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Is the plant nucleus a mechanical rheostat?

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Abstract

Beyond its biochemical nature, the nucleus is also a physical object. There is accumulating evidence that its mechanics plays a key role in gene expression, cytoskeleton organization, and more generally in cell and developmental biology. Building on data mainly obtained from the animal literature, we show how nuclear mechanics may orchestrate development and gene expression. In other words, the nucleus may play the additional role of a mechanical rheostat. Although data from plant systems are still scarce, we pinpoint recent advances and highlight some differences with animal systems. Building on this survey, we propose a list of prospects for future research in plant nuclear mechanotransduction and development.

Introduction

Living organisms adapt their physiology and development to environmental cues, notably through transcriptional control. They also respond to internal cues. In particular, growth and shape generate patterns of mechanical stress. In turn, cells resist or yield to mechanical forces by modulating their mechanical properties. This applies to the matrix [1], the cytoskeleton [2], as well as the nucleus [3], with important consequences on gene expression and development [4].

We recently found that nucleus shape and mechanics depend on osmotic conditions, and that a nuclear regulator controls this response [5]. Here we review key features of nuclear mechanics and mechanotransduction based on data in mammals, yeast, and more recently plants, to highlight shared principles and plant specificities.

The three structural compartments of the nucleus

The nucleus is surrounded by the nuclear envelope (NE). The NE consists of two lipid bilayer membranes, namely outer (ONM) and inner (INM) nuclear membranes, which are separated by a ~35–50 nm perinuclear space. These membranes fuse together at the sites of Nuclear Pore Complex (NPC) giving rise to an ultra-donut topology [6]. Both NE components, notably LINC complexes (Linker of Nucleoskeleton and Cytoskeleton) and NPC may contribute to changes of mechanical properties of the nucleus in animals [7]. In plants LINC complexes and NPC have been identified [8].

The nucleoskeleton is connected to the NE by the inner nuclear membrane. It forms a filament meshwork of 10-30 nm composed of coiled-coiled proteins, called lamina in animals and plamina in plants [9,10]. While lamins form the lamina in animals, no orthologs of lamins but rather functional homologs have been identified in plants [11–13].

Last, the nucleus contains DNA wrapped around histones to form the nucleosomes. The nucleosomes are organized into 3D higher-order structures, where each chromosome occupies a territory called CT (for chromosome territory) in all eukaryotes, the organization of which can be modulated by mechanical forces [14]. Particularly in Arabidopsis, each CT forms a rosette like structure where transcriptionally active euchromatin loops emanate from the central cluster of condensed inactive heterochromatin which form chromocenters, located at the nuclear periphery [15,16].

Given their direct and indirect roles in transcription, these three compartments have attracted considerable attention in biology. Because they are also physical components, they are the targets of mechanical deformation and regulation, and have become a hot topic of study in biophysics too.

The nucleus as a physical object

The nucleus has specific mechanical features. When probed through the diffusion of internalized nanoparticles, the nuclear structure reveals transient ~300 nm sized micro-domains with elastic trapping and low elastic moduli (~20 Pa) and viscosities (~50 Pa.s) [17]. When the whole nucleus is deformed under constant loading (creep experiment), it displays a time-scale free weak power law behavior, with a viscoelastic modulus ranging from 1 to 10 kPa, and an exponent $\alpha \sim 0.2-0.3$ [18]. This corresponds to a mechanical behavior dominated by elasticity, with, at a typical time scale of a second, an apparent elastic modulus of about 5 kPa, and an apparent viscosity of ~300 Pa.s. More generally, this kind of behavior is observed in many out-of-equilibrium complex systems with multiscale structure and dynamics [19], like dense suspensions of colloidal particles (muds, shaving foams, emulsions)[20,21].

Importantly, the nucleus viscoelastic modulus correlates with cell identity. For example, during human stem cell differentiation, nuclei stiffen ~6-fold relative to cell cytoplasm. Consistently, nuclei of primary human fibroblasts are ~2 times stiffer than nuclei from Marrow-derived human stem cells and their stiffness correlates with the level of expression of lamins [22].

The ability of the nucleus to react to forces also entails energy requirements and dissipation. In that sense, and like most biological objects, the nucleus belongs to the family of active materials [23]. The idea that the nucleus may be an active mechanosensitive element has gained more and more momentum in the past decades [24], also building on the characterization of its structural elements and their physical link to the cytoskeleton [14,25]. In sum, there is now ample evidence that the mechanical properties of the main mechanically-relevant elements of the nucleus (nuclear envelope, lamins and chromatin) modulate nuclear mechanosensing, leading to the concept of a nuclear rheostat ([26], Figure 1).

The dynamic mechanical properties of chromatin

The nucleus displays a plastic behavior and strain hardening (stiffening with increased deformation) reminiscent of the non-linear stress-strain relationship of chromatin fibers [18]. This suggests that chromatin may play a dominating role in nuclear mechanics. In fact, in contrast to the classical view of nuclear mechanics depending mainly on a stiff nucleoskeleton

(lamins) surrounding a softer nucleoplasm (chromatin), recent studies indicate that modifications of histone state are sufficient to dictate nuclear rigidity independently of lamins in animals [27]. Nuclear mechanical properties have also been measured in the plant model *Arabidopsis* and may be linked to nuclear shape and chromatin status [5].

In mammals, when the balance shifts towards an increase of the transcriptionally less active state, condensed heterochromatin, and decrease of the transcriptional state of the gene-rich active less condensed euchromatin, nuclei become stiffer [27–29]. This response was revealed by playing on chromatin compaction and cytological studies through quantification of relative euchromatin/heterochromatin levels, using either inhibitors of histone post-translational modifications (histone deacetylation, histone methylation, histone demethylation) or genetics (overexpression of nucleosomal binding proteins). In plants, only one study was conducted in differentiated tissues using mutants exhibiting decondensed heterochromatin (*ddm1*, *atxr5atxr6*) and no obvious nuclear deformation was observed (nuclear sphericity and volumes). However, the analyses were conducted on fixed nuclei, which can modify the mechanical properties of the nucleus [30]. The nucleus also follows a power-law rheology when subjected to osmosis regulation [18]: isolated nuclei from epidermal cells increase their volume up to 200% and dilute the DNA content when removing salts in the media, whereas the nucleus becomes wrinkled, due to chromatin condensation, in high salt concentrations.

The dynamic mechanical properties of lamins

Lamins are nuclear intermediate filaments which can form the fibrous layer in the lamina but they are also found in soluble form in the nucleoplasm [31]. Depending on their locations, lamins have different functions. While lamin A/C and B interact with heterochromatin at the nuclear periphery [32], only lamin A/C interacts with euchromatin via lamin-associated polypeptide 2 α allowing a more direct regulation of gene expression [31]. Because lamin A interacts with chromatin, they can regulate nuclear viscosity, whereas lamin B rather modulate nuclear elasticity [33,34]. Interestingly using super-resolution microscopy, lamin B1 was shown to form an outer concentric ring, in a curvature-dependent localization to restrain outward protrusions of the stiff lamin A/C network facing the chromatin [35]. Such organization may help to explain the differential mechanical properties of lamins [33,34].

Both protein levels and folding degree of lamin A seem to scale with tissue stiffness: protein levels are increasing during differentiation in human cells [33] whereas lamins unfolding, through their phosphorylation, was induced in cells growing on soft matrix [36].

In plants, while nucleoskeleton structure was identified by SEM and TEM [37,38] no true lamin exists. Yet specific functional homologs are present [10]. This includes the CRWN (CROWDED NUCLEI) coiled-coil domain proteins found initially in carrot as NMPC (Nuclear Matrix Constituent proteins) [39] and further identified in Arabidopsis as CRWN1-4 [11,40]. While CRWN1 and CRWN4 are exclusively located at the nuclear periphery to mediate chromatin tethering, CRWN2 and CRWN3 are found in the nucleoplasm [40]. Using FRET experiments, CRWN1 was shown to interact with the nucleoplasm N-terminus domain of SUN1 (Sad1-UNC-84, [41]). Other proteins were shown to interact physically with SUN1 using yeast two hybrid, such as the plant specific lamin-like KAKU4 [42] or the chromatin associated protein PWO1 (PROLINE-TRYPTOPHANE-TRYPTOPHANEPROLINE INTERACTOR OF POLYCOMBS1, [43]). In Arabidopsis while CRWN1 and KAKU4 may maintain nuclear morphology through their interaction with the NE [42,44], they can deform the NE independently [42]. Interestingly, genetic interactions between single and double mutants, reveal that *PWO1* and *CRWN1* control nuclear size and shape in the same genetic pathway and control expression of a similar set of target genes repressed by the repressive histone marks H3K27me3.[43]. In the same trend, LINC complexes were shown to contribute to heterochromatin organisation and transcriptional gene silencing in plants [30]. Yet, very little is known about the contribution of these factors to nuclear mechanics. With the current data, only nuclear shape can be used as a proxy of nuclear mechanical properties. As a future direction of research, the scaling of nuclear deformation and chromatin organization with mechanical stress levels should be investigated in plants. Further studies could also correlate changes in plamina and nuclear mechanics to gene expression, including HI-C data and epigenetic landscape, as well as nuclear translocation of specific transcription factors.

The nuclear envelope as a transducer of cytoplasmic cues

The NE has its own mechanical properties. The elasticity, viscosity and plasticity of the NE is supported and modulated by several key proteins [45]. The geometric gap between the nuclear membranes is mostly maintained via the SUN1 and SUN2 proteins [46]. SUN1 and SUN2

proteins are located at the INM and interact, via their C-terminus SUN domain, with the KASH (Klarsicht/ANC-1/SYNE homology) domain of KASH family proteins located at the ONM. These SUN-KASH complexes form the LINC complexes and are found across all eukaryotes [46–50]. In the case of vertebrates, SUN1 is also connected to lamins A/C [51].

In a cellular context, the dynamics of actomyosin and microtubules can generate compressive and pulling stresses on the nucleus [52]. The NE plays a key intermediary role. For instance, disrupting the perinuclear actin cap through actin depolymerization leads to an increase of nuclear volume in mouse fibroblasts [53]. Similarly, untethering chromatin from the inner nuclear membrane induces nuclear deformation and reduces nuclear rigidity in *S. pombe* [54]. In plants, the presence of a large vacuole may further constrain the nucleus in a thin cytoplasmic compartment. Consistently, actin depolymerization in leaf epidermal cells does not change the elongated shape of nuclei [44]. Yet, LINC complexes are associated to actin via Myosin XI-i in plant cells [55] and impaired LINC functions prevent nuclear elongation in differentiated tissues [56,57]. Therefore, the shape of plant nuclei depends on NE factors and the cytoskeleton.

Interestingly, cortical microtubules align with maximal tensile stress directions in plant cell walls [58,59] and cytoplasmic microtubules are connected to the nuclear envelope through the microtubule nucleation complexes and regulatory factors [60,61]. Yet, how cortical stress may affect microtubule nucleation or NE properties is unknown.

The mechanical regulation of gene expression through the nucleus properties

Because the cytoskeleton and NE components are relatively stiff, cortical mechanical cues can change nucleus shape rapidly, leading to subsequent chromatin changes (Figure 2). For instance, the perinuclear actin cap can induce nuclear deformation mediated by LINC complexes and lamins A/C in 30 seconds [25,62,63]. Disrupting LINC complexes through SUN1 perturbation in fibroblasts cells leads to different transcriptional responses on soft versus stiff substrates [4]. Unfolding of lamins through their dephosphorylation affect gene expression within 10 minutes [36]. Last, destabilization of lamins under stress induces global chromatin reorganization, release of sequestered transcription factors as well as

modifications in setting repressive histone marks H3K27me3 mediated by the polycomb complex PRC2 [64] (Figure 2).

In parallel to the propagation of stress through the internal structural elements of the cell, cortical cues may indirectly reach the nucleus through protein translocation to the nucleus. In particular, the well-known Hippo pathway-YAP/TAZ involves the traffic of the transcriptional activator β -catenin from the cytoplasm to the nucleoplasm through the NPC [65]. Note that because NPCs are directly connected to nucleoskeleton, chromatin, and LINC complexes [66], the passive nuclear entry of the co-transcriptional factor YAP also depends on the physical deformation of the nucleus [67].

Chromatin is actually a site where mechanical and biochemical cues largely overlap [22,27,29,54]. In response to mechanical stress, changes in gene transcription may be modified either by changes of gene position inside the nucleus or by changes of the chromatin state itself. For instance, direct stretching of chromatin through mechanical forces (using RGD-coated magnetic beads) can induce expression of a GFP-tagged gene in hamster cellular line, and this involves actin and LINC complexes. This is triggered through a change in the spatial chromatin organization, i.e. a change in the location of the transgene [14]. Upon cell mechanical constraint, actomyosin induces the nuclear translocation of HDAC3 leading to decreased level of histone acetylation (permissive mark for gene expression) in mouse embryo fibroblast cells leading to a geometry-dependent transcriptional response. Such response is reversible [68,69]. On the contrary, inhibition of actin leads to the recruitment of the histone methyltransferase G9a to the NE and thus increases the level of repressive marks H3K9me2/3 in T-lymphocyte cells [70]. Interestingly, using an active 3D mechano-chemical model, also integrating cell geometric constraints, one can predict nuclear mechanics and architecture patterns [71].

In plants, the situation might be different at the molecular level, knowing for instance that there is no plant homolog of the YAP/TAZ pathway. However, the relationship between nuclear mechanics and gene expression might apply to all kingdoms. In this respect, we recently unraveled a link between nucleus, shape, mechanics and touch-response gene expression in response to hyperosmotic stress [5]. Interestingly, touch-response genes are also induced in response to conditions of changes in light conditions [72]. This is also true when

plants are subjected to sound vibrations [73]. Even though nuclear shape changes have not been explored in these latter cases, one could speculate that the plant nucleus integrates multiple environmental cues in part through its mechanics to regulate gene expression.

Functional implications of nuclear shaping in development

During development, tissues change their shape or mechanical status, and the resulting mechanical conflicts can transduce mechanical cues to cells and, arguably, nuclei. Although most of the knowledge on nuclear mechanics and mechanotransduction has been generated from studies in single cells in culture, this should also apply to cells in a tissue context. This starts to be addressed [74].

For instance, during epidermal morphogenesis in humans, actin-driven force decreased the level of the lamin-binding protein emerin at the INM inducing a loss of anchoring of heterochromatin at the NE and changes in transcriptional programs mediated by the polycomb PRC2, with important consequences for cell identity [75]. Furthermore, impaired NE functions, notably lamins A, lead to a wide range of diseases called laminopathies, such as muscular dystrophies and progeria [76]. Thus, nuclear mechanics shows functional regulation or correlation through a range of physical and pathological conditions.

Plant tissues are usually much stiffer than animal ones, because plant cells are highly pressurized with a turgor pressure in the MPa range, and surrounded by a stiff cell wall. Yet, plant cells are still experiencing mechanical conflicts, the pattern of which is determined by tissue shape and growth. Cortical microtubule arrays play a major role in guiding cellulose synthase complex (CSC) to regulate the cell wall and its physical properties. As mentioned above, cortical microtubules align with the direction of maximal tensile stress in the cell wall, thereby reinforcing the cell wall to resist tensile stress [58]. γ tubulins are present at the NE, where they nucleate cytoplasmic microtubules, together with GIP proteins (gamma-tubulin complex protein 3 (GCP3) interacting Proteins) [77]. Interestingly, γ tubulins are also found at the INM in a complex with SUN1 and GIPs which form a complex with the centromeric chromatin via CENH3 [78,79]. Although GIPs are conserved across species, they are found on both sides of the NE only in plants. Indeed, GIPs are not only associated with microtubule nucleation complexes outside the nucleus (like their human homolog MOZART1 [80]), but

also with the centromeres close to the inner side of the NE [77,78]. The GIP- γ tubulin hub might thus have a specific role in nuclear mechanotransduction in plants. Consistently, the *gip1gip2* mutant exhibits constitutive induction of touch-response genes [5].

Impaired GIP activity lead to irregular shape and lobulated nuclei in both meristems and differentiated root tissues [77] as well as severe developmental defects, with the presence of callus on differentiated tissues [61]. Such effects are not shared with other NE proteins. In particular, most of the nuclear envelope proteins characterized in LINC complexes identified so far regulate nuclear shape, yet, they do not necessarily induce major developmental defects when impaired [56,57]. This may in part be due to genetic redundancy. For instance, single *crwn* mutants have no growth defects, whereas *crwn1crwn2* and *crwn1crwn2crwn4* exhibit defective development, like stunted plants [40]. When compared to wild type, these mutants exhibit smaller and denser nuclei with fewer, more aggregated, chromocenters. Interestingly, only CRWN1 and CRWN4 allow tethering of heterochromatin at the nuclear periphery [81]. CRWN1 interacts with PWO1, and both control nuclear size [43]. PWO1 physically interacts with the polycomb complex PRC2 mediating H3K27me3 repressive marks [82]. Whereas mechanical regulation of nuclear architecture was linked to cell fate decisions in mammals [83,84], this remains to be explored in plants.

Perspectives for plant science: the role of the nucleus in multi-stress responses

In contrast to animals, plants exhibit a plastic postembryonic development that largely depends on environmental cues. In line with the established role of nuclear mechanics in animal development, plant development also relies on nuclear mechanotransduction. Yet the exact role of nuclear shape, mechanics and structural elements in signaling and development remains to be investigated. Conducting this research in plants will not only unravel conserved and divergent mechanisms in a walled context, it will also help to understand how the nucleus integrates cues from the environment.

In a recent study in *Arabidopsis*, we show the importance of nuclear mechanics in roots exposed to osmotic stresses. Throughout mechanical assessment of nucleus stiffness by atomic force microscopy and microrheometry, we revealed that hyperosmotic stress leads to nucleus shrinking, stiffening and chromatin remodeling. We also observed a strong induction

of touch-response genes. Importantly, these responses were reversible upon return to iso-osmotic conditions. We propose that chromatin behaves like a mechanosensitive gel in response to osmotic stresses (Figure 3) [5].

Interestingly, the *gip1gip2* mutant nuclei mimicked a hyper-osmotic phenotype. This further suggests that not only NE envelope proteins play an important role in the plant response to mechanical cues, whether such cues are emanating internally from growth or externally from the environment. Consistently, we found that *gip1gip2* plants are more resistant to harsh osmotic conditions. This suggests that the absence of GIP may actually prime the plant to hyperosmotic conditions (Figure 3).

Based on these recent results, and building on the comparative analysis of nucleus mechanics and mechanotransduction in animals, we thus propose that the nucleus also acts as a mechanical rheostat in plants. Why would plants be competitive model systems to address this question?

Plant cells do not move. Thus the relation between tissue stress and nucleus behavior is more amenable to be investigated in plants. While turgor pressure and the presence of a stiff plant cell wall represent obvious mechanical differences between plant and animal cells, two important remarks regarding mechanotransduction can be made. First, plant protoplasts, i.e. plant cells without their walls, display mechanical properties that are remarkably similar to that of animal cells. However, these features are dependent on the microtubule cytoskeleton, while they are mainly supported by the actin network in animal cells [2]. Second, in plants, the microtubule network organization and orientation is dependent on both cell shape [85][86] and the direction of maximal stress in the cell wall [58]. Thus, any external or internal cues leading to cell shape changes and/or mechanical stresses in the cell wall, may lead to signal propagation through the microtubule network and the NE to the internal nuclear structure. In this context, the nuclear sensitivity to cell shape [87] and subsequent chromatin modifications [68,71] observed in animal cells could also be at play in plant cells. However, in plant cells, the link between cell shape and nuclear shape and activity might be dependent on microtubules rather than actin, as in animal cells, and the forces needed to induce cell shape modifications and mechanotransduction should be orders of magnitude higher than those involved in animal cell mechanosensing.

Finally, the analysis of multi-stress responses is also facilitated in plants due to their plastic development and sessile nature, meaning that eco-devo study of nuclear mechanotransduction can be envisioned in plants. This may also help to understand plant responses to abiotic and biotic stresses too [88,89]. Altogether, nuclear mechanotransduction appears as a new field of research in the plant community, with implications going far beyond a comparison with animal nuclei.

REFERENCES AND RECOMMENDED READING

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

*of special interest

Bi et al., 2017 Genome Res.: Using the nucleoporin NUP136/NUP1 fused to GFP in RE-ChIP experiments in different Arabidopsis tissues, the authors show that 10 to 20% of chromosome regions are anchored at the nuclear periphery and are enriched in TE and H3K27me3-marked genes.

Nmezi et al., 2019 PNAS: Using high resolution microscopy STORM, the authors show that Lamin B1 forms an outer concentrating ring adjacent to the INM, the localization of which is strain-dependent. Lamins B stabilize nuclear shape and prevents protrusions from the underlying Lamins A/C network.

Chumova et al., 2019 Cells: In Arabidopsis, the γ tubulin initially associated with the microtubule nucleation complexes at the ONM, are found to co-localize with SUN at the INM. They are also present in complexes associated with GIP, suggesting new roles of these proteins at the NE.

Damodaran et al., 2018, Mol Biol Cell: The authors show the importance of fibroblast geometry in changing the chromatin condensation state and the transcriptional response to compressive forces.

Shivashankar, 2019, Curr. Opin. Cell Biol.: In this review, the author discusses the contribution of mechanical cues in changing nuclear architecture and cell fate transitions in mammals.

Miroshnikova et al., 2019, Curr. Opin. Gen. Dev: The authors present the latest advances linking mechanics and epigenetic gene regulation during differentiation.

**** of outstanding interest**

Stephens et al., 2018 Mol Biol. Cell: The authors show that modifications of histone state are sufficient to dictate nuclear rigidity independently of lamin perturbation. For instance, chromatin decompaction via increased acetylation is sufficient to decrease nuclear stiffness without perturbing lamins.

Mikulski et al., 2019 Plant Cell: The authors show that PWO1, which interacts with the polycomb complex PRC2, also interact physically with lamin-like CRWN1. This reveals mechanisms for repressing chromatin at the nuclear periphery in plants.

Hu et al., 2019 Genome Biol.: The authors show that lamin-like CRWN1 is needed to anchor repressed chromatin domains to the nuclear periphery in Arabidopsis. CRWN1 has a direct interaction with repressive heterochromatin regions, highlighting chromatin interaction with the lamina in Arabidopsis.

Alisafaei et al., 2019, Proc Natl Acad Sci U S A.: The authors develop a 3D chemo-mechanical model considering the reciprocity in dynamics between extracellular matrix, cytoskeleton and nucleus using micropatterning experiments.

Goswami et al., 2020 Current Biol. : In this paper, the authors propose that plant nuclei may act as a mechanical rheostat in response to osmotic stress with concomitant changes in nuclear rigidity, shape and mRNA levels of touch-response gene. The absence of GIP may prime the plant to respond to hyperosmotic conditions.

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Figure legends

Figure 1: Changes of cell and nuclear shapes under mechanical stress.

Under high cell stress, the nucleus is more compact with nucleoskeleton enrichment and spatial chromatin reorganization

Figure 2: The features of chromatin under mechanical stress

Changes of nuclear architecture under mechanical stress lead to chromatin condensation, clustering of chromocenters, repressive histone mark modifications inducing altered accessibility for the transcription of differentiated gene, and release of transcription factors from the nuclear periphery

Figure 3: Nuclear mechanical response in plants under hyperosmotic stress

Upon hyperosmotic stress, the nucleus is more compact with clustered chromocenters and induction of touch-response gene expression. The nuclear envelope proteins GIPs may act as negative regulators of this response.





