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Nuclear forces and cell mechanosensing

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Abstract

Cells respond to mechanical signals, but the subcellular mechanisms are not well understood. The nucleus has recently emerged as an important mechanosensory organelle in the cell, as it is intimately connected to the cytoskeleton. Mechanical forces applied to cells that act on membrane-embedded receptors are transmitted through the cytoskeleton to the nuclear surface. Interfering with linkers of the nucleus to the cytoskeleton causes defects in cell mechanosensing and cell function. In this chapter, we discuss recent work in this area, highlighting the role that the nuclear linkages with the cytoskeleton play in cellular mechano-transduction.

1. Introduction

Cells in the body are exposed to both 'active' and 'passive' mechanical stimuli. For example, endothelial cells that line the blood vessels are constantly exposed to shear stresses and cyclic stretching imposed by the pulsatile flow of blood, actively remodeling their cytoskeleton and overall morphology. Adherent cells are also exposed to widely varying mechanical cues from the extracellular matrix (ECM) depending on the organ they inhabit- neurons, for example, are surrounded by much softer tissue than smooth muscle cells or osteoblasts. These passive cues also elicit a response from cells. The mechanisms by which cells respond to mechanical stimuli are of strong current interest in the emerging area of mechanobiology.

Cells can transduce mechanical signals into a biochemical response. This process is known as mechano-transduction; however there is no singular mechanism by which this happens. Mechanical forces applied to cells, which transmit signals ~40-fold faster than diffusion of some chemical signals [1], can cause conformational changes in heterodimeric integrin proteins in cell-matrix adhesion sites. This can ultimately alter signaling pathways and gene expression. Mechanical stimuli can open ion channels (see review by Morris [2]), alter binding of proteins in focal adhesions [3], and cause changes in overall cell morphology [4] (also see review by Ingber [5]). In recent years, it has become recognized that the nucleus of the cell can act as a mechanosensory organelle (see review by Wang et al.[6]), which not only experiences and transmits forces directly but also influences cell mechanosensing, through mechanisms that are beginning to be understood.

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In this chapter, we review the evidence that supports the concept that the nucleus mediates mechanosensing. We discuss how force propagation occurs to the nuclear surface, how cytoskeletal coupling to the nucleus is necessary for mechanosensing and how the nucleus should be seen as an integrated component with the cytoskeleton in models for cell mechanosensing.

2. Cytoskeletal forces are exerted on the nucleus

Early evidence that the nucleus is under tension came from Ingber and coworkers in 1992, who showed that perturbing actomyosin forces altered cell and nuclear shape [7]. In a landmark paper in 1997, they showed that tugging on integrin receptors in the cell membrane causes nuclear distortion and motion [8]. This established the concept that forces applied externally to the cell are propagated to the nuclear surface, consistent with mechanical models of the cell cytoskeleton that are 'hardwired' to the nuclear envelope [9,10,11121314]. These external forces have now been shown to induce clearly-detectable nuclear deformation [8,15,16,17,18,19,20,2122]. The F-actin cytoskeleton plays a major role in propagating the mechanical forces from integrin receptors to the nuclear surface, although the molecules which connect the nucleus to the cytoskeleton have only recently been identified.

In recent years, members of the so-called LINC complex (for Linker of Nucleoskeleton to the Cytoskeleton) have been discovered in the nuclear envelope [23,24,25,26]. The LINC complex is comprised of two protein families that span the nuclear envelope, and physically connect the cytoskeleton to the nucleoskeleton. The SUN (Sad1p, UNC-84) domain proteins span the inner nuclear membrane (INM) and translumenally bind the KASH (Klarsicht/ ANC-1/Syne Homology) domain proteins that span the outer nuclear membrane (ONM) (Figure 1). In this way the KASH and SUN domain proteins create a mechanical tether that connects both membranes of the nuclear envelope. The KASH domain proteins bind to various cytoskeletal constituents, whereas the SUN domain proteins associate with the nuclear lamina. Thus, the mechanical connections created by the LINC complex can integrate the forces of the cytoskeleton and the nucleus.

The LINC complex is functionally well conserved in eukaryotes, including single celled organisms such as yeasts, however the number and nature of the KASH and SUN domain constituents varies between divergent species. In mammals there are five Sun domain proteins (SUNs 1–5), but only SUN 1 and SUN2 appear widely expressed. SUNs 3–5 are predominantly, if not exclusively expressed in the testis. SUN1 and SUN2 have been shown to associate with the nuclear lamina, however the role of any additional nucleoplasmic associations of SUN domain proteins in LINC complex function remains unclear. The crystal structure of the large SUN 2 lumenal domain has revealed that the protein forms a trimeric [27,28] oligomer, mediated by a lumenal coiled-coil domain. Each of the three SUN domains in this trimer binds to a unique KASH domain. This oligomeric association likely enhances the physical strength the LINC complex to transfer forces between the cytoskeleton and nucleus.

There are six mammalian KASH domain proteins (nesprins 1–4, LRMP and KASH5), only three of which (nesprins 1–3) are generally ubiquitous. Nesprin 1 and nesprin 2 bind to actin, and to dynein and kinesin [29,30], whereas nesprin 3 binds plectin, an intermediate filament-associated cytolinker. Nesprin 4 is predominately expressed in highly polarized epithelial cells and its loss leads to hearing defects in mice and humans associated with perturbation of nuclear positioning [3132]. KASH5 expression appears limited to meiotic cells where it binds dynein to move chromosomes during homologous recombination [33,34]. Predominantly expressed in lymphocytes and taste cells, LRMP does not appear to interact with the cytoskeleton but instead binds to the calcium channel IP3 receptors [33,35]. There are multiple splice isoforms of nesprin 1 and nesprin 2 that do not contain the ONM-targeting KASH domain. Many of these KASH-less isoforms likely have functions other than formation of the LINC complex [36,37,38,39,40].

The LINC complex is the only known structure by which cytoskeletal stresses can be directly transferred to the nuclear surface (Fig. 1). Since the cytoskeleton ultimately connects to focal adhesions [41,42] (also see review by Geiger, Spatz and Bershadsky [43]), the LINC complex enables a mechanical linkage between the nucleus, the cytoskeleton, and the extracellular matrix [20,25,26].

3. The LINC complex transmits cytoskeletal forces to the nuclear surface

The nucleus has been suggested to be a cellular mechanosensor [6], and besides being a key player in the physical signaling pathway, it is possible that the LINC complex is involved in chemical signal transduction pathways as well [44,45,46]. The LINC complex is essential for efficient migration [17,47,48], normal structure [48,49], function [17,48], and maintaining nuclear shape and position [17,48,50,51,52]. For a review on disrupted LINC complexes causing defects in mechano-transduction, see the recent review by Jaalouk and Lammerding [53]. The LINC complex has been found to be a key player in force transmission between the nucleus and cytoskeleton [17,48], and an intact LINC complex is required for nuclear positioning, cell polarization, and normal propagation of cytoskeletal forces [17].

It has been demonstrated that external forces applied to the apical surface of a living cell propagate through the cytoskeleton and all the way to the nucleus [8] and that forces applied to integrins can cause motion of intranuclear organelles [22]. Chancellor *et al.* recently showed that nesprin-1 knockdown significantly increased the nuclear height, suggesting an essential role of nesprin-1 in flattening the nucleus in endothelial cells [54,55]. Inhibiting myosin activity similarly produced a vertically rounded nucleus. Chancellor *et al.* proposed a model in which actomyosin force pulls laterally on the nucleus and flattens it to the shape of a disk. In this model, the nucleus acts as a scaffold that balances actomyosin forces internally while the substrate balances them externally. In the absence of nesprin-1, the pulling force on the nucleus is substantially reduced and the nucleus is free to relax vertically into a rounded shape [54] while the excess force is now balanced at an increased number of adhesion sites with the substratum.

In a series of recent papers, Gundersen and coworkers showed that dorsal actin bundles (on top of the nuclear surface) are directly linked to the nucleus via TAN (for Transmembrane

Actin-associated Nuclear) lines assembled from nesprin2giant and SUN2 proteins [47,56]. The authors suggest that the TAN lines across the nuclear membrane function in a manner similar to focal adhesions across the cellular membrane in that both assemblies are linked to actin cables and transmit mechanical force [47,57]. They also showed in fibroblasts that emerin and myosin IIB function to polarize nuclear movement and flow of actin, which suggests a new role of the nuclear envelope in establishing cytoskeletal polarity and directional actin flow [58].

Recently, Khatau *et al.* suggested that apical stress fibers on top of the nucleus shape it by squeezing from the top as the fibers contract [59]. The authors call these distinct bundles the 'actin cap'. These bundles terminate at a small distinct subset of focal adhesions, which are proposed to regulate mechanosensing via the actin cap. The actin cap associate focal adhesions have been shown to be larger in size than conventional focal adhesions, are located only at the periphery, and experience fast turnover dynamics[60]. Wirtz and coworkers have proposed that the actin cap and its associated focal adhesions play a key role in the fast and efficient physical pathway for mechano-transduction by providing a continuous mechanical linkage from the ECM to the nucleus [60,61,62]. Coupling of the actin cap to the nuclear lamina occurs via the LINC complex [59,63,64] and its associated nesprins.

Like actin bundles, microtubule motor proteins can also generate tension that is transmitted to the nuclear surface through the LINC complex. For example, Splinter *et al.* showed that by binding to the nuclear membrane at their cargo end, dynein and kinesin-1 can pull the nucleus in opposite directions as they walk. Kinesin-1 pulls the nucleus away from the centrosome, while dynein pulls it towards the centrosome [65]. The combined activities of these two processive motor proteins control nuclear translation and rotation [66,67,68]. Wu et al. showed that dynein walking on microtubules in the vicinity of the nucleus can produce nuclear rotations [69]. They also modeled the rotation of the nucleus computationally to show how this could mechanically occur in the cell. As mentioned previously, nesprin 4, and likely nesprins 1 and 2, function to position the nucleus within the cell through the action of microtubule motors. KASH5 (and its orthologs) functions to transmit microtubule motor forces through the nuclear envelope directly to meiotic chromosomes [33,3470,71,72].

4. The role of the nucleus in cell mechanosensing

Although the exact mechanisms are not completely understood, cells have been shown to sense and respond to different mechanical cues from their surroundings such as shear stress [73], substrate strain [74], and substrate rigidity [75]. Evidence that the nuclear force balance is important in this cell mechanosensing has come from studies in which the LINC complex was disrupted. For example, endothelial cells were found to lose their ability to re-orient in response to uniaxial cyclic strain upon knockdown of nesprin-1 [54]. Because the nucleus no longer acts as an internal scaffold to balance actomyosin tension, the nesprin-1 deficient cells apply increased traction on the substratum, resulting in stronger adhesion and less propensity to reorient in response to mechanical strain.

There is evidence that nuclear forces might regulate gene expression. Changing nuclear shape by controlling the degree of cell spreading alters protein synthesis [76]. In response to

cyclic strain, lamin A/C deficient and emerin-deficient mouse embryonic fibroblasts (MEF) have impaired expression of genes lex-1 and Egr-1 [20,55]. Philip *et al.* showed that in response to shear stress, lamins are upregulated and reorganized [77]. More recently, defects in lamin A/C have been demonstrated to impair nuclear translocation of MKL-1, a transcription factor [78].

In NIH/3T3 fibroblasts, the nuclear shape has been shown to depend on the rigidity of the underlying substrate [79]. The nucleus takes a spherical shape on soft substrates, likely due to the smaller actomyosin tension and a flattened ellipsoid on rigid substrates where higher forces are generated in cells [79]. Tuning the actomyosin tension by changing the substrate rigidity enables control of nuclear shape. Disrupting the LINC complex via KASH overexpression or inhibiting myosin II eliminates this shape dependence of nucleus on substrate rigidity, suggesting that the coupling of the nucleus to the cytoskeleton is essential for mechanosensing [79]. The cell motility and the cell spreading area both correlate with the underlying-substrate rigidity in a manner that depends on the nuclear linkages to the cytoskeleton; on softer substrates, cells have lower speed and spreading area, whereas they have higher speed and spreading area on stiffer substrates, and KASH overexpression ablated this trend [79]. Separately, Swift and coworkers have demonstrated that the lamin A levels are proportional to the tissue rigidity [80], indicating that lamin-A stabilizes the nucleus under stress. Consistent with this, LINC complex disruption decreases cellular mechanical stiffness [49].

CONCLUSIONS

In conclusion, physical connectivity from the nucleus to the cytoskeleton and cell membrane is required for normal cell mechanosensing. Force transmission from external receptors to the nuclear surface requires an intact nuclear lamina and physical connectivity between the nucleus and the cytoskeleton by the LINC complex. Ultimately, how the integrated nuclear-cytoskeleton integrates mechanical stimuli with complex intracellular signaling pathways and gene regulatory networks will require a systems biology approach that seeks to understand cell mechanosensing in an integrated manner.

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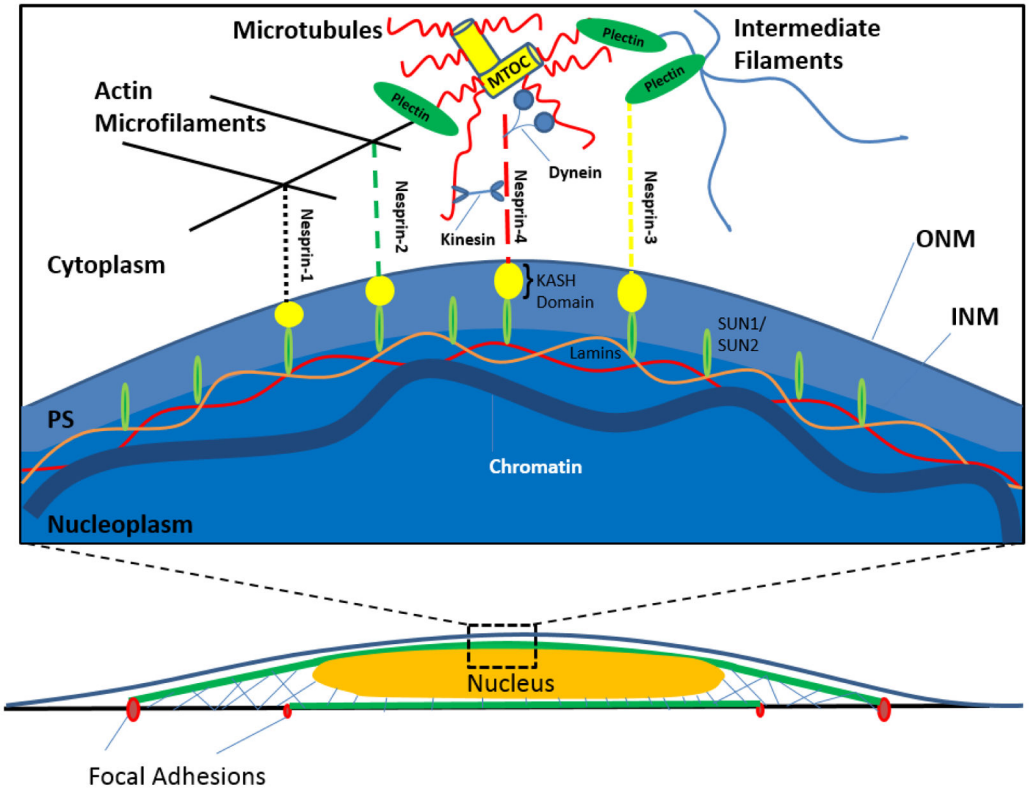

Figure 1.

The LINC complex is formed by the SUN domain proteins spanning the inner nuclear membrane (INM) and translumenally binding the KASH domain proteins that span the outer nuclear membrane (ONM). The SUN domain proteins associate with the nuclear lamina, whereas the KASH domain proteins bind to various cytoskeletal constituents through the nesprin protein family (nesprin 1–4). Nesprin 1 and nesprin 2 bind to actin, and to dynein and kinesin, whereas nesprin 3 binds plectin, an intermediate filament-associated cytolinker.