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Nuclear envelope dynamics in connection to chromatin remodeling

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### Abstract

The nucleus is a central organelle of eukaryotic cell undergoing dynamic structural changes during cellular fundamental processes such as proliferation and differentiation. These changes rely on the integration of developmental and stress signals at the nuclear envelope (NE), orchestrating responses at the nucleo-cytoplasmic interface for efficient genomic functions such as DNA transcription, replication and repair. While in animals, correlation has been already established between NE dynamics and chromatin remodeling using last generation tools and cutting-edge technologies, this topic is just emerging in plants, especially in response to mechanical cues. This review summarizes recent data obtained in this field with more emphasis on the mechanical stress response. It also highlights similarities/differences between animal and plant cells at multiples scales, from the structural organization of the nucleocytoplasmic continuum to the functional impacts of NE dynamics.

Key words: nuclear envelope, cytoskeleton, nucleoskeleton, mechanical cues, chromatin, epigenetics.

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## Introduction

The nucleus is a central organelle in eukaryotic cells, where the nuclear envelope (NE) compartmentalizes chromatin by means of two phospholipid bilayer membranes. The outer nuclear membrane (ONM) is derived from the endoplasmic reticulum (ER) and is separated from the inner nuclear membrane (INM) by a perinuclear space of about 30-50 nm (Stewart *et al.*, 2007). The INM is connected to the nucleoskeleton, a filamentous meshwork of 10-30 nm, composed primarily of lamins in animals, with functional analogs in plants and fungi (Ciska and Moreno Diaz de la Espina, 2014). The NE is perforated by nuclear pore complexes (NPCs) allowing molecular exchanges between nucleus and cytoplasm. Peripheral nucleoskeleton and NPCs allow chromatin tethering at the nuclear periphery and are required for proper genome organization and activity (Boruc *et al.*, 2012; Bi *et al.*, 2017; Hu *et al.*, 2019; Tang *et al.*, 2022a; Tang *et al.*, 2022b). The nucleoskeleton is also connected to the cytosol and the cytoskeleton through NPCs and Linker of Nucleoskeleton and Cytoskeleton (LINC) complexes (Zhou *et al.*, 2015; Kirby and Lammerding, 2018). In animals, cytoskeleton networks extend towards the cell periphery with the assembly of actin microfilaments (MFs) at the cellular cortex (Chugh and Paluch, 2018). Conversely, in walled plant cells, microtubules (MTs) are mainly present at the cortex to control cell shape through cellulose deposition while MFs are mostly involved in vesicle trafficking and organelle movements (Smith, 2003). Another specific feature of acentrosomal plant cells is that the NE acts as a Microtubule-Organizing Center (MTOC) forming radial MT arrays extending through the cytoplasm which reorganize during pre-spindle assembly upon mitosis entry (Masoud *et al.*, 2013; Ambrose and Wasteneys, 2014). Finally, intermediate filaments (IFs) form an intricate network of complex filamentous structures, exclusively found in animals, that extends from the cell membrane to the nucleus. IFs are master integrators of cell and tissue mechanics (van Bodegraven and Etienne-Manneville, 2021) and rearrange themselves to serve as stress buffers (Sanghvi-Shah and Weber, 2017).

All living organisms perceive mechanical cues from their environment and integrate them at the cellular level to respond and to adjust their behaviour for proper development and survival (Tsata and Beis, 2020). Both external and internal mechanical stimuli induce cellular deformation and/or constraints which are sensed at the cell periphery and transduced in biochemical and mechanical responses. Cytoskeleton reorganization and chromatin structural changes participate in such mechano-transduction and influence all genomic functions including transcriptional gene expression programs (Graham and Burrige, 2016; Fal *et al.*, 2017) which are important drivers for development and differentiation in both animals and

plants (Trinh *et al.*, 2021;De Belly *et al.*, 2022). The NE itself constitutes a site for nuclear mechano-transduction, where biochemical and mechanical stimuli are transferred to the nucleus. In animals, this occurs either through direct physical interactions at the NE between the cytoskeleton and the nucleoskeleton or *via* translocation of macromolecular factors from the cytoplasm to the nucleus through NPCs (Cho *et al.*, 2017;Fal *et al.*, 2017;Uhler and Shivashankar, 2017). Such mechanical perturbation influences nuclear migration and morphodynamic changes affecting key genomic functions (Dos Santos and Toseland, 2021;Long and Lammerding, 2021;Dupont and Wickström, 2022). As plants are sessile organisms, they are constantly subjected to external mechanical stresses such as wind, rain or wounding for aerial parts and osmotic pressure and soil rigidity for roots. While relevant cortical mechanosensing pathways start to be deciphered in plants (Colin and Hamant, 2021), the nuclear mechano-transduction linking nuclear mechanics to specific gene expression patterns and cell fate decisions remains elusive (Fal *et al.*, 2017).

Recently, we have established that nuclear morpho-dynamics are functionally connected to chromatin remodeling and gene expression as well as changes in nuclear mechanical properties (Goswami *et al.*, 2020b;Fal *et al.*, 2021a). In this context, beyond a simple physical barrier, the NE appears as a highly dynamic platform controlling communication at the nucleo-cytoplasmic interface, which changes shape and/or organization allowing developmental responses and stress adaptation. This process partly relies on epigenetic modifications impacting specific transcriptional programs for cell differentiation and identity (Song *et al.*, 2020). Epigenetic adjustments can be induced by simple cell deformations, for example in response to the surrounding matrix in animals (Alisafaei *et al.*, 2019) or to a prolonged mechanical stimulation in plants (Brenya *et al.*, 2022). Together, these gave rise to the model of the mechanical priming of cell identity and stress resistance *via* epigenetic processes (Brenya *et al.*, 2022;Li *et al.*, 2022).

Here, we reviewed the state-of-the-art knowledge about the impact of cellular deformation on nuclear shape, structure and mechanics through nucleo-cytoskeleton coupling in both animals and plants. As a follow-up, we discussed the subsequent mechanically-induced chromatin changes and their consequences on the spatial genome organization and epigenetic landscape ultimately resulting in transcriptional reprogramming.

### **Integration of mechanical cues from the cell periphery to the nucleus**

Cells interact physically with their environment and can perceive mechanical constraints. These mechanical cues are sensed at the cell periphery and transmitted to the nucleus to be converted into coordinated cellular responses. This relies on specific subcellular structures in animal cells and walled plant cells, especially at the nucleo-cytoplasmic interface (Figure 1).

### ***Mechanosensing at the cell periphery***

In animals, cells can be constrained during migration and/or tissue morphogenesis, but also in response to external mechanical forces. Such forces are driven by the stiffness of the surrounding extracellular matrix inducing deformations of the plasma membrane (Shin, 2018) which may regulate gene expression through direct force transmission and chromatin stretching (Joshi *et al.*, 2022). Cell geometric constraints can also be obtained using micropatterned substrates, inducing cellular shape changes which are transmitted to the nucleus through cytoskeletal physical links (Alisafaei *et al.*, 2019). Resulting mechanical signals are sensed by focal adhesion complexes, mainly formed by transmembrane proteins of the integrin family that connect the plasma membrane to the extracellular matrix and transmit mechanical tension to the actin-myosin cytoskeleton. Cell-cell junctions with cadherins are also key mechanosensitive modules (Mathieu and Manneville, 2019). In parallel, mechanosensitive (MS) ion channels embedded in the plasma membrane, such as Piezo1 and 2, integrate various mechanical cues typically by increasing cytoplasmic  $\text{Ca}^{2+}$  concentration. Their activation mainly triggers cytoskeleton modulation (Qin *et al.*, 2021). Interestingly, Piezo1 is also present at the endoplasmic reticulum (ER) and there, upon cell stretching, can mediate heterochromatin reduction via  $\text{Ca}^{2+}$  release from the ER, thus promoting chromatin mobility and decreasing NE tension (Nava *et al.*, 2020).

In plants, the high turgor pressure (around the Mpa range) is the primary cause of mechanical stress during plant development as it exerts pulling forces on cell walls (Trinh *et al.*, 2021). Cell wall deformation and remodeling can also transduce external mechanical signals for changes in gene expression as observed at the boundary region of the shoot apical meristem (Landrein *et al.*, 2015). Similarly, touching seedlings lead to an increase of cell wall stiffness and a decrease of cell elongation, together resulting in the modulation of the expression of touch-responsive genes (Wu *et al.*, 2020). In this context, plant mechano-sensing and transduction at the cell periphery begin to be elucidated (Trinh *et al.*, 2021), with  $\text{Ca}^{2+}$  signaling also playing a central role (Hamilton *et al.*, 2015). At the plasma membrane, MS ion channels named Mid1-complementing activity (MCA) 1 and 2 correlate with  $\text{Ca}^{2+}$  influx and mechanosensing in *Arabidopsis* roots (Nakagawa *et al.*, 2007). Also at the plasma membrane,

the receptor-like kinase FERONIA (FER) acts as a mechanosensor regulating Ca<sup>2+</sup> signaling and the expression of touch responsive genes (Shih *et al.*, 2014;Feng *et al.*, 2018). Contrary to animals, Piezo1 and 2 locate exclusively to the vacuole tonoplast in *Arabidopsis* (Radin *et al.*, 2021). Because the tonoplast may have more freedom of movement than the plasma membrane in walled plant cells, locating certain mechanosensory proteins to the tonoplast might be more effective for mechanosensing (Radin *et al.*, 2021).

### ***Importance of MFs and MTs dynamics in mechano-transduction***

*In vitro*, both MFs and MTs polymerize faster under tensile stress (Trinh *et al.*, 2021) and MFs branch upon compression-induced bending (Risca *et al.*, 2012). In animals, the influence of cytoskeleton organization on nuclear morphology and chromatin dynamics in driving cell differentiation is nowadays well documented. For example, during early differentiation of human hematopoietic stem cells, MT constraints induce nuclear invaginations associated with heterochromatin reorganization and modification in expression of specific hematopoietic genes (Biedzinski *et al.*, 2019). Similarly, cytoskeleton components were found to shape nucleus of mouse embryonic stem (ES) cells and to influence interactions of the pluripotency transcription factor OCT4 with chromatin, thus potentially affecting pluripotency (Romero *et al.*, 2022). At the plant cellular cortex, the cytoskeleton reorganization is also driven by mechanical stress, with a major role for cortical MTs as tension sensors, able to align along the maximal tensile stress directions in tissues (Hamant *et al.*, 2008;Hamant *et al.*, 2019). Organogenesis of plant cells within their tissue context, along with the regulation of cell wall plasticity, can also generate compression forces. At the boundary between the central shoot apical meristematic zone and the developing organ primordia region, nuclear compression was observed with changes in heterochromatin organization and gene expression (Landrein *et al.*, 2015;Fal *et al.*, 2021a). Together with the key role played by MTs in integrating mechanical stress to coordinate patterns of apical morphogenesis at the *Arabidopsis* shoot apex (Hamant *et al.*, 2008), this highlights the importance of MT reorganization for cellular shaping upon mechanical stress in plants.

### **The NE as a continuum between nucleoplasm and cytoplasm**

The NE contains many protein complexes linking cytoskeleton and nucleoskeleton. We describe hereafter key NE components and their respective functional implications by emphasizing differences and peculiarities between animals and plants, notably in terms of mechanical stress response (see Figure 2 and Table 1).

### *NPCs, responsive gateways at the nucleo-cytoplasmic interface*

NPCs are huge protein conglomerates (40–120 MDa) tunneling the NE at regular intervals where the ONM and INM are fused. NPCs are composed of hundreds of nucleoporin proteins (NUPs) assembled in a cylinder subdivided in four main substructures, namely the cytoplasmic filaments, the outer and inner rings forming the core component and the nuclear basket (Lin and Hoelz, 2019) (see Figure 2). NPCs selectively control the nucleocytoplasmic movement of macromolecules such as proteins and messenger ribonucleoproteins across the NE, thereby playing a key role in regulating gene expression and protein synthesis (Walde and Kehlenbach, 2010). While mechanisms underlying NPC transport selectivity remain elusive, recent evidences support that their structural and constituent dynamics may serve as a strategy to adjust NPC transport capacity under different cellular and physiological conditions (Hakhverdyan *et al.*, 2021). In animals and yeast, NPC density is constant over a range of nuclear sizes. Nevertheless, altered NPC composition can affect nuclear size and morphology (Jevtic *et al.*, 2014). Among other functions, NPCs, especially via their nuclear basket, are involved in regulating genomic functions by controlling chromatin organization and spatial arrangement (Krull *et al.*, 2010; Kadota *et al.*, 2020). Interestingly, many NUPs also have DNA-related functions inside the nucleoplasm, irrespective of their structural role within NPCs, enabling them to dynamically, rather than permanently, associate to the NPCs (Richards *et al.*, 2022).

NPC and NUP molecular functions in plants are far less described than in animals. In *Arabidopsis*, the plant specific nuclear basket NUP1/NUP136 can interact with heterochromatic domains such as pericentromeric regions enriched in repressed transposing elements (TEs) or silenced protein-coding genes (Bi *et al.*, 2017). NUP136 and the other plant specific nuclear basket component NUP82 were found to interact with the euchromatin binding factor guanylate-binding protein (GBP)-like GTPase (GBPL3). GBPL3 acts as a central connector between NPCs, nucleoskeleton, chromatin remodelers, transcription regulators and components of RNA splicing and processing machinery to coordinate gene expression during plant development and stress responses (Tang *et al.*, 2022b). Together with a physical link with the plant nucleoskeleton protein CRWN1/2 (functional analogs of animal lamins), GBPL3 acts as a chromatin remodeler and transcriptional regulator to coordinate stress responsive gene expression (Tang *et al.*, 2022b). Interestingly, NUP136 and CRWN1 are separately involved in nuclear shaping (Tamura and Hara-Nishimura, 2011; Tamura *et al.*, 2015). A mutation of the plant specific NUP CPR5 (CONSTITUTIVE EXPRESSION OF PR GENES 5), present at the

NPC trans-membrane ring, also leads to defects in nuclear shape and changes in gene expression (Gu *et al.*, 2016). Interestingly, the mis-regulated genes in *cpr5* mutants show significant overlaps with genes mis-regulated in the transcriptome of *gip1gip2* mutant also showing altered nuclear shape (Goswami *et al.*, 2020b). This highlights an intricate functional network at the NE for gene and nuclear shape regulation whose dynamic spatial orchestration still needs clarifications.

There is also evidence for a major role of NPCs in mechano-transduction in animals (Matsuda and Mofrad, 2022). In response to mechanical forces, two related mechanisms are proposed to affect nuclear import and accumulation of some specific transcription factors. Either the NPC diameter increases inducing structural changes of the nuclear basket or transcription factors change their conformation to increase their affinity with the nuclear transport receptor (Matsuda and Mofrad, 2022). In fission yeast, NPC diameter was shown to vary according to NE tension (Zimmerli *et al.*, 2021) and in mammalian cells, NPC stretching allows the shuttling of epigenetic and transcription factors, such as the mechanosensor and transducer YAP/TAZ (Elosegui-Artola *et al.*, 2017). In plants, NPCs are important regulators of gene expression in response to stress (Tamura, 2020) but their link to mechano-transduction have not yet been investigated.

### ***The LINC complexes, physical links between cytoskeleton and nucleoskeleton***

LINC complexes are the other main protein complexes present at the NE linking nucleoskeleton to cytoskeleton. The primary function of this link is to control nuclear positioning and movement (Tatout *et al.*, 2014;Burke, 2019) (see Figure 2). The LINC complexes are composed of two transmembrane protein families, namely the Sad-1/UNC-84 (SUN) domain proteins which span the INM and interact with nuclear components, and the C-terminal Klarsicht/ANC-1/Syne-1 Homology (KASH) domain proteins which span the ONM and interact with cytoplasmic components (Tatout *et al.*, 2014;Burke, 2019). SUN proteins contain a SUN domain located at the perinuclear space that is overall well conserved across eukaryotes and a nucleoplasmic domain that is much less conserved. Compared to SUN proteins, KASH proteins are far less conserved, with the KASH domain being highly variable in sequence and size (Meier, 2016). The tryptophan–proline–proline (WPP)-interacting proteins (WIPs) were the first animal KASH analogs identified as being able to bind SUN proteins at the NE in *Arabidopsis* (Zhou *et al.*, 2012). Other KASH analogs were identified in *Arabidopsis* including Toll-Interleukin-Resistance KASH protein (TIK) and SUN-interacting NE proteins 1–4 (SINE1–4) (Groves *et al.*, 2020). Apart from the non-conserved KASH



domain, the N-terminal cytoplasmic part of the KASH proteins is also highly diverse, as are the functions of KASH proteins. In animals and plants, interactions between various KASH proteins and SUN1/2 proteins in the lumen of the NE constitute physical bridges at the nucleocytoplasmic interface and allow the formation of various LINC complexes mediating differential associations between cytoskeleton and nucleoskeleton. In animals, the LINC complexes interact directly with the MFs through the N-terminal actin-binding domain of KASH proteins such as the two vertebrate paralogues Nesprin1 and 2 (Burke and Roux, 2009). Similarly, WIPs and WPP interacting tail anchored proteins (WITs) oligomerize in *Arabidopsis* to form a LINC complex at which Myosin XI-i attaches and interacts with long cables of cytoplasmic actin (Groves *et al.*, 2020). Beside this, a more direct and tissue-specific interaction was described for stomatal guard cells in which the KASH protein SINE1 directly attaches to MFs through a LINC complex involving SUN1/2 for nuclear positioning (Zhou *et al.*, 2014). While LINC may associate to MTs through motor proteins such as kinesin, dynein or fascin (*i.e.*, known to promote cell migration) in animals (Burke and Roux, 2009), there is no such evidence in plants.

Adding another layer of complexity, direct functional associations between LINC complexes and NPCs were reported in animal cells for the control of NPC assembly/distribution and the transport of LINC complex components (Jahed *et al.*, 2016). Reinforcing such association, SUN2, but not SUN1, was found to directly bind NUP210, forming a complex able to tether the replicative histone H3 variants H3.1/H3.2 and the chromatin reader BRD4 at the nuclear periphery to regulate gene expression during metastasis in mouse (Amin *et al.*, 2021).

As for NPCs, LINC complexes have been identified as nuclear mechano-transduction actors, but so far only in animals (Fal *et al.*, 2017). For example, forces transmitted *via* the KASH protein Nesprin-1 in isolated nuclei led to increased nuclear stiffness (Guilluy *et al.*, 2014). Accordingly, NESPRINs were shown to transfer mechanical forces from actomyosin to the nucleus through LINC complexes (Arsenovic *et al.*, 2016) and to contribute to the induction of a mechanically responsive gene program (Banerjee *et al.*, 2014). Local stresses applied to integrins can propagate to LINC complexes through the actin cytoskeleton and lead to chromatin unpacking as well as epigenetic changes promoting transcription (Tajik *et al.*, 2016). Finally, in fibroblast, both SUN1 alteration and changes in substrate rigidity affect transcription (Alam *et al.*, 2016).

### ***The tight connections between NE, nucleoskeleton and chromatin***

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Inside the nucleus, both NPCs and LINC complexes interact with a thin fibrous protein meshwork closely juxtaposed between the nucleoplasmic face of the INM and the chromatin (Figueiras *et al.*, 2019) (see Figure 2). In metazoan, this meshwork is named the nuclear lamina and is mainly composed of type V IF lamin proteins (*i.e.*, A and C-type lamins plus several minor tissue specific isoforms in most differentiated cells and B-type lamins expressed ubiquitously). Lamins play major roles in controlling nuclear rigidity and chromatin organization and are key elements for mechanosensing and nuclear mechano-transduction (Swift *et al.*, 2013; Vahabikashi *et al.*, 2022). In mammalian cells, A/C and B lamins interact with heterochromatin to form lamina-associated domains (LADs) enriched in heterochromatin at the nuclear periphery and interact as well with euchromatin domains to promote gene expression (Vahabikashi *et al.*, 2022). For example, in the progeria syndrome the accumulation of progerin, a dominant-negative A-type lamin protein, disrupts heterochromatin-lamina interactions and results in disturbed nuclear shape and spatial chromatin organization leading to gene expression alterations (McCord *et al.*, 2013).

In plants, no IFs or nuclear lamins were identified, but functional homologs were regrouped as nuclear matrix constituent proteins (NMCPs) (Masuda *et al.*, 1997). NMCPs assembly produces an intricate filamentous network called plamina, including filament bundles across the nuclear periphery (Masuda *et al.*, 2021). They are widely conserved in land plants and CROWDED NUCLEI 1 to 4 (CRWN1-4), identified in *Arabidopsis*, belong to this family (Ciska and Moreno Diaz de la Espina, 2014). CRWN1 and 4 interact and redundantly modulate chromatin organization at the nuclear periphery through their direct binding with chromatin regions named plant LADs (PLADs) (Hu *et al.*, 2019). This link with chromatin was further reinforced by the discovery that CRWN1 interacts with the chromatin and polycomb-associated component PROLINE-TRYPTOPHANE-TRYPTOPHANE-PROLINE INTERACTOR OF POLYCOMBS1 (PW01), possibly linking repressive H3K27me3-marked chromatin and the nuclear periphery in *Arabidopsis* (Mikulski *et al.*, 2019). In addition, CRWN1 directly associates with SUN1 (Graumann, 2014), while the NMCP-binding protein KAKU4 indirectly associates with SUN1 *via* interaction with CRWN1 (Goto *et al.*, 2014). CRWN1 and CRWN4 are key factors maintaining nuclear morphology. In the contrary to *crwn2* or *crwn3* mutants (Wang *et al.*, 2013), *kaku4* and *crwn1* mutants exhibit drastic abnormalities in nuclear shape in differentiated tissues and their combination had neither synergistic nor additive effects (Goto *et al.*, 2014). The plant specific nuclear envelope-associated proteins (NEAPs) are anchored at the INM and directly interact with SUN proteins. Further connecting NEAPs with chromatin organization and gene regulation, a putative transcription factor called AtbZIP18 was identified

among the NEAP interactors (Pawar *et al.*, 2016). More recently, the plant NE transmembrane protein (PNET2) was identified as a *bona fide* INM protein interacting with CRWN1 in Arabidopsis (Tang *et al.*, 2022a). PNET2 together with KAKU4 contribute to the proper maintenance of genome architecture and transcriptome programming during plant development and stress response. Interestingly, the simultaneous overexpression of PNET2 and KAKU4 induces more severe nuclear deformations than when they were overexpressed separately (Tang *et al.*, 2022a). Finally, suggesting a physical link between the nucleoskeleton and NPCs, NUP82 and 136 were revealed to bind CRWN proteins (Mermet *et al.*, 2021). Together, tight functional connections exist between cytoskeleton, NE, nucleoskeleton and NPCs to regulate gene expression in plants but the importance of the plasma in mechanical response remains to be investigated.

### **Chromatin remodeling upon NE dynamics and mechanical stress**

Nucleosome is the main structural unit of eukaryotic chromatin and consists of DNA wrapped around a core histone octamer (2x (H2A, H2B, H3 and H4)). Chromatin is dynamically organized and can promote DNA compaction in heterochromatin or relaxation in euchromatin at different scales to affect genomic functions (Dogan and Liu, 2018). Among mechanisms affecting directly or indirectly chromatin compaction, epigenetic processes, including DNA methylation, histone variant incorporation and histones post-translational modifications (PTMs) were involved in regulating all DNA related processes (Lloyd and Lister, 2022; Mansisidor and Risca, 2022). On a larger scale, chromatin during interphase forms functional loop domains allowing each chromosome to occupy an individual territory. Physically, chromatin is considered as a viscoelastic gel displaying changes in macromolecular crowding (Mitchison, 2019). In recent years, chromatin organization and dynamics has emerged as an instrument of mechanical stress response in both animals and plants (Uhler and Shivashankar, 2017; Goswami *et al.*, 2020a).

#### ***Impact on constitutive heterochromatin***

In both animals and plants, chromocenters are predominantly composed of silent, condensed and gene-poor pericentromeric heterochromatin, and are attached in a non-random way to the nuclear periphery *via* lamins or functional analogs (Fransz *et al.*, 2002; Rullens and Kind, 2021). A recent report on epidermis stem cells highlights the fact that a majority of the observed heterochromatin decondensation induced under short time stretching tensions happens mostly in non-coding regions, resulting in no major transcriptional changes (Nava *et al.*, 2020). More

recently, a decrease of H3K9me3 constitutive heterochromatin mark levels accompanied by a decrease of DNA methylation and A/C-type lamin content at the nuclear periphery was reported after squeezing mice isolated nuclei through a microfluidic device (Song *et al.*, 2022). Based on these results, the mechanically-induced chromatin softening resulting from the constitutive heterochromatin decompaction was proposed to decrease nuclear stiffness to protect the genome against mechanical stress-induced DNA damages.

In plants, few examples illustrate the effect of mechanical forces or NE destabilization on constitutive heterochromatin but correlations with stress and chromatin/nuclear softening are far from being clear. In *Arabidopsis* shoot apical meristem, tissue curvature generates nuclear compression at the boundary between organs and meristem. This nuclear compression correlates with decreases in DNA methylation and chromocenter numbers and an increase in the expression of the abiotic stress related linker histone H1.3 (Fal *et al.*, 2021a). Upon hyperosmotic stress in root meristematic cells, while nuclei become smaller, less spherical and stiffer, the number of chromocenters was found decreased, suggesting a heterochromatin reorganization (Goswami *et al.*, 2020b). On the contrary, the nuclear rigidity was found decreased with more diffuse heterochromatic signals upon hypoosmotic conditions (Goswami *et al.*, 2020b). Further supporting the links between NE and constitutive heterochromatin compaction, chromocenters were also found affected in differentiated tissues when plasma and LINC complexes components were mutated. Indeed, despite similar changes in nuclear morphology (*i.e.*, smaller but more spherical), an increased compaction of chromocenters in *crwn1crwn2* mutants correlates with a maintenance of their transcriptional silencing, while altering LINC complexes causes chromocenter decondensation and defects in their silencing (Poulet *et al.*, 2017). Together, these works illustrate the complexity of the functional links between the NE, the plasma and constitutive heterochromatin that may vary depending on examined tissues *e.g.* the cell wall stiffness differs between meristematic and differentiated root tissues (Somssich *et al.*, 2016).

### ***Regulation of facultative heterochromatin***

Facultative LADs harbor developmentally regulated genes controlled by Polycomb complexes involved in trimethylation of histone H3 lysine 27 (H3K27me3) at the nuclear periphery. Their interaction with lamins is reported in numerous tissues to allow the regulation of gene expression via chromatin distortion resulting from NE deformation by mechanical stress conditions and/or during cellular differentiation (Bianchi *et al.*, 2015). In human epidermal stem cells, application of long-term bi-axial stretches prevents cells from realigning to

minimize strain on the nucleus and provokes the accumulation of the silencing H3K27me3 mark at epidermal differentiation genes, thus preventing epidermal stem cell differentiation (Le *et al.*, 2016). Thus, beyond rapid chromatin remodeling coping mechanisms dedicated to release tensions on the nucleus, long-term mechanical deformations can actually modify cell fate (Dupont and Wickström, 2022).

Similar mechanisms exist in plants. In the shoot apical meristem, transcriptional repression and activation dynamically occur to specify cell fate and to promote organized cell growth and differentiation (Nguyen and Gutzat, 2022). For example, expression of the shoot meristem maintenance homeobox gene *SHOOT MERISTEMLESS (STM)* is quantitatively correlated to curvature in the saddle-shaped boundary domain of the shoot apical meristem, where tissue curvature generates nuclear compression (Landrein *et al.*, 2015). Because *STM* repression during organogenesis relies on the deposition of H3K27me3 by the Polycomb Repressive Complex 2 (PRC2) (Kim *et al.*, 2012), it would be interesting to determine whether mechanical stress at the boundary helps to keep a low H3K27me3 level at *STM*. In any case, this example suggests a striking difference as to the functional link between mechanical stress and H3K27me3 in animals and plants. One possible explanation could originate from the limited cell-fate plasticity of the unipotent epidermal stem cells compared to the pluripotent character of plant stem cells. Another interesting finding was that defects at the nuclear periphery in *Arabidopsis* can lead to premature aging effects such as the presence of cell death lesions through aberrant H3K27me3 deposition. Thus, stress-related genes were found constitutively up-regulated in *crwn* mutants due to a decreased in H3K27me3 levels at their loci (Choi *et al.*, 2019).

In animals, the mechanistic/mammalian target of rapamycin (mTOR) regulates PRC2 mediated gene silencing (Harachi *et al.*, 2020) and nuclear architecture in response to stress (Lamm *et al.*, 2020). Additionally, mTOR is also able to sense interruptions between chromatin and NE, since lamin deficiency leads to mTOR hyperactivation (Ramos *et al.*, 2012; Chiarini *et al.*, 2019). In plants, TOR has been recently involved in H3K27me3 deposition and PRC2 mediated silencing of genes involved in development and stress responses (Dong *et al.*, 2022; Ye *et al.*, 2022). Together with the growing proofs that TOR also controls cytoskeleton organization and dynamics (Cao *et al.*, 2019; Dai *et al.*, 2022), the position of TOR at the nexus between cytoskeleton and nuclear dynamics (Dong *et al.*, 2023) become increasingly evident in plant cells.

### ***Regulation of euchromatin***

Histone acetylation and trimethylation of H3K4 are typical euchromatic marks that positively correlate with gene transcription. In mouse melanoma cells, the histone deacetylases (HDAC) inhibitor trichostatin A (TSA) was used to soften stiff nuclei and alter chromatin structure in order to inhibit cell migration (Gerlitz and Bustin, 2010). Because TSA also leads to increased tubulin acetylation and stability resulting in reduced cytoskeletal stiffness (Fischer *et al.*, 2020), its impact on nuclear rigidity probably reflects a combined effect on both euchromatin and cytoskeleton. Inversely, forcing animal cells (*i.e.*, mammary epithelial cells, mesenchymal stem cells or fibroblast) into micropatterned substrates to alter cellular geometry results in smaller and stiffer nuclei, global histone deacetylation, chromatin condensation and overall reduction in gene expression (Dupont and Wickström, 2022). Besides this, a strong positive correlation was observed between nuclear volume and histone acetylation, suggesting that changes in nuclear morphology might enhance accessibility to transcriptional machinery and hence regulate total levels of transcription (Jain *et al.*, 2013). The notion that active histone marks positively respond to changes in mechanical force was further explored in melanoma aggregates at which tissue curvature promotes H3K4 methylation and H3 acetylation to increase expression of pro-oncogenic genes (Lee *et al.*, 2020). As a possible mechanism, the cytoplasmic-to-nuclear redistribution of HDAC3 was reported to depend on actomyosin contractility (Jain *et al.*, 2013). In plants, only indirect proofs have been reported so far. On one side, nuclei change their shape during root elongation from spherical in meristem to spindle-shaped in epidermis (Meier *et al.*, 2016). On the other side, using TSA to inhibit HDAC results in a hyperacetylation of histones H3 and H4 and alters the expression of specific genes involved in root cellular patterning (Xu *et al.*, 2005). Together, nuclear shape and histone acetylation may function in mediating positional cue to direct gene patterning in the root epidermal cells.

Gene positioning inside the nucleus is critical for expression (Egecioglu and Brickner, 2011). In yeast, most transcription factors are capable of tethering target gene to NPCs, thus promoting their expression (Brickner *et al.*, 2019). Accordingly, specific NPC components are attached to chromatin loops harboring actively transcribed genes (Bianchi and Lanzaolo, 2015). Relocation of chromatin close to NPCs for high transcriptional activity is also observed in animals, with several NPC components being responsive to mechanical signals (Matsuda and Mofrad, 2022). This is the case for NUP210, which was recently found to promote chromatin accessibility at the nuclear periphery in response to extracellular mechanical signals during metastasis (Amin *et al.*, 2021). In *Drosophila*, NUP107, a core component of the outer ring sub-complex, and NUP93, a core component of the inner ring sub-complex, were found to associate

with actively transcribed genes and Polycomb-silenced regions, respectively, revealing a complex landscape of NE-genome interactions (Gozalo *et al.*, 2020). This duality has a central role in cellular differentiation and its disequilibrium is associated with specific diseases (Bianchi and Lanzaolo, 2015).

In plants, NPCs are largely surrounded by repressive heterochromatin domains (Barneche and Baroux, 2017; Bi *et al.*, 2017; Gozalo *et al.*, 2020) and some of their components can interact with heterochromatic factors such as LIKE HETEROCHROMATIN PROTEIN1 (LHP1) (Chen *et al.*, 2020). Reminiscent of bacterial operons, silent biosynthetic gene clusters in *Arabidopsis* were found at the nuclear periphery associated with heterochromatic domains, while transcriptionally active ones relocate away from the nuclear periphery (Nutzmann *et al.*, 2020). In contrast, several light-inducible loci were reported to relocate from the nuclear interior to the periphery upon their activation in response to light stress in *Arabidopsis* (Feng *et al.*, 2014). Similarly, artificial targeting of a luciferase reporter gene to the NPC using the Lac Operator/Lac Repressor system results in its increased expression (Smith *et al.*, 2015). Further supporting that NPCs act as transcriptional hubs to promote gene expression, the euchromatin binding factor GBPL3 interacts with the nuclear basket components NUP82 and NUP136, as well as with CRWN1 (Tang *et al.*, 2022b), to coordinate expression during plant development and stress responses (Bi *et al.*, 2017). Together, NPCs and the nuclear periphery seem to play dichotomous functions in both animal and plant cells and the question whether these functions are differently driven by mechanical forces remains to be answered.

### **NE dynamics and its functional relevance**

Changes in nuclear structure and morphology modulate key cellular and genomic functions, thus being critical for cell differentiation and organism development (Kalukula *et al.*, 2022). For that reason, particular nuclear shapes were correlated to specific cell identities and/or tissue contexts in both animals and plants (Meier *et al.*, 2016; Deolal and Mishra, 2021).

#### ***Nuclear shaping during development and in response to extracellular constraints***

Changes in nuclear shape usually reflect altered nuclear mechanics and are highly relevant to normal development and physiology, as well as for responses to stress and diseases in both animals and plants (Skinner and Johnson, 2017; Goto *et al.*, 2021). For example, lobulated nuclei occur in the most mature form of neutrophils, making nuclei more deformable and helping neutrophils to easily pass through small gaps in endothelium and extracellular matrix (Hoffmann *et al.*, 2007). Besides altered cytoskeleton organization, differentiation of bovine

and human mesenchymal stem cells implies changes in nuclear shape, stiffness and organization due to the restructuration of A/C-type lamin network and an increase in heterochromatin content. Even if these changes can be both consequences and mediators of differentiation, the nucleus seems to act as a mechanostat to modulate mechano-sensing during differentiation (Heo *et al.*, 2016). Further supporting this, the size of nuclei was found decreased and their aspect ratio increased, while at the same time, A/C-type lamins were more expressed and redistributed toward the nuclear periphery in human mesenchymal stem cells undergoing adipocyte differentiation (McColloch *et al.*, 2019). Similarly, during the step-wise differentiation program that governs epidermal stratification, epidermal cells decrease their intrinsic tension and undergo marked nuclear changes with decreased nuclear volume and transcriptional activity, as well as increased heterochromatin amount and relocation toward the nuclear interior (Miroshnikova *et al.*, 2019). Beside this, the nucleus can perceive tension, compression or shear from extra-cellular environment through cytoskeleton reorganization (Kirby and Lammerding, 2018). Under hypo-osmotic stress, the nucleus expands through maximal nuclear lamina stretching capacity, while under hyper-osmotic stress, the nucleoplasm contracts, and the nucleus shrinks (Finan and Guilak, 2010). By expanding surface tensions at the NE, mechanical stimuli increase NPCs diameter and consequently affect all NPC related functions (Allen and Strader, 2021). Also, since ONM forms a continuum with the ER which contains MS ion channels, tensions at the NE activate these channels, leading to Ca<sup>2+</sup> release impacting cell contractility (Lomakin *et al.*, 2020) and chromatin organization (Nava *et al.*, 2020).

During plant root development, besides cell shape modifications, nuclei change from rounded in the meristem to elongated in the differentiation area (Meier *et al.*, 2016). Nuclear migration in *Arabidopsis* growing root hair (Singh *et al.*, 2021b) or pollen tube (Zhou and Meier, 2014) is also accompanied by nuclear shape changes. In contrast to animal in which nuclei are moved by motor proteins along the MT cytoskeleton, the actin cytoskeleton and a myosin motor physically interact with the NE through a SUN-WIP-WIT bridge to enable nuclear movement in root hair (Tamura *et al.*, 2013). In addition, hyper-osmotic stress results in marked chromatin condensation (Martins *et al.*, 2012). In *Arabidopsis* root meristematic cells, similar changes were observed, with nuclei and heterochromatic chromocenters shrinking upon hyperosmotic stress and mechanoresponsive genes being induced (Goswami *et al.*, 2020b). Even if knowledge is just emerging in plants, the nucleus appears to act as a mechanical rheostat during development and stress response (Goswami *et al.*, 2020a ; Fal *et al.*, 2017).



### ***NE dynamics impacts on chromatin during cell cycle and upon DNA damage***

During the transition from G1 to S/G2 phase, nuclei from proliferating human cells change their shape (Chu *et al.*, 2017). Interestingly, inhibition of myosin II during G1 phase prevents nuclear flattening and impedes progression to S phase (Aureille *et al.*, 2019). In plants, chromatin also undergoes drastic changes affecting its degree of compaction during the cell cycle (Pecinka *et al.*, 2020). During cell division, the NE disassembles upon entry into mitosis and reforms in telophase around the two separated sets of daughter chromosomes. In animals, a MT-induced tearing of the nuclear lamina seems to contribute to the NE breakdown (Beaudouin *et al.*, 2002). Then, upon mitosis exit, the NE reassembles around decondensed chromosomes through the binding of INM proteins to chromatin (Ulbert *et al.*, 2006). In plants, NE breakdown is also dictated by MT dynamics with the relocation of the nucleoporin RAE1 on spindle MTs (Masoud *et al.*, 2013). In mammalian cells, SUN1 and a membrane-associated histone acetyltransferase hALP contribute to chromosome decondensation at the end of mitosis during NE reformation (Chi *et al.*, 2007). Following NE dynamics, *Arabidopsis* SUN1 orthologs changed their localization dynamically during mitosis (Oda and Fukuda, 2011). However, the underlying mechanisms of NE reformation are not yet understood.

In human cancer cells, mechanical forces can increase DNA replication stress and genome instability thereby contributing to tumorigenesis. Indeed, nuclear deformations resulting from cell migration in tight spaces or external cell compression were found to cause DNA damage associated with replication stress without NE rupture (Shah *et al.*, 2021). One explanation could be that torsional stress in DNA increases due to physical deformations of the nucleus. This explanation is supported by the fact that the ataxia telangiectasia mutated and Rad3 related (ATR) protein, which is an upstream regulator of replicative stress, has been reported to be mechanosensitive (Kumar *et al.*, 2014). ATR-defective cells exhibit altered nuclear morphology and mechanical properties, together with an aberrant perinuclear chromatin organization and an increased heterochromatinization (Kidiyoor *et al.*, 2020). In *Arabidopsis*, *crwn1crwn4* double mutants are hyper sensitive to genotoxic stress and show reduced anchoring of RAD54 at the nuclear periphery (Hirakawa and Matsunaga, 2019). Similarly, *gip1gip2* mutants present an increased genome instability due to the impaired recruitment of RAD51 at double strand DNA breaks at the nuclear periphery of root meristematic nuclei (Singh *et al.*, 2021a). Therefore, the NE in eukaryotes contributes to homologous recombination repair and genome stability at the nuclear periphery.

## Outlook: A need to develop tools for live cell imaging linking nuclear mechanics and chromatin remodeling

Up to now most of nuclear and cytoplasmic membrane shape changes were evaluated through morphological and physical parameters using technical approaches such as micro-rheometry, Atomic Force Microscopy (AFM) or optical tweezers (Goswami *et al.*, 2020a). In order to quantify and visualize intracellular membrane tensions *in cellulo*, new tools have to be developed. In animals, the Fluorescent Lipid Tension Reporter (FlipTR) can measure external membrane tensions based on lifetime measurements (Colom *et al.*, 2018). More recently, the development of a HaloTag-Nuclear Localization Signal photocleavable fluorescent probe to evaluate tensions in the NE seems very promising (Lopez-Andarias *et al.*, 2022). In plants, recent development of an imaging microviscosity toolbox for cells and tissues has enabled to specifically visualize tensions at the plasma membrane and cell wall (Michels *et al.*, 2020). Förster Resonance Energy Transfer (FRET) protein bioSensors of osmotic stress such as SENSOR EXPRESSING DISORDERED PROTEIN 1 (SED1), based on the *Arabidopsis* intrinsically disordered AtLEA4-5 protein, has already been developed and used to track the effects of osmotic stress on living bacteria, plant and human cells (Cuevas-Velazquez *et al.*, 2021). Non-destructive and non-invasive methods such as the new type of optical elastography named Brillouin microscopy, based on photon-phonon interactions, can be used to evaluate cellular and tissue mechanical properties in 3D (Prevedel *et al.*, 2019) and also intra-nuclear mechanics (Liu *et al.*, 2022). Live cell imaging of macromolecular crowding will bring as well new information about changes of cell physical properties in response to mechanical cues. Recently, the development of genetically encoded multimeric nanoparticles (GEMs) as micro-rheology probes has allowed to evaluate biophysical properties of the cytoplasm and nucleoplasm of yeast and human cells (Delarue *et al.*, 2018). At the chromatin level, live-cell imaging has to be addressed in different genetic backgrounds by modifying epigenetic status through directed global and local histone modifications using chromatin bodies and Cas9 approaches (Fal *et al.*, 2021b).

Altogether, current and future technical improvements will contribute to further address and unravel mechanobiology processes in the very particular context of walled plant cells. These recent technology developments will also allow to investigate in more detail reciprocal interplays between chromatin, nucleoskeleton, NE and cytoskeleton impacting nuclear mechanics in the context of plant growth and development. Lastly, considering mechanical stress acclimation/adaptation of plants, the expected new findings will certainly contribute to understand how a mechanical stress may confer transcriptional memory and promote plant

defense priming to (eventually) respond more efficiently to other abiotic and biotic stresses (Brenya *et al.*, 2022).

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## Figure Legends:

### Figure 1: Mechanical connection from the plasma membrane to the NE in animal mesenchymal cells and differentiated plant cells.

In both cell types, MFs (in red) are connected to protein complexes at the plasma membrane complexes: to focal adhesions allowing cell-matrix connection in animals, and to plasmodesmata allowing cell-cell communication in plants. The other extremities of MFs are connected to the NE via LINC complexes. A particularity of the animal cell, in comparison to plants, is the presence of elongated membrane structures called lamellipodia which allow cell movement along the surrounding matrix and are formed by the polymerisation of MFs pushing against the plasma membrane. Another animal specificity is the presence of IFs (in blue) establishing connections with hemidesmosomes and LINC complexes. MTs (in green) are nucleated from  $\gamma$ TuRCs at the centrosome in animal cells and plus-ends connect either to the plasma membrane through crosslinks with actin and IFs, or to the NE with LINC complexes. In acentrosomal plant cells, endoplasmic MTs nucleate from both the plasma membrane and the NE. Cortical MTs (here indicated in pale green in the cell background) guide the movement of cellulose synthase complexes (not shown) and align perpendicularly to the direction of cell elongation. Cortical MTs reorient during mechanical stress to follow the direction of the strain. Characterized mechanosensory receptors are indicated in both models (FER, Piezo). Mitochondria (red), chloroplasts (green) and the vacuole (orange) are also represented. Nuclear structures are detailed in Figure 2.

**Figure 2: Protein complexes and functional modules involved in the organisation and dynamics of the NE in animal (left) and plant cells (right).**

Cytoskeleton attachment to the NE differs significantly between animals and plants. While MTs can bind to Nesprin4 specific LINC complexes via kinesin in animal cells (A), the only way reported so far in plants for their interaction to the NE is through  $\gamma$ -TuRC and associated GIP1/2 proteins present at the ONM (H). The  $\gamma$ -TuRC positioning may involve a possible TSA1/trans-NE complex which is yet to be fully described. GIP1/2 are also found at the INM associated to the centromere (CENH3). MFs bind through the LINC complexes in both models but the attachment differs significantly at the ONM: while Nesprin1/2 is used in animal cells (D), different KASH proteins are used in plants (F), namely the WIP1/2/3 and WIT1/2. It is interesting to highlight that WIP1/2/3 interact with SUN1/2 proteins, WIT1/2 do not. The stabilisation of the interaction with MFs *via* Myosin XI-i also involves two additional proteins, namely WPP and RanGAP. Other KASH proteins such as SINE1/2 can bind to MFs and were shown to also be necessary for MT patterning, but in a way not yet determined (G). Additional KASH proteins in animals such as Nesprin-3 can bind Vimentin-based IFs (C) while IFs are absent in plants. Other KASH proteins (TIK, SUN3/4) have been identified as interacting with SUN complexes in plants, but their function still remains unclear. The cytoskeleton network allows the mechanical propagation of tensile and shearing forces from the cellular periphery to the NE, resulting in its mechanical deformation, but this deformation can also result from the induced condensation/decondensation of the chromatin from the inside of the nucleus.

Chromatin (pale blue) tethering to the nuclear periphery has been observed in both models and requires the presence of lamins (A/C and B-type lamins) in animal cells and lamin-like proteins (CRWN1/4, KAKU4) in plants. Both lamins and lamin-like proteins bind to the SUN complexes (highly conserved between both reigns) with the addition of lamin-associated proteins which are specific to animals (Emerin, Man1, Nur1, Lem2) and plants (PNET2) (B, H). At INM, NEAP1/2/3 interact with the TF bZIP18 (E). Some lamin and lamin-like proteins can also be found attached to the chromatin in the nucleoplasm, especially A/C and B lamins in animals and CRWN2/3 in plants. The chromatin tethered to the nuclear periphery is highly enriched in heterochromatin and repressing complexes such as PRC2 which maintain transcriptional repression through the deposition of H3K27me3 epigenetic marks. The nucleoplasm apart from the nucleolus is on the contrary mostly composed of euchromatin.

Compared to the rest of the nuclear periphery, euchromatin is highly enriched at the NPCs to promote gene expression, involving the nuclear pore basket components NUP2 and NUP160 in animals (A), and the basket proteins NUP82, NUP1/NUP136 and the ring protein CPR5 in plants (G). Other proteins of the basket were shown to be necessary for heterochromatin organisation (*i.e.*, TPR, NUP153 and NUP210 in animals, NUP1/NUP136 in plants), or for the regulation of chromatin attachment to the NPC (NUP155, NUP93 and NUP62 in animals). Other proteins such as NUP107 were shown to be more specifically involved in the activation of DNA replication.

NPCs are also important for the shuttling of mechanoresponsive factors through the NE. In animals, TOR is mechanically activated through Piezo1-related  $Ca^{2+}$  signalling from the ER and actively regulates gene expression (B). In plants, it is activated by FER and phosphorylates the PRC2 component FIE, resulting in FIE shuttling through the NPC for the regulation of gene expression (E). Interestingly, we can highlight that TOR seems to regulate dynamics of the cytoskeleton in a reign-specific way: while it was shown to regulate MT formation in animals, it appears to rather regulate the formation of MFs in plants. Finally, other proteins have been shown in animals to shuttle through the NPC as a response to tensile stress on the NE: G-actin for instance, which can be used as a transcription factor, is exported outside of the nucleus to help the polymerisation of a perinuclear ring of F-actin preventing NE rupture (D). YAP/TAZ

is another mechanoresponsive transcription factor which necessitates F-actin connection at LINC complexes to be transferred through the NPC for the regulation of stress responsive genes. The question marks indicate the absence of knowledge for the interactors.

**Table 1: NE components and their involvement in mechanosensing.**

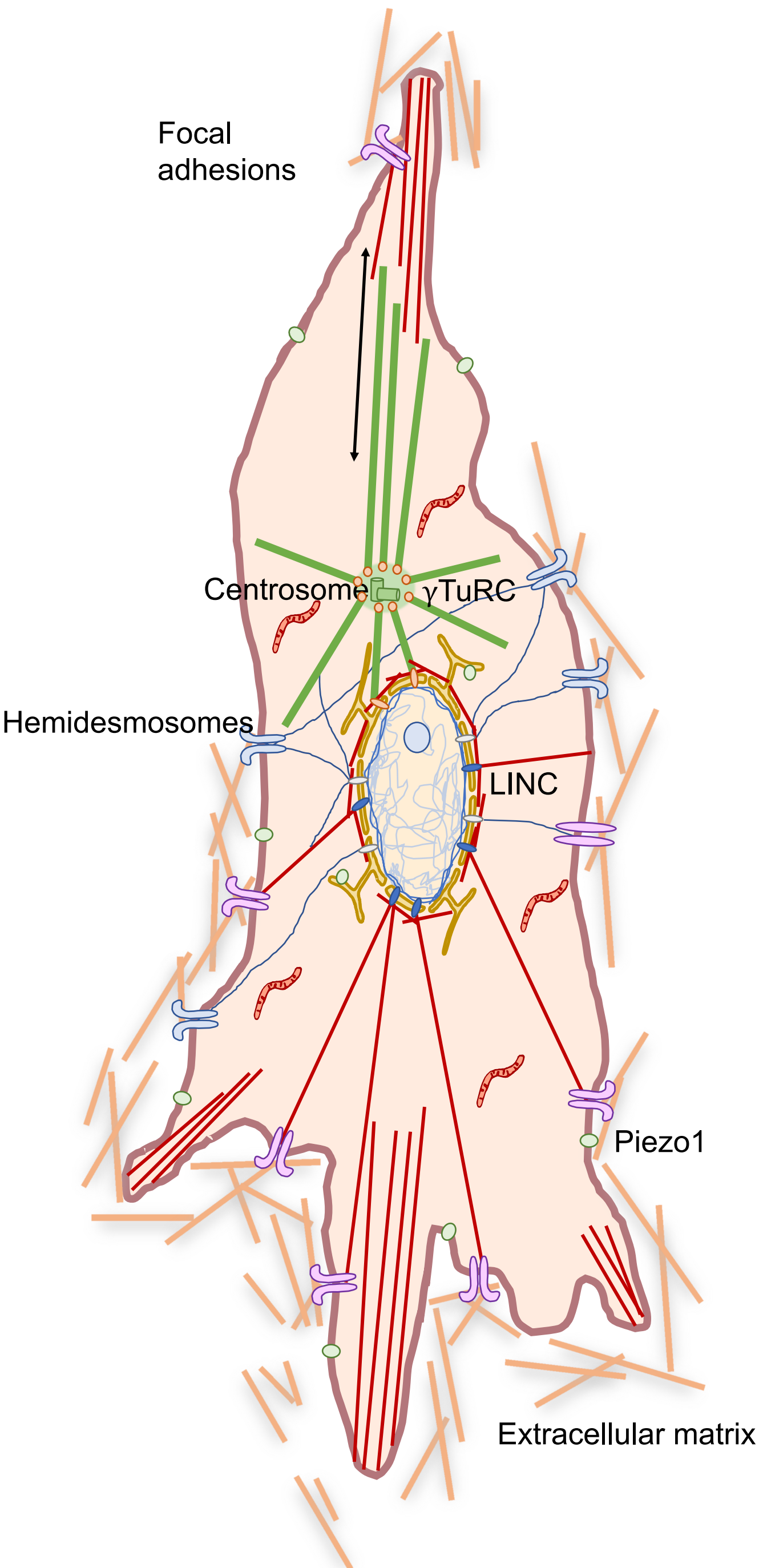
**Supplementary S1-List of related publications to Table 1**

Table 1 : NE components and their involvement in mechanosensing.

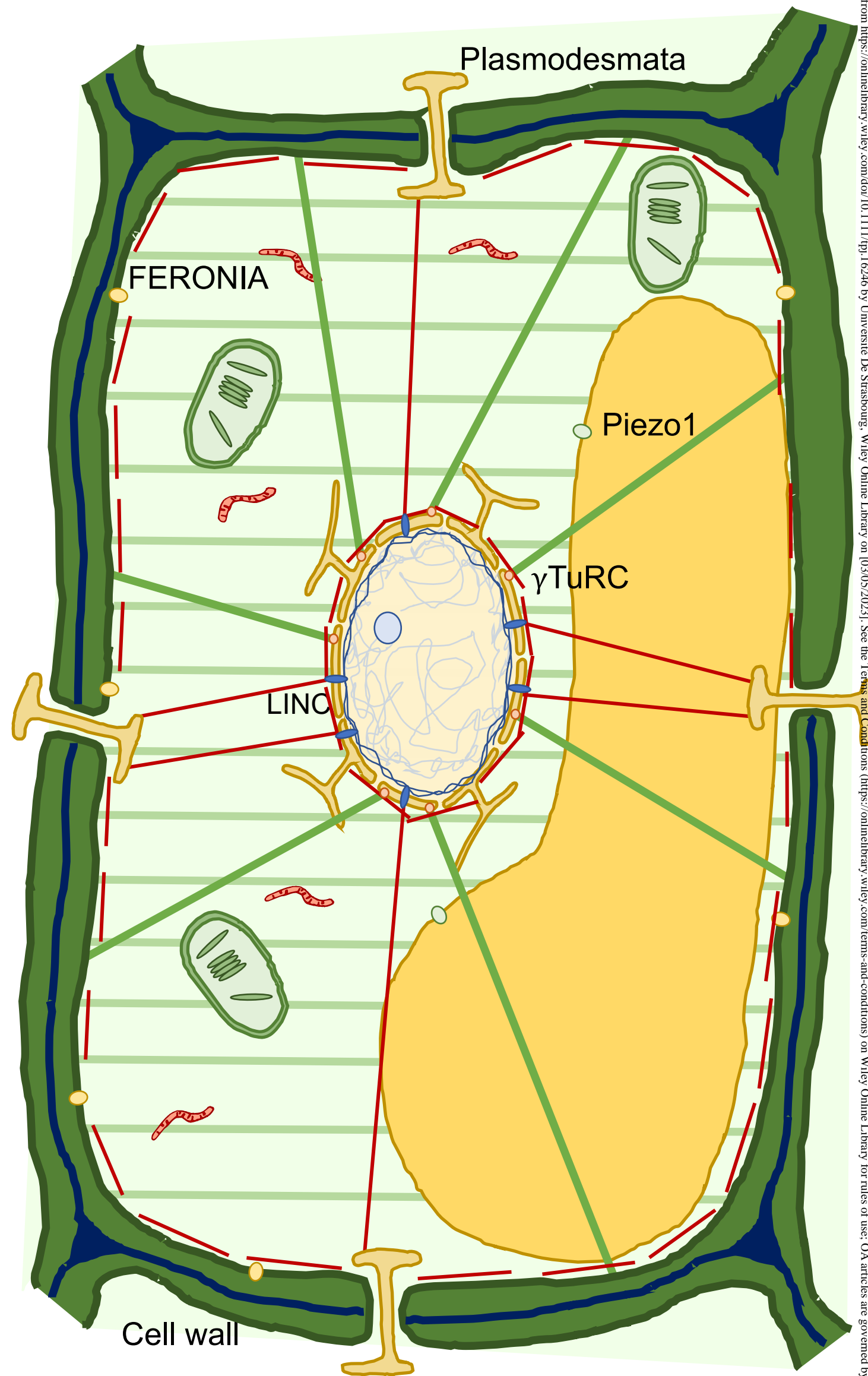
Table 1 : NE components and their involvement in mechanosensing.

Animal cells proteins	Role	References	Functional homogs proteins in plants	Role	References
<b>Linker of Nucleoskeleton and Cytoskeleton (LINC) Complex</b>					
<b>KASH proteins</b>					
<b>Nesprin1</b>	Connection to actomyosin. Involved in nuclear mechano-transduction.	Bruke and Roux, 2009; Guilluy et al., 2014; Arsenovic et al., 2016	<b>WIP1</b>	Interacts with SUN1/2/3, WITs, RANGAPs and WPPs. Controls nuclear shape.	Tatout et al., 2014
<b>Nesprin2</b>	Connection to actin. Involved in gravity response.	Bruke and Roux, 2009; Touchstone et al., 2019	<b>WIP2</b>	Interacts with SUN1/2, WITs, RANGAPs and WPPs. Controls nuclear shape.	Groves et al., 2020
<b>Nesprin3</b>	Connection to Vimentin IFs via plectin.	Bruke and Roux, 2009	<b>WIP3</b>	Interacts with SUN1/2, WITs, RANGAPs and WPPs. Controls nuclear shape.	Groves et al., 2020
<b>Nesprin4</b>	Connection to MTs via kinesin.	Bruke and Roux, 2009	<b>TIK</b>	Interacts with all SUNs but SUN5. Controls nuclear size.	Groves et al., 2020
			<b>SINE1</b>	Interacts with SUN1/2 and SINE2. Connection to Actin. Controls nuclear positioning. Necessary for MT and actin patterning.	Zhou et al., 2014; Groves et al., 2020; Biel et al., 2020; Biel et al., 2022
			<b>SINE2</b>	Interacts with SUN1/2 and SINE1. Necessary for MT patterning. Necessary for Piezo-related Ca <sup>2+</sup> oscillations.	Groves et al., 2020; Biel et al., 2020; Biel et al., 2022
			<b>SINE3</b>	Interacts with SUN1/2.	Groves et al., 2020
			<b>SINE4</b>	Interacts with SUN1/2.	Groves et al., 2020
<b>KASH-associated proteins</b>					
			<b>WIT1</b>	Interaction with WIPs, RANGAPs and WPPs. Connection to actin via Myosin XI-I. Association with NPC. Controls nuclear shape.	Tatout et al., 2014; Groves et al., 2020
			<b>WIT2</b>	Interaction with WIPs, RANGAPs and WPPs. Connection to actin via Myosin XI-I. Affects nuclear shape.	Tatout et al., 2014; Groves et al., 2020
<b>SUN proteins</b>					
<b>SUN1</b>	Regulates chromatin elasticity and epigenetic changes. Promotes beta-catenin association with cytoskeleton upon mechanical stress.	Sankaran et al., 2019; Ghosh et al., 2020; Tajik et al., 2016	<b>SUN1</b>	Connects to KASH proteins to lamina and plasma and interacts with LADs. Interacts with SUN3/4. Controls chromocenters condensation and positioning from the nuclear periphery. Controls nuclear shape.	Alam et al., 2016; Poulet et al., 2017; Groves et al., 2020
<b>SUN2</b>	Binds NUP210 to interact with histone H3.1/H3.2 and BRD4 to regulate gene expression. Promotes beta-catenin association with cytoskeleton upon mechanical stress. Involved in gravity response.	Sankaran et al., 2019; Touchstone et al., 2019; Amin et al., 2021	<b>SUN2</b>	Connects to KASH proteins, to lamina and plasma and interacts with LADs. Interacts with SUN3/4. Control nuclear shape	Groves et al., 2020
			<b>SUN3</b>	Found in NE as well as ER. Interacts with others SUNs, WIP and TIK.	Graumann et al., 2014
			<b>SUN4</b>	Found in NE as well as ER. Interacts with SUN1/2/3. Specific to KASH protein TIK. Affects nuclear size with SUN5. Implicated in chromocenters condensation and distance from the nuclear periphery.	Graumann et al., 2014; Poulet et al., 2017
			<b>SUN5</b>	Found in NE as well as ER. Interacts with SUN3. Affects nuclear size with SUN4. Implicated in chromocenters condensation and distance from the nuclear periphery.	Graumann et al., 2014; Poulet et al., 2017
<b>Nucleopore complex (NPC)</b>					
<b>NUP1</b>	Necessary for the nuclear peripheral positioning of active genes via TREX2.	Tan-Wong et al., 2009	<b>NUP1/NUP136</b>	Plant specific. Interaction with heterochromatin (TE, PcG repressed genes). Interaction with the euchromatin binding factor GBPL3. Involved in nuclear shaping and mRNA export. Regulates the expression of immune related genes. Recruits repressed chromatin to the NPC	Tamura and Hara-Nishimura, 2011; Barneche and Baroux, 2017; Bi et al., 2017; Gozalo et al., 2020; Goto et al., 2021; Wu et al., 2022; Tang et al., 2022
<b>NUP2</b>	Interacts with the promoter of active genes.	Tan-Wong et al., 2009	<b>NUP82</b>	Plant specific. Interaction with the euchromatin binding factor GBPL3. Regulates the expression of immune related genes.	Tang et al., 2022; Wu et al., 2022
<b>NUP62</b>	Suppress chromatin attachment on NUP155.	Breuer and Ohkura 2015	<b>NUP98</b>	Regulates shade induced gene expression	Wu et al., 2022
<b>NUP93</b>	Controls transcriptional activation - association with PcG repressed regions. It is also an enhancer activator. Regulates chromatin attachment to the NPC by recruiting NUP62.	Breuer and Ohkura 2015; Gozalo et al., 2020; Zhu et al., 2022	<b>NUP CPR5</b>	Plant specific. Regulates nuclear shape and gene expression	Gu et al., 2016
<b>NUP107</b>	Associates to actively transcribed genes. Facilitates loading of ORC on specific chromatin regions for replication with NUP160.	Gozalo et al., 2020; Richards et al., 2022			
<b>NUP153</b>	Interacts with chromatin architectural proteins allowing rapid gene response to developmental cues.	Boumendil et al., 2019; Kadota et al., 2020			
<b>NUP155</b>	Regulates chromatin attachment to the NPC by recruiting NUP62.	Breuer and Ohkura 2015			
<b>NUP160</b>	Facilitates the loading of ORC on specific chromatin regions for replication with NUP107.	Richards et al., 2022			
<b>NUP210</b>	Regulates chromatin accessibility at the nuclear periphery.	Amin et al., 2020			
<b>TPR</b>	Contributes to heterochromatin exclusion zones. Interacts with NUP153.	Krull et al., 2010; Boumendil et al., 2019			
<b>Lamina/Plamina</b>					
<b>A-Type Lamins</b>	Modulate cortical and cytoplasmic stiffness. Maintain NE rigidity. Bind to heterochromatin and to NESPRIN2 and 3 and regulate heterochromatin marks. Prevent NE rupture during cellular stretching.	Bianchi and Lanzuolo, 2015; Cho et al., 2017; Vahabikashi et al., 2022; Song et al., 2022	<b>CRWN1</b>	Necessary for chromatin binding at the nuclear periphery and implicated in chromocenters formation. Interacts with GBPL3 to coordinate stress responsive gene expression. Involved in Nuclear shaping. Interacts with SUN1/2, KAKU4, NTL9 and PWO1. Necessary for RAD54 recruitment at the nuclear periphery.	Goto et al., 2015; Poulet et al., 2017; Hirakawa & Matsunaga, 2019; Hu et al., 2019; Pontvianne and Liu, 2020; Tang et al., 2022
<b>B-Type Lamins</b>	Modulate cortical and cytoplasmic stiffness. Maintain NE rigidity. Bind to heterochromatin and to NESPRIN2 and 3 and regulate heterochromatin marks. Prevent NE rupture during cellular stretching. Interacts with chromatin via euchromatin lamin associated domains (eLADs).	Bianchi and Lanzuolo, 2015; Pascual-Reguant et al., 2018	<b>CRWN2</b>	Controls nuclear shape. Interacts with Chromatin from the nucleoplasm. Implicated in chromocenters formation.	Poulet et al., 2017; Groves et al., 2020
<b>C-Type Lamins</b>	Prevent NE rupture during cellular stretching. Bind to heterochromatin and regulate heterochromatin marks.	Cho et al., 2017; Song et al., 2022; Vahabikashi et al., 2022	<b>CRWN3</b>	Interacts with Chromatin from the nucleoplasm.	Groves et al., 2020
			<b>CRWN4</b>	Necessary for chromatin binding at the nuclear periphery. Controls nuclear shape and size. Interacts with KAKU4, PWO1, PUX3/4/5. Necessary for RAD54 recruitment at the nuclear periphery.	Hirakawa & Matsunaga, 2019
			<b>KAKU4</b>	Interacts with CRWN1, CRWN4 and PUX3/4/5, and GBPL3.	Tang et al., 2022
<b>Lamina and Plamina/INM associated proteins</b>					
<b>Emerin</b>	Transferred from the INM to the ONM after chromatin detachment from the lamina to help actin polymerisation around the NE in response to shearing forces.	Brachner and Foisner, 2011; Cho et al., 2017	<b>PNET2</b>	Interacts with GBPL3, KAKU4 and CRWN1. Associates with nucleosome enriched chromatin and maintains chromatin organization. Necessary for growth and stress responses.	Tang et al., 2022
<b>Man1</b>	Binds heterochromatin at the nuclear periphery.	Brachner and Foisner, 2011; Tang et al., 2022	<b>NEAP1</b>	Interacts with SUN1/2 and bZIP18. Controls nuclear size and maintains heterochromatin.	Pawar et al., 2016
<b>Lem2</b>	Binds heterochromatin at the nuclear periphery.	Pieper et al., 2020	<b>NEAP2</b>	Interacts with SUN1/2 and bZIP18.	Pawar et al., 2016
<b>Nur1</b>	Binds heterochromatin at the nuclear periphery.	Pieper et al., 2020	<b>NEAP3</b>	Interacts with SUN1/2 and bZIP18. Controls nuclear size and maintains heterochromatin.	Pawar et al., 2016
			<b>PWO1</b>	Association with CRWN1 necessary for the regulation of specific genes.	Mikulski et al., 2019
<b>Others</b>					
			<b>GIP1</b>	Regulates NPC distribution around the NE. Necessary for MT nucleation on the NE. Interaction with centromeres. Controls centromeric cohesion, nuclear size and expression of touch responsive genes	Janski et al., 2012; Nakamura et al., 2012; Batzenschalger et al., 2013; Batzenschalger et al., 2015; Goswami et al., 2020b
			<b>GIP2</b>	Regulates NPC distribution around the NE. Necessary for MT nucleation on the NE. Interaction with centromeres. Controls centromeric cohesion, nuclear size and expression of touch responsive genes.	Janski et al., 2012; Nakamura et al., 2012; Batzenschalger et al., 2013; Batzenschalger et al., 2015; Goswami et al., 2020b





Animal cell



Plant cell

