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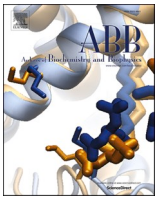

Cell stretchers and the LINC complex in mechanotransduction

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ABSTRACT

How cells respond to mechanical forces from the surrounding environment is critical for cell survival and function. The LINC complex is a central component in the mechanotransduction pathway that transmits mechanical information from the cell surface to the nucleus. Through LINC complex functionality, the nucleus is able to respond to mechanical stress by altering nuclear structure, chromatin organization, and gene expression. The use of specialized devices that apply mechanical strain to cells have been central to investigating how mechanotransduction occurs, how cells respond to mechanical stress, and the role of the LINC complexes in these processes. A large variety of designs have been reported for these devices, with the most common type being cell stretchers. Here we highlight some of the salient features of cell stretchers and suggest some key parameters that should be considered when using these devices. We provide a brief overview of how the LINC complexes contribute to the cellular responses to mechanical strain. And finally, we suggest that stretchers may be a useful tool to study aging.

1. Introduction

Mechanical forces are important contributors to a number of biological processes, including organogenesis, carcinogenesis, degenerative diseases and aging (reviewed in Refs. [1,2]). Cells in metazoan organisms form extensive connections to the extracellular matrix (ECM) and to other cells, and these connections transduce the mechanical forces from the environment to the cells. The anatomical position of cells largely dictates the types of forces a cell is exposed to. For example, endothelial cells in blood vessels experience shear forces produced by fluid flow [3], chondrocytes within articular cartilage experience compressive load [4] and cardiomyocytes experience tensile forces caused by cardiac contraction [5]. Each cell type experiences a distinct set of mechanical forces. The ability of cells to respond to mechanical changes in their environment by altering their own structural and biochemical attributes is central to the process of mechanotransduction [6]. Because many mechanically induced cellular changes require a change in transcriptional activity, mechanotransduction depends, at least in part, on a physical link between the cytoskeleton and the nucleus. Proteins belonging to the Linker of Cytoskeleton and Nucleoskeleton (LINC) complex play a key role in forming this connection and transducing mechanical stimuli to the nucleus [7]. In this review we will provide a brief overview of the key LINC complex proteins involved in the process of mechanotransduction. We will discuss some of the tools that have been developed to aid in studying mechanobiology and mechanotransduction. And finally, we will raise the question whether cell stretchers could be useful tools to study aging.

2. Extracellular matrix

Metazoan organs and tissues are developmentally formed and maintained through the interaction of cells and their extracellular matrix (ECM). The ECM is essential for maintaining the three-dimensional structure of tissues, for defining the biomechanical properties of those tissues and for determining cell fate and differentiation [8,9]. A number of proteins with fibrous characteristics (e.g., fibronectin, laminin, collagen, etc.) help to define the mechanical attributes of the ECM. The ECM not only provides a dynamic environment for tissue morphogenesis [10], but it also affects cellular function by acting as a key communication conduit between cells and the surrounding environment [9]. In most instances, the ECM is the first point of contact for cellular interaction with mechanical strain.

Integrins form a key connection between cells and the ECM. Comprised of a family of transmembrane proteins that reside in the plasma membrane, integrins serve as mechanical linkages between the cytoskeleton and the ECM [11,12]. When activated, the integrin

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extracellular domain binds ECM proteins, such as fibronectin [12], while the cytoplasmic domain binds to the actin cytoskeleton through a variety of adaptor proteins. When integrins bind ECM ligands, they cluster to initiate the assembly of multi-protein focal adhesion (FA) complexes. These FA complexes drive the reorganization of the actin cytoskeleton in response to mechanical stimuli [13]. In addition, integrins have been shown to affect the microtubule and intermediate filament networks as well [14–18]. Therefore, by transducing extracellular stimuli into intracellular changes, integrins and FA complexes form an essential first step in the mechanotransduction chain.

3. Cytoskeleton

Once integrins and FA complexes transmit forces to the inside of the cell, the cytoskeleton is the key recipient of these forces. The cytoskeleton is an important mediator in many physiological functions including cargo transport, cell division, cell polarity, stiffness, cell signaling, and ECM patterning and is well known to contribute to the shape and mechanics of the cell [19]. Indeed, microtubules, actin filaments and intermediate filaments have each been shown to respond to mechanical stimuli.

Microtubules, the stiffest cytoskeletal component [20], are very effective at resisting forces. For example, microtubules are key in mediating the increased stiffness and viscosity that cardiomyocytes undergo in response to pressure overload [21]. In addition, cardiomyocytes upregulate β-tubulin in response to mechanical stimulation [22].

Actin filaments are less stiff than microtubules, though they have the ability to assemble into highly organized stiff bundles in the presence of actin crosslinking proteins such as α-actinin and fascin [23]. Bundled actin is required to form specialized structures such as filopodia, lamellipodia, stress fibers and focal adhesions [23]. Actin filaments also have the ability to associate with the motor protein myosin, an association that results in contractile functions and facilitates cellular stress responses such as formation of actin stress fibers [24]. In addition, the actin-myosin filaments contribute to focal adhesions assembly and maturation [24].

Intermediate filaments (IFs) are the least stiff of the cytoskeletal proteins, but they have the highest tensile strength and are effective in resisting shear forces [25–27]. This means they play an important role in cellular and nuclear resilience to mechanical stress [28–30]. In addition, through the role of crosslinking proteins such as plectin, IFs can be found in bundles with other IFs or other cytoskeleton components, further broadening their role in mechanobiology [31].

While each of the cytoskeletal components has distinct characteristics, a significant amount of cooperation and crosstalk between the different cytoskeletal components exists. It is therefore difficult to isolate specific mechanotransduction functionality to any one component. Indeed, all three have been shown to contribute to the mechanical transduction from integrins to the nucleus [32]. Once a mechanical signal reaches the nucleus, LINC complexes play a key role in transmitting these signals into the nucleus [7].

4. Linker of nucleoskeleton and cytoskeleton (LINC) complexes

The LINC complexes consist of an outer nuclear membrane KASH domain protein and an inner nuclear membrane SUN domain protein, which form a physical connection in the perinuclear space (PNS), the space between the outer and inner nuclear membranes [33]. The mammalian KASH domain family contains six tail anchored proteins (Nesprins 1–4, KASH5 and LRMP) which all share the SUN interacting KASH (Klarsicht/ANC-1/Syne-1 homology) domain that juts into the PNS [33]. The N-terminus of most KASH domain proteins have been shown to interact with cytoskeletal components. Nesprins 1 and 2 interact with the cytoplasmic dynein/dynactin complex as well as kinesin, affecting both the nuclear anchorage and nuclear movement in neuronal cells [34]. Additionally, both nesprins 1 and 2 have a calponin homology domain (CHD) which allows them to interact with F-actin directly [35]. Nesprin 3 interacts with the adapter protein plectin, through which it interacts with IFs and integrin α6β4 in keratinocytes [36]. Nesprin 4 interacts with microtubules via the motor protein kinesin [37,38]. KASH5 interacts with microtubules via the dynein/-dynactin complex [39,40]. Only LRMP has no reported cytoskeletal interactions.

SUN proteins constitute the inner nuclear membrane (INM) component of the LINC complex, interacting with the KASH domains of nesprins in the PNS [33]. The SUN-KASH interaction consists of two adjacent SUN domains in a SUN trimer forming a binding pocket for the KASH domain [41]. Different length KASH domain have been shown to affect the strength of the SUN-KASH interaction, with longer KASH domains supporting greater mechanical force [42]. Furthermore, recent evidence supports the formation of higher order 6:6 complexes, which would allow for even higher resilience to mechanical tension on the LINC complex [43]. The physical connection between SUN and Nesprins allows the LINC complex to transmit forces directly to the inside of the nucleus, to a variety of SUN interacting proteins, including nuclear lamins [44].

The nuclear lamina is a filamentous network of proteins that resides just under the inner nuclear membrane [45]. It is composed of a mix of A-type lamins (lamins A/C) and lamins B1 and B2 and gives the nucleus mechanical resilience [46,47]. Lamin A expression correlates with tissue stiffness. As such, it is highly expressed in tissues that are subjected to high mechanical stress such as muscle and cartilage, but expression is low in tissues that experience little mechanical stress, such as neurons and adipose [48,49]. Lamins are necessary for maintaining nuclear structure and organization, including organization of chromatin and spacing of nuclear pores [50–53]. Mechanical strain on the nucleus induces chromatin remodeling [54–56] and lamins are a key contributor to mediating these transcriptional changes [57].

5. Tools for studying mechanotransduction

There has been a recent increase in the number of investigative tools that allow cells and tissues to be exposed to mechanical stress in a controlled experimental setup. Some systems apply forces to populations of cells grown on deformable substrates [58]. Other systems use optical tweezers or atomic force microscopy to investigate the effects of mechanical strain on individual cells or subcellular compartments [59,60]. The largest variety of devices is found in the uniaxial and biaxial mechanical stretchers. Some of these are commercially available (e.g. STREX [61] and FlexCell [62,63]) but the majority are custom-made (e.g. Refs. [64–72], to highlight a few.) Stretcher design is directly driven by experimental needs, and most stretchers do not address a variety of experimental scenarios (e.g., uniaxial vs biaxial strain, microscopic vs biochemical analysis, static or cyclic strain) leading to substantial heterogeneity in design.

The most common stretcher designs allow for the investigation of cell populations grown on a 2D surface. These stretchers have been used to examine the effects of mechanical strain on several cellular functions, including cell division [73], cellular reorientation [74], nuclear deformation [75] and gene expression [76]. These 2D stretchers will be the focus of this review. However, we briefly want to highlight some examples of interesting stretchers that do not fall into this general category. A stretcher engineered by Bianchi et al. allows for uniaxial stretching of neurons within a 50 μm wide groove. Interestingly, this design allows for simultaneous patch clamping and Ca^{2+} imaging of stretched neurons [77]. Dudani et al. designed a pinched-flow hydrodynamic micro stretcher that allows for single cell stretching [78]. And finally, a micro mechanical device developed by Minami et al. allows for high resolution time-lapse observation of stretched cells [79]. In addition, some groups have designed stretchers that can apply mechanical stimulation to cells grown in 3D [80]. These devices are interesting

because of their physiological relevance. However, the additional dimension introduces complexities in design and analysis that are challenging to address, which is perhaps why the majority of cell stretchers have focused on 2D for now.

6. Substrate considerations

Most stretching devices use a flexible substrate to transmit the mechanical strain to cells. Cells are either grown on, or adhered to, the flexible substrate which is then distended during mechanical stimulation. Examples of materials that have been used include hydrogels, polyethylene terephthalate (PET) and polydimethylsiloxane (PDMS). The experimental design will dictate the required stiffness, thickness, transparency, and elasticity of the substrate material. The choice of any substrate brings with it a number of biological consequences. For example, stiffness is a key consideration when selecting substrate. Stiff substrates favor the generation of focal adhesions and increases the traction forces generated between the cell and the ECM [81]. In addition, stiff substrates have been reported to affect nuclear stiffness in some cell types [82]. And finally, substrate stiffness plays a key role in the differentiation of certain cell types [49,83–86]. Other key factors to consider in substrate selection are optical properties and elasticity. The optical properties are particularly relevant for experiments involving imaging, while the elasticity of the substrate dictates how much mechanical load can be applied during the experiment.

Hydrogels comprise a very diverse group of substrates. These are available in different combinations and functionalizations such as polyacrylamide hydrogels, fibrin hydrogels and self-assembling peptide hydrogels. Because cells can be embedded into hydrogels, they are of special interest for 3D culture and 3D mechanical stimulations [87–89]. Polyethylene terephthalate (PET) is a relatively stiff thermoplastic polymer resin. It is most commonly used as a thin film ($\leq$1 mm), which, when bent, causes tensile strain to attached cells [67,90].

The most commonly used material for cell stretching applications is PDMS. Its good optical clarity, flexibility, and biocompatibility make it well suited to a number of applications. In addition, the PDMS stiffness is easily modulated, allowing for a wide range of stretching applications. However, PDMS requires surface functionalization with a suitable ECM protein to support cell adhesion [66,91].

7. Stretching protocol considerations

Arguably one of the most important parameters to consider when designing a mechanical strain experiment is the stretching protocol. Cyclic vs static, amplitude or percentage of strain, time of hold at both stretched and unstretched positions, frequency, and total time of stretching are all important parameters that contribute to the biological effects of stretching. The most common ranges for strain amplitude and frequency reflect physiologically relevant conditions [92–94]. Therefore, a frequency of 0.5–1.2 Hz and a 10%–40% strain are the most commonly reported values [68,76,77,95,96]. A recent study powerfully illustrates the importance of considering these stretch parameters: epidermal progenitor cells were stretched at 5%, 20% or 40% at 0.1 Hz for either 30 min or 6 h. Not only did each percentage of stretch have distinct cellular responses, but the responses were also different for each time point [97]. Another example can be seen in studies that stretched chondrocytes at 10% biaxial strain and 0.5 Hz. Cyclic stimulation for three hours resulted in an anabolic response with an upregulation of collagen type II and aggrecan expression [98,99]. However, beyond three hours the expression of these proteins dropped and chondrocytes began expressing proteins indicative of a catabolic state [98,99].

8. Molecular effects of stretching

A number of cellular responses to mechanical strain are well-documented (Fig. 1). Uniaxial cyclic stretching causes a cellular reorientation and nuclear rotation in fibroblasts and endothelial cells [76,96,100,101]. In addition, mechanosensitive transcriptional factors such as YAP/TAZ and MRTF-A translocate from the cytoplasm into the nucleus in response to mechanical stimulation [76,102–105]. The actin filament network rearranges into a perpendicular alignment to the direction of stretch [106,107]. And finally, mechanical strain stretches and unfolds the chromatin, allowing for the binding of the transcription factors and a subsequent activation of gene expression [108]. Because the LINC complex is a key mediator in intracellular force transmission [7,44,109] it is involved in all the above effects of mechanical stretching.

9. The LINC complex: structural and morphological changes in response to mechanical stimulations

One of the key morphological responses to cyclic stretching is a

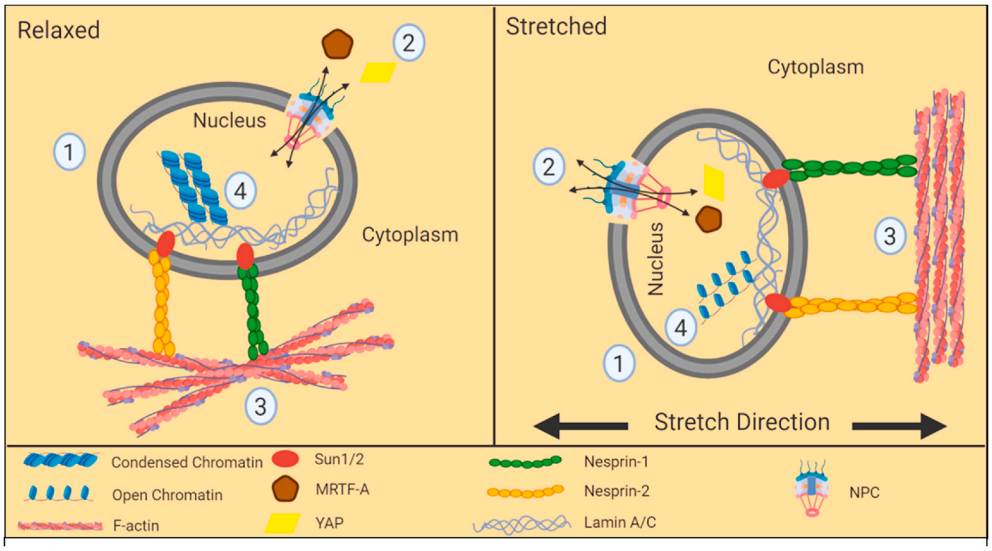

Fig. 1. Characteristics of cellular changes in response to cyclic mechanical strain. 1) Cell and nucleus reorientation. 2) Nuclear translocation of transcription factors. 3) Rearrangement of actin filaments. 4) Chromatin decondensation. Created with BioRender.com.

cellular reorientation and rotation of the nucleus [76,96,100,101]. LINC complex proteins Nesp1, Nesp2 and SUN1 have been shown to be essential for this response. When any one of these proteins was knocked down, cells did not re-orient nor rotate their nucleus [96,101]. Furthermore, the transmission of force to the nucleus in stretched cells was substantially reduced in the absence of Nesp1, where nuclei exhibited a rounded, relaxed shape. However, cells lacking Nesp1 attempt to compensate for the absence of the Nesp1-mediated nuclear-cytoskeletal connection by increasing actomyosin tension through increased focal adhesions. As a result, Nesp1 knockdown fibroblasts have abnormal focal adhesion, migration, and cyclic strain-induced reorientation [96,110]. Interestingly, temporary disassembly of focal adhesions in Nesp1 knockdown cells restored stretch-induced reorientation [96], highlighting not only the importance of the LINC complex, but also the role of actin dynamics in mechanotransduction.

In mechanically active cardiomyocytes, Nesprins 1 and 2 are important for maintaining not only the general cell architecture, but also nuclear organization. Deletion of both Nesp1 and Nesp2 led to an alteration in nuclear position and shape, as well as changes in the localization patterns of both Lamin A/C and Emerin [111]. As a final example, Nesprin 3 is important in human aortic endothelial cells, which respond to flow-induced shear stress in a Nesp3-dependent manner [112].

10. The LINC complex: signaling and transcriptional responses to mechanical stimulations

In addition to the changes in cellular organization and architecture, LINC complex components also mediate transcriptional changes in response to mechanical stress. Activation of NFkB signaling is an early response to mechanical stretching, where NFkB translocates from the cytoplasm to the nucleus and then back to the cytoplasm within the first 60 min of cyclic stretching [100]. In mouse embryonic fibroblast (NIH3T3) where LINC complex function is impaired by overexpression of either dominant negative Sun1 or Nesp2, cyclic stretching results in prolonged NFkB activity due to a persistent NFkB nuclear localization [100]. Therefore, a fully functional LINC complex is required to efficiently shuttle NFkB out of the nucleus.

Another well-established mechanosensitive transcription factors is YAP/TAZ, which translocate from the cytoplasm to nucleus under mechanical stimulation [76,102,104,105]. Various LINC complex and NE components have been shown to be important for YAP/TAZ localization. For example, mutations in LMNA or Nesp1 in muscle stem cells results in an increased nuclear localization and accumulation of YAP [113]. By contrast, disrupting the LINC complex by using a dominant-negative Nesp1 or Nesp2, impairs the nuclear translocation of YAP and its co-factor TAZ [104]. Finally, some mutations in LMNA reduced YAP activation in response to cyclic stretching [114].

However, mechanical forces not only impact transcription factor translocation, but they also induce chromatin structural changes that allows for an increase in transcription [108,115]. Mechanical force on the nucleus causes chromatin unfolding, exposing the unfolded chromatin to transcriptional factors, resulting in upregulation of gene expression [108]. Using the *DHFR* (dihydrofolate reductase) gene as an example, shear-stress-induced chromatin stretching lead to upregulation of DHFR expression in a LINC complex dependent manner. When SUN1/2 were knocked down, the stress-dependent upregulation of DHFR was abolished [108]. In addition, Lamin A, Lamin B and Emerin also played an important role in mediating the stress-induced chromatin changes, as upregulation of DHFR was also lost when any one of these proteins was knocked down [108]. While compact chromatin has been shown to interact with SUN1 [108,115], and this physical linkage between chromatin and the LINC complex can mediate gene regulation [116,117], other NE components clearly also play an important role as seen with the examples of DHFR and the role of Lamins and Emerin. Nevertheless, the LINC complex is central to the transmission of force from the cytoskeleton to chromatin and affects not only transcription, but chromatin flow and the chromatin-driven mechanical properties of the nucleus [59].

11. Using stretchers to study aging?

The process of aging induces a number of mechanical changes in tissues and cells. Changes in the extracellular matrix (ECM) plays a significant role in the aging of tissues [118,119]. For example, aged tendons present with reduced collagen fiber assembly and alterations in tenocyte morphology, which results in deterioration of the viscoelastic properties of the tendons and reduces their ability to transmit mechanical forces [120]. In skin, a reduced water content and increased collagen crosslinking leads to loss of elasticity and increased stiffening with age [121–123].

In addition to changes in ECM characteristics, intracellular changes have also been reported in a number of tissues, including cardiac tissue. It is thought that cardiomyocytes remodel the sarcomere in response to aging, although many of the same proteins that are involved in the age-dependent remodeling are also involved in pathological remodeling of the cardiomyocytes [124–126]. It is difficult to distinguish the age-dependent from the disease-associated changes and a clear understanding of pathology-induced vs age-induced changes for most of these proteins is consequently missing [127]. If cellular stretching could be used as a model to mimic aging, it would allow for the dissection of which changes are associated with normal aging vs pathological conditions.

Changes in chromatin methylation have been well established in the process of aging (recently reviewed in Refs. [128–130]). H3K9me3 is a key modification that is lost in the process of aging and results in loss of heterochromatin. Indeed, H3K9me3 is also affected in premature aging diseases, such as Hutchison-Gilford progeria syndrome (HGPS) and Werner syndrome [131,132]. Both disorders are linked to mutations of the nuclear envelope protein Lamin A [133–135]. It has been shown that a loss of heterochromatin in HGPS fibroblasts contributes to the nuclear envelope herniations that are characteristic of nuclei from HGPS [136]. Indeed, treating these fibroblasts with methylstat to increase heterochromatin helps to restore normal nuclear morphology [136]. The loss H3K9me3 is therefore an important contributor to aging (both normal and premature).

It has recently been shown that mechanical stretching can alter the heterochromatin content of cells [97]. The cellular response to stretch was directly dependent on the stretching protocol. A large stretch (40%) resulted in a rapid decrease in H3K9me3 heterochromatin followed by reorientation of the cytoskeleton perpendicular to the direction of the stretch, and eventual re-establishment of the H3K9me3 levels. However, a more subtle stretch of 5% had lasting effects and reduced the H3K9me3 levels for the duration of the stretch experiment [97]. The intriguing question is whether such a stretching protocol could be used to mimic aging in a cellular system. For example, since many of the sarcomere changes that are thought to be associated with aging in cardiomyocytes have been mostly studied in disease states, the correct stretching protocol could possibly be used to age these cells and differentiate between the changes that drive aging versus disease.

12. Conclusions

While much of this review has focused on the LINC complex, other nuclear envelope proteins also clearly play an important role in mechanotransduction. Particularly lamin A/C has been well established for having important roles in cellular mechanical responses [45,114,137], on which we only touched briefly here. Other examples include lamin B receptor, which has been shown to play an important role in organizing chromatin [50], and LEM domain proteins, such as Emerin, which interacts with the LINC complex as well as chromatin (through the Barrier to Auto-integration Factor (BAF)) [138].

While the main focus here was the role of the LINC complex in dynamic stress, it is clear that the LINC complex plays an equally important role in static tension, such as variations in substrate stiffness. Substrate stiffness-induced morphological and transcriptional changes are dependent on LINC complex proteins as well as other nuclear envelope proteins, such as lamins [49,57,82,139]. Indeed, the LINC complex modulates matrix rigidity-induced gene expression by tuning the nuclear stiffness to match that of the surrounding substrate [57,140]. Some of the LINC complex-dependent responses to static versus dynamic stress may in fact be difficult to tease apart, since cyclic stretching has an inherent change in substrate rigidity, with stretched cells experiencing a stiffer substrate than unstretched cells. Though this change in substrate rigidity is transient in cyclic stretching, it is nonetheless a factor to consider.

While the central function of the LINC complex in mechanotransduction is well established, some interesting questions remain to be answered, particularly when considering the cross-talk and interconnectedness between different cytoskeletal elements, and the heterogeneity of LINC complex components. How do cells balance the forces that maintain genetic integrity, cellular morphology and function, and, ultimately, survival? What are the factors that drive cellular and nuclear mechanobiology in aging? Mechanical stretching devices have already helped to answer some aspects of these questions, and will no doubt continue to play a significant role in the field of mechanobiology.

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