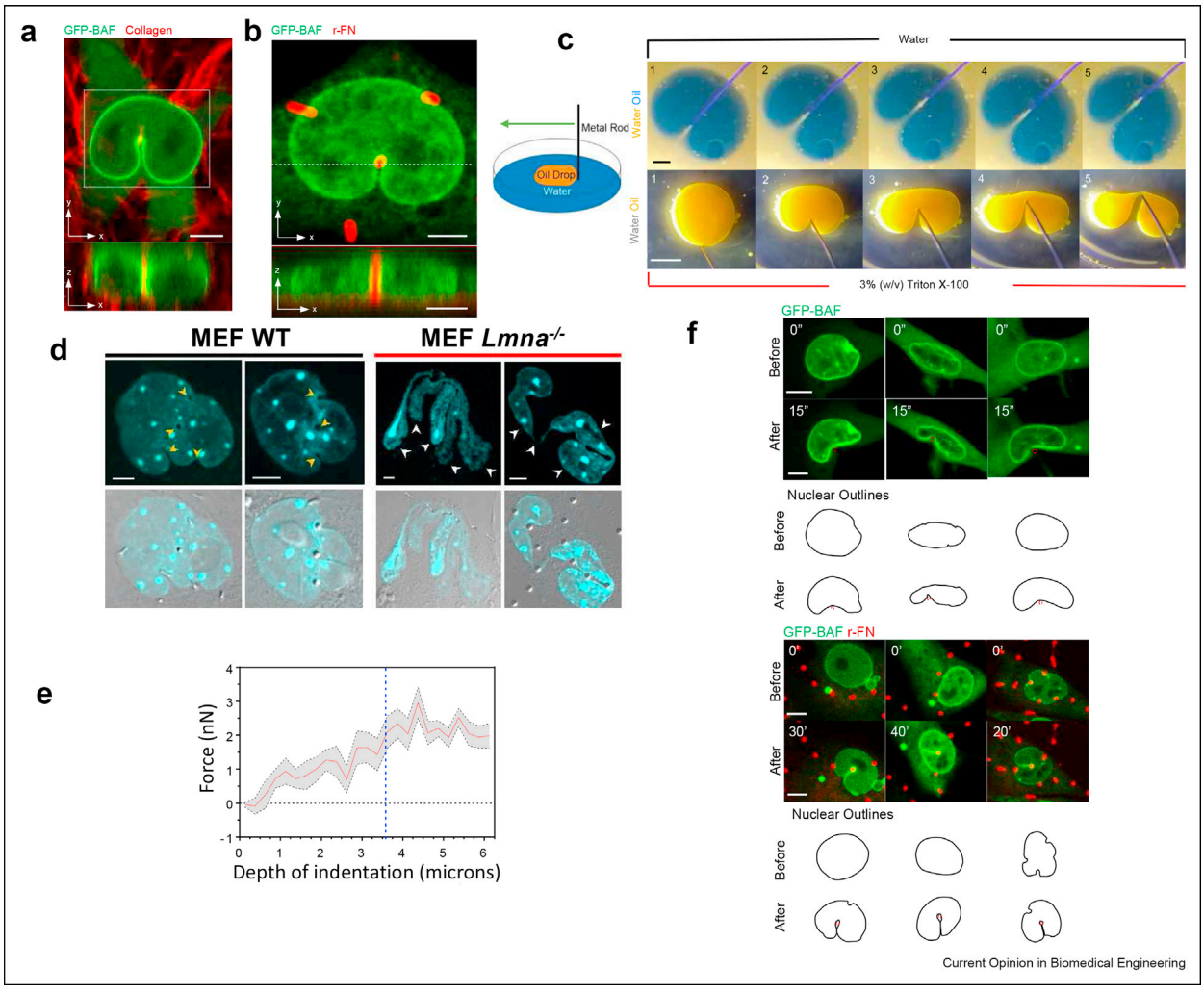
The mechanical rigidity of the nuclear lamina enables the nucleus to withstand the forces of bending and stretching that cells encounter when migrating through narrow interstitial spaces *in vivo* [6,7]. This rigidity is largely attributed to the presence of A-type lamins (Lamins A and C), as cells deficient in lamin A/C exhibit greater deformation under external mechanical forces (reviewed in [8]). Although the nuclear lamina is only about 15 nm thick [9], perturbing this structure profoundly impacts the deformation response of the entire nucleus. How the lamina, and in particular, the A-type lamins, contribute to the overall nuclear mechanical response to mechanical force remains an open question. In this paper, we discuss the recently proposed nuclear drop model [10] that explains the role of A-type lamins in nuclear deformation in migrating cells.

Evidence for the nuclear drop model

Liquid drops with surface tension tend to deform in ways where their free surfaces are of constant curvature, reflecting the minimization of surface energy. Consistent with this, in the nuclei of migrating fibroblasts in collagen gels, we found many instances in which a single collagen fiber (~0.4-μm diameter) caused an invagination in the cell nuclear surface (Figure 1a) with the free surfaces nearly constant in curvature like that of a drop [10]. Similar deformations were found in cells migrating against an array of PDMS microposts fabricated on flat substrates (Figure 1b). These shapes intuitively suggest that the nucleus behaves more like a drop than an elastic solid in these migrating cells. Figure 1c (top panel) shows shapes of an oil drop in water indented with a thin metal wire. The shapes are remarkably like the shapes of the nuclei in Figure 1a and b.

Mechanical parameters likely to be important for the nuclear drop are intranuclear pressure and nuclear

Figure 1



Evidence for the nuclear drop model. Modified from Katiyar et al. [10] (**a**) Representative images of a fibroblast (expressing GFP-BAF, green) cultured in 0.5 mg/mL 3D collagen gel (collagen fibers labeled with NHS ester dye in red). Top and bottom panels show the horizontal and vertical cross-section views (Scale bar is 5 μm) (**b**) (Top) Maximum intensity projection image of a fibroblast stably expressing GFP-BAF (green) deformed against microposts (red) (Bottom) X-Z reconstruction of confocal z-stacks shows nuclear envelope (green) and micropost (red) in the axial direction (Scale bar is 10 μm). (**c**) (Top) An oil drop (blue) in water (yellow) indented with a metal wire (diameter is 0.5 mm) (Bottom) An oil drop (yellow) in 3% (w/v) Triton X-100 in water indented with the same metal wire (Scale bar is 5 mm). (**d**) Images of fixed Hoechst 33,342 stained MEF WT and MEF *Lmna*$^{-/-}$ nuclei deformed around microposts. Yellow arrowheads point to the micropost locations, and white arrowheads indicate wispy finger-like nuclear extensions around the microposts (Scale bar is 5 μm). (**e**) Plot shows the magnitude of force, calculated from micropost deflections that indent the nucleus, for mean values pooled from n = 10 cells from at least three independent experiments. Grey area represents SEM. The vertical dashed line (blue) indicates a plateau in the force. (**f**) (Top) Images of nuclei of GFP-BAF expressing fibroblasts deformed with a 1-micron diameter Tungsten microneedle at fast time scales (~15 s) (Bottom) Nuclei deformed around microposts in the same cell type over tens of minutes (Scale bar is 5 μm). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

surface tension. Nuclear shapes in migrating MEFs which lacked the *Lmna* gene that encodes lamin A/C (*Lmna*$^{-/-}$) were heavily distorted when deformed against PDMS microposts [10], in contrast to nuclei in wild-type (WT) MEFs (Figure 1d). This behavior is consistent with a role for lamin A/C in conferring surface tension upon the nuclear drop, likely due to the resistance of the nuclear lamina to areal expansion. Consistent with this concept, decreasing surface tension of the oil drop in water by treating with a surfactant (Figure 1c, bottom panel), produces extreme shape distortion like nuclear shapes in *Lmna*$^{-/-}$ MEFs.

The force of indenting the nucleus is on the order of 10–15 nN as measured by AFM for an indentation depth of 4–6 μm [11]. We measured the deflection force generated when nuclei in migrating cells deformed against polydimethylsiloxane (PDMS) microposts. We

detected an average force of ~2 nN for an indentation depth of 4–6 μm (Figure 1e, [10]) which is much smaller than forces measured by AFM (10–15 nN). This suggests that, in cells, the nucleus deforms very differently from the elastic deformation apparent in AFM experiments. Further, when an elastic object is indented, it resists with a force that increases with the degree of indentation. Instead, the force of indentation for the nucleus plateaus with increasing indentation depth (Figure 1e, [10]). This plateauing is again consistent with drop-like behavior of the nucleus; as for a drop, the resisting force will reach a maximum once the tensed surfaces become parallel to the direction of indentation (assuming constant surface tension). Indeed, when nuclei were indented rapidly (~15 s) by a 1-μm diameter Tungsten microneedle, the nuclei displayed kidney-bean-like morphologies typical of solid-like deformation (Figure 1f, top panel) rather than the nuclear shapes generated by cellular forces that deform the nucleus around microposts over several minutes (Figure 1f, bottom panel).

The unfolded lamina imparts surface tension on the nuclear drop

One distinctive feature of the nuclear drop model is that nuclear deformation occurs while maintaining nearly constant area of the nuclear lamina. When a sphere is deformed to another shape at constant volume, the area must increase, because the sphere is a shape with minimum surface area for that volume. Nuclei in rounded cells are generally modeled as roughly spherical [12], such that when they become flattened during the process of cell spreading, the lamina must be assumed to stretch. However, we and others have found that the nuclear lamina is not taut in rounded cells, but it contains excess surface in the form of numerous folds and wrinkles [13–16]. In this state, the nuclear drop does not support a surface tension nor nuclear pressure. When cells spread or elongate, the lamina eventually becomes smooth and taut. At this point, the nuclear lamina supports a surface tension, and a pressure develops in the nuclear interior. The nuclear drop now resists further deformation since it would require stretching of the taut lamina or compression of the nuclear volume. This resistance is too large for cellular forces to overcome, which explains why the nucleus typically reaches a steady-state shape exhibiting a smooth lamina in fully spread cells. Also, the presence of wrinkles and folds in the nucleus in rounded cells suggests that the bending resistance of the lamina surface does not govern nuclear shaping.

The excess area of the nuclear lamina (over a sphere of the same volume) along with a viscous nuclear interior allows the nucleus to take on highly deformed, non-spherical states (*i.e.*, rounded with folds or invaginations in the nuclear lamina or flattened or elongated with a smooth lamina) without extending the lamina area or compressing the nuclear volume. These two simple geometric constraints of constant volume and constant (excess) area permit the diverse range of nuclear shapes observed in various cell types and contexts without requiring a static force on the nucleus to explain the deforming shape. Consequently, for small strain rates corresponding to cellular shape changes during cell migration or spreading, neither the nuclear interior nor the nuclear lamina significantly resists deformation. Hence, the nuclear shape can freely conform to the moving cell boundaries by stresses transmitted through the cytoplasm [17]. Only when the nucleus is so highly deformed that lamina is smoothed and the nucleus becomes pressurized, as in fully spread cells, does the nucleus resist deformation like a liquid drop with surface tension.

Implications of the nuclear drop model

The nuclear drop model represents a fundamental rethink of how the nuclear lamina resists nuclear deformation and contributes to nuclear shape in response to cellular forces. Much like a liquid drop surface where the molecularly thin interface governs surface tension and drop shape under external forces, the 15-nm thin lamina imparts a surface tension on the nuclear drop to resist nuclear deformation as well as to establish nuclear shape. However, unlike the constant surface tension and variable surface area of a liquid drop, the surface area of the lamina is nearly inextensible, and the surface tension only emerges when the nucleus becomes pressurized, and the lamina becomes taut.

The nuclear drop model posits that chromatin, sub-nuclear organelles, and the nucleoplasm resist changes in nuclear volume but do not appreciably resist shear deformation or store elastic mechanical energy on physiological times scales. This is consistent with many studies in the field showing that sub-nuclear, membrane-less structures display liquid drop-like behavior themselves [18–21]. The drop model is consistent with findings from others that elastic forces in the nuclear interior rapidly dissipate on the time scale of seconds, and that nuclear contents behave as a viscous fluid on longer time scale [22,23]. In the drop model, chromatin state [24] and osmotic imbalances between the nucleus and cytoplasm [25] are interpreted as contributing to the nuclear pressure. This picture is consistent with nuclear envelope blebbing, and the subsequent rupture observed under confinement [7,26–28], a clear sign of nuclear pressure in cells. Importantly, the nuclear lamina is permeable, and as such, its molecular integration with the nuclear envelope is critical for sustaining a fluid pressure across the nuclear envelope.

The nuclear drop model offers orthogonal explanations for the emergence of abnormal nuclear shapes in

disease. For example, perturbations to nuclear lamins or to chromatin structure that occur in human diseases like cancer cause abnormal nuclear shapes in the model, not because of a softening of the elastic chromatin, but rather due to removal of surface tension and/or pressure in the nuclear drop, which allows the nucleus to deform without any geometric constraints.

The nuclear drop model also has implications beyond explaining nuclear shape. As discussed above, the model anticipates that surface tension develops in the nuclear lamina only when the nucleus becomes deformed enough to unfold the lamina. At this point, the translocation of transcription factors like YAP through stretched nuclear pores is expected to occur [29]. As another example, the drop model is likely to be important for mechanistic studies of nuclear positioning [30], which seek to explain how nuclear position arises from a balance of microtubule and F-actin motor-based forces on the nucleus. Whether the nucleus behaves like a drop, or an elastic solid, could lead to distinct explanations for the nuclear response to positioning forces.

Conclusions

Drop-like behavior of the nucleus is apparent from the shapes that are produced upon the deformation of the nucleus around slender obstacles as shown in Figure 1, as well as from observations of nuclear blebbing in many papers which are clearly suggestive of a nuclear pressure. Whether drop-like behaviors apply also to a wider range of nuclear deformations, for example, during deformation through confining spaces, or during shape transitions from circular shapes to elongated shapes [31], remains to be demonstrated. Measurements of nuclear pressure or the tension of the nuclear lamina inside cells, as well as how these vary across cell types, could be very useful in building a more complete picture of the properties of the nuclear drop. Likewise, how molecular structural components of the nucleus, such as the different nuclear lamins and chromatin remodeling proteins, determine properties of the nuclear drop will be important to determine. Overall, the nuclear drop model may help clarify how mechanical forces cause nuclear deformation in cells, how they impact gene expression [32], and how anomalies like nuclear rupture or nuclear dysmorphia occur in human diseases such as cancer.

Declaration of competing interest

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Data availability

No data was used for the research described in the article.

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