Actin on and around the Nucleus

Patricia Davidson, Bruno Cadot

CellPress
OPEN ACCESS

Review

Actin on and around the Nucleus

Patricia M. Davidson[1,2,*] and Bruno Cadot [1,*]

Actin plays roles in many important cellular processes, including cell motility, organelle movement, and cell signaling. The discovery of transmembrane actin-binding proteins at the outer nuclear membrane (ONM) raises the exciting possibility that actin can play a role in direct force transmission to the nucleus and the genome at its interior. Actin-dependent nucleus displacement was first described a decade ago. We are now gaining a more detailed understanding of its mechanisms, as well as new roles for actin during mitosis and meiosis, for gene expression, and in the cell's response to mechanical stimuli. Here we review these recent developments, the actin-binding proteins involved, the tissue specificity of these mechanisms, and methods developed to reconstitute and study this interaction *in vitro*.

Preamble: The Nucleus and the Surrounding Actin

The nucleus was once considered a simple, static reservoir for the genetic material of the cell. We now know that it plays a wide range of roles, from controlling mechanical sensing to regulating gene expression. Similarly, actin structures around the **nuclear envelope (NE)** (see Glossary) were first described decades ago, but their role was initially unclear. The discovery of the transmembrane **linker of nucleoskeleton to cytoskeleton (LINC)** complexes in the early 21st century established that nuclear lamins and chromatin inside the nucleus mechanically connect to the cytoskeleton outside the nucleus [1]. The NE and the actin cytoskeleton (Boxes 1 and 2) are now generating renewed interest as active partners in gene expression. NE proteins are implicated in a wide variety of diseases and their connections to actin may thus play important roles in many physiological processes, likely in a tissue-dependent manner (Figure 1).

Here, we discuss the recently described roles that NE-associated actin plays, including displacement of the nucleus within the cell, **NE breakdown (NEBD)**, gene expression, and cellular responses to stress. An entire parallel field has also risen from the (long controversial) idea that actin can assemble and perform functions inside the nucleus, although we do not discuss nuclear actin in this review.

Actin Functions around the Nucleus
Actin for Positioning Nuclei: Anchoring and Moving Nuclei into Position

Actin mediates nuclear movement to a particular functional position within the cell in many tissues and is responsible for maintaining this position. One striking example is the interkinetic movement of nuclei in pseudostratified epithelia, first described in 1935 [2], in which nuclei are displaced from the basal to the apical surface of the cell to undergo mitosis. The roles of actin and microtubules in mediating nuclear movement differ significantly depending on the tissue, most likely due to the geometry and the thickness of the epithelial layer, which determine the mechanical constraints and the distance the nucleus must move [3]. Microtubules are required for nuclear movement in the highly elongated cells of the rodent neocortex, whereas in the zebrafish retina and hindbrain, nuclear displacement toward the apical surface depends on actomyosin contraction at the nucleus rear [4,5]. In mouse models, removal of the **Klarsicht, nuclear anchorage protein 1 (ANC-1), synaptic nuclear envelope (Syne) homology (KASH)** domain of Nesprin-2 or removal of both of the **Sad1p, UNC-84 (SUN)**-containing proteins SUN1 and SUN2 impairs interkinetic

Highlights

Direct connections between the actin cytoskeleton and the nucleus govern nuclear positioning, nuclear movement during cell polarization and migration, nuclear movement before and after mitosis and meiosis, nuclear envelope breakdown, mechanotransduction, and gene expression.

The nucleus directly connects to actin through transmembrane proteins (LINC complex proteins) complemented by a large family of actin-associated proteins that interact with proteins of the nuclear envelope.

Actin can act indirectly on the nucleus to displace it, to protect it from external forces, and to dampen mechanical stimuli. However, the compression exerted by actin can cause nuclear rupture.

Interactions between the nucleus and actin are studied *in vitro* using isolated nuclei and reconstituted actin networks.

[1]INSERM – Sorbonne Université UMR974 – Center for Research in Myology, Paris, France
[2]Current address: 4Dcell, Montreuil, France

*Correspondence:
patricia.davidson@4dcell.com
(P.M. Davidson) and
bruno.cadot@inserm.fr
(B. Cadot).
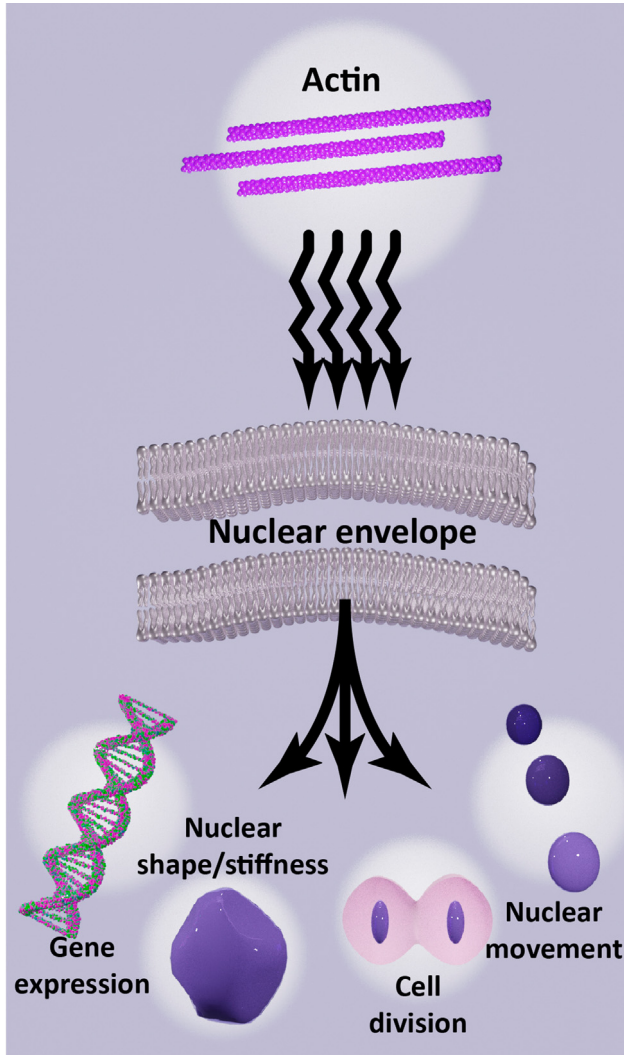
Figure 1. The Interaction between Actin and the Nuclear Envelope (NE) Has Several Implications Decisive for Cell Biology. The NE is a physical barrier between the cytoplasm and the genetic information. Multiple studies in different systems have shown that actin in the cytoplasm interacts with the NE in several ways (wavy arrows) and can thus influence (curved arrows) gene expression, NE stiffness, cell division, and nuclear movement.

Trends in Cell Biology

Glossary

Actin-related protein 2/3 complex (Arp2/3): a seven-subunit protein complex that serves as nucleation sites for new actin filaments in eukaryotic cells; binds to existing filaments and initiates the growth of a new filament.

Calcium-mediated actin reset (CaAR): a process in which a calcium burst induces accumulation of actin around the nucleus.

Cell division cycle 42 (Cdc42): small GTPase regulating multiple cellular functions by affecting cytoskeletal organization.

Endoplasmic reticulum (ER): organelle continuous with the ONM; involved in protein maturation and transport.

Formin homology 2 domain-containing 1 (FHOD1): involved in the assembly of actin structures in a Rho-dependent way.

Inner nuclear membrane (INM): the lipid bilayer facing the nucleoplasm.

Inverted formin 2 (INF2): accelerates the polymerization and depolymerization of actin.

IQ motif-containing GTPase activating protein 1 (IQGAP1): involved in the dynamics and assembly of the actin cytoskeleton.

Klarsicht, ANC-1, Syne homology (KASH): a conserved domain of fewer than 30 amino acids known to interact with a SUN domain in the perinuclear space between the two lipid bilayers of the NE.

Lamin-associated polypeptide 1 (LAP1): localized in the INM; binds both lamin A and lamin B.

Leucine repeat adaptor protein 35 (LRAP35): interacts with MRCK or Dock8 to promote cell migration.

Linker of nucleoskeleton and cytoskeleton (LINC): protein complex comprising Nesprin and SUN proteins; spans the entire NE; implicated in mechanotransduction.

Myocardin-related transcription factor A (MRTF-A): predominantly nuclear, associates with SRF to control gene expression regulating the cytoskeleton.

Myotonic dystrophy kinase-related Cdc42-binding kinase (MRCK): involved in actin organization, actin retrograde flow, and actomyosin contraction, determinant for cell migration and cell protrusion.

movement during retinal development [6], but in a mouse model in which the actin-binding domain of Nesprin-2 has been deleted, no clear nuclear positioning defects could be observed [7]. This actin-dependent mechanism is thus likely to rely on an as-yet unidentified connection between SUN proteins and actin. In the developing zebrafish hindbrain, actomyosin contractility at the rear of the nucleus is driven by the Rho–ROCK pathway, while formin-like-3 nucleates actin behind the nucleus in the retina [8,9]. Coordinated actin polymerization creates a pushing force to move the nucleus toward the apical surface of pseudostratified epithelial in both of these mechanisms. Similarly, Diaphanous, the sole Dia-class formin in *Drosophila*, and Rok, the activator of myosin II, move the nucleus to the apical face of the developing wing disc before mitosis [10]. Strikingly, dependence on this formin grows with increasing tissue density, indicating a mechanism that is turned on in a crowded environment, when mechanical constraints on the nucleus increase. All of these studies suggest that, during nuclear movement in pseudostratified epithelial cells, actin acts at the rear of the nucleus to push it forward through actomyosin contractility with formin-dependent mechanisms (Figure 3A).
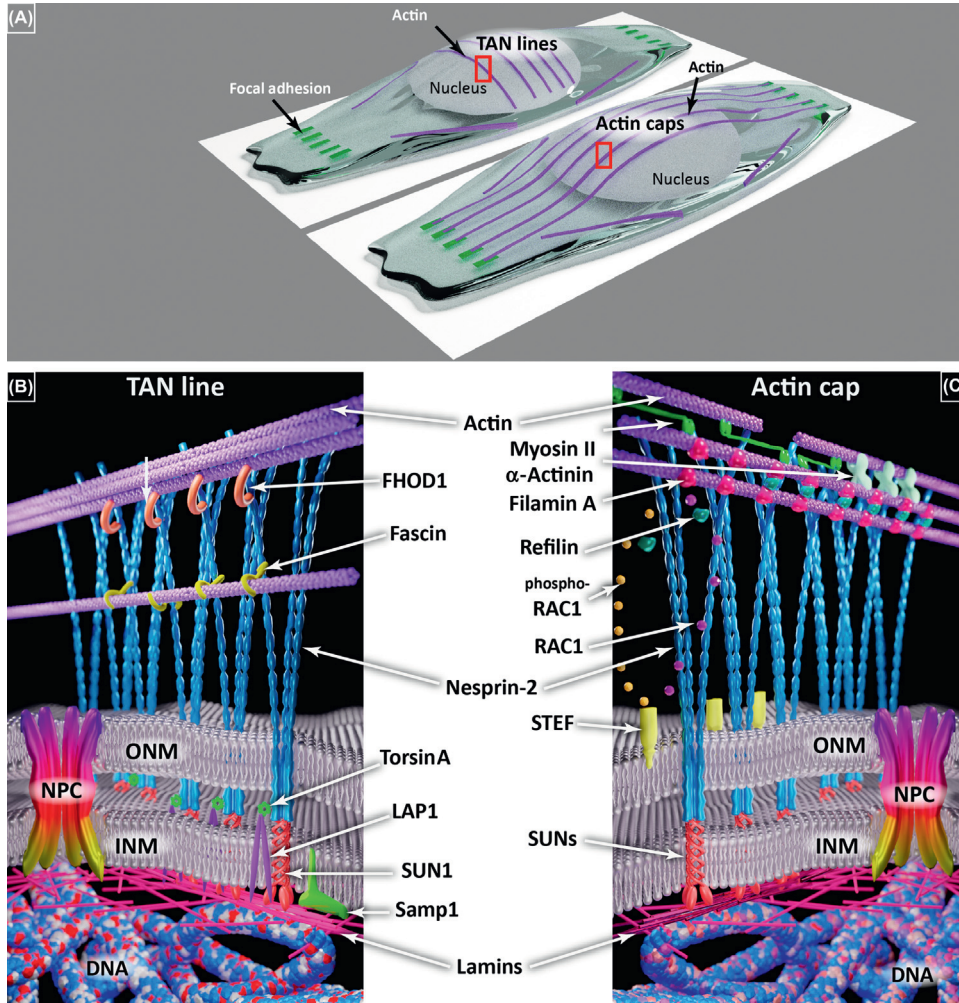
Figure 2. Differences between Transmembrane Actin-Associated Nuclear (TAN) Lines and Perinuclear Actin Caps. (A) TAN lines are associated with actin transverse arcs, parallel with the edge of the cell front, and are not connected to focal adhesions. Actin caps are longitudinal actin fibers initiated at focal adhesions. Both require the linker of the nucleoskeleton and the cytoskeleton (LINC) complex comprising Nesprins (blue) and Sad1p, UNC-84 (SUN) proteins (red) in (B,C). (B) Several partners of the TAN lines have been identified on both sides of the nuclear envelope (NE), such as formin homology 2 domain-containing 1 (FHOD1) (orange), fascin (yellow), TorsinA (light green), lamin-associated polypeptide 1 (LAP1) (purple), and Samp1 (dark green). (C) Various partners are involved in actin cap formation and maintenance, such as myosin II (fluo-green), α-actinin (light green), and Refilin (dark green) that interacts with filamin A (red) in a Rac1 (blue)/phospho-Rac1 (dark yellow) -dependent manner driven by Sif and Tiam1-like exchange factor (STEF) (light yellow). Both actin caps and TAN lines are connected to lamins (pink) and then DNA (blue-white-red ribbon).

Nuclear anchorage protein 1 (ANC-1): Nesprin homolog in *Caenorhabditis elegans*.

Nuclear envelope (NE): a double lipid bilayer evenly punctured by nuclear pores.

Nuclear envelope breakdown (NEBD): occurs at the beginning of the M phase of the cell cycle, to allow microtubules to interact with the chromosomes.

Nuclear localization sequence (NLS): targets proteins toward the nucleus interior.

Nuclear pore complex (NPC): large protein complex spanning the NE; controls the passage of molecules between the cytoplasm and nucleoplasm.

Outer nuclear membrane (ONM): the lipid bilayer facing the cytoplasm.

Sad1p, UNC-84 (SUN): proteins embedded in the INM connecting the lamin meshwork to Nesprins; part of the LINC complex.

Serum response factor (SRF): transcription factor that binds to serum response elements upstream of the transcription initiation of several genes; when associated with MRTF, controls the expression of cytoskeleton-regulating genes.

Sif and Tiam1-like exchange factor (STEF): a GEF that modulates Rac1 activity.

Synaptic nuclear envelope (Syne): gene encoding KASH proteins; initially discovered in muscle; five different genes have been discovered in mammals and homologs were found in other species.

Transmembrane actin-associated nuclear (TAN) lines: structures involving Nesprin-2G and actin at the NE.

Muscle cells, which are created by fusing many myoblasts together, contain several evenly spaced nuclei. This spacing is controlled by microtubule motors and is followed by an actin-dependent displacement of nuclei to the periphery of the cell. This outward movement is characterized by squeezing of the nucleus; it is excluded from the cell's center by the progressive desmin-dependent crosslinking of myofibrils, without an active connection identified between the cytoskeleton and the nucleus [11]. In the hypodermal syncytium of *Caenorhabditis elegans*, the KASH protein ANC-1 anchors nuclei in place, and the mechanism was long assumed to be actin dependent [12]. However, recent results from the same authors contradict this assumption,

Box 1. Actin

Actin is a highly conserved, abundant. 42-kDa globular protein. It is essential in eukaryotic cells, in which it can be found in its monomeric form (G-actin) or its polymerized form (F-actin). In its monomeric form, actin plays roles in gene regulation; for example, through the binding and sequestration of MRTF proteins in the cytoplasm to prevent the activation of **SRF (serum response factor)** genes in the nucleus. Actin monomers are polarized and assemble from both the + (or barbed) end and the − (or pointed) end; however, addition of monomers to the barbed end is more rapid. The rate-limiting step in actin filament formation is the creation of stable dimers and trimers. Under physiological conditions, actin-sequestering proteins (e.g., profilin) prevent the spontaneous dimerization of actin. Filament formation is thus initiated by nucleation proteins. Three major types of actin nucleators have been identified. Formins and tandem monomer-binding nucleators (e.g., spire, cordon blue) nucleate linear actin filaments, whereas the Arp2/3 complex nucleates actin branches from pre-existing filaments [100].

The length and organization of actin filaments is further regulated through a large family of actin-binding proteins. We have listed some of the relevant proteins around the nucleus in Table I. Capping proteins stabilize filament length. Crosslinking proteins (e.g. α-actinin, fascin) stabilize filaments into arrays of parallel or mesh-like structures. Actin filament turnover is regulated by proteins that depolymerize the actin network. The actin cytoskeleton is thus a highly dynamic structure that is constantly evolving.

Actin assemblies form a range of diverse structures in the cell [72]: the lamellipodium, a broad, flat cell protrusion at the leading edge of migrating cells, is formed from a sheet of Arp2/3-nucleated branched actin, while filopodia – thin, dynamic cell extensions – are formed from parallel actin filaments nucleated by formins and bundled together by actin crosslinkers such as α-actinin and fascin. The cell cortex, a thin layer of actin meshwork underlying the plasma membrane, comprises crosslinked actin filaments, the spacing of which is determined by the specific crosslinkers present. Antiparallel actin bundles form the stress fibers, which form contractile structures actuated by non-muscle myosin II motors. All of these structures serve as scaffolds and active participants in the functioning of the cell.

Table I. Actin-Binding Proteins around the NE

| Protein	Reported localization outside the nucleus	Associated protein	Function	Refs
Transmembrane proteins				
Nesprin-1	ONM	Emerin	Cytoskeleton interaction	[101]
Nesprin-2	ONM	FHOD1, fascin, Emerin	Cytoskeleton interaction	[20]
Emerin	ONM	NMII	Defective heterochromatin anchoring to the nuclear lamina	[60]
	ONM/ER	Nesprin-1	Nuclear front–rear polarity	[102]
	ONM	Actin	Binds and stabilizes pointed end of actin filaments, increased polymerization	[103]
Cytoplasmic proteins				
Amphiphysin	ONM	Nesprin-2, CLIP170	Required for nucleus positioning in *Caenorhabditis elegans*; binds Nesprin-2 at SR48-49	[104]
Fascin	TAN lines, dorsal side	Nesprin-2 (SR51-53)	Bridges Nesprin-2 and actin	[21]
FHOD1	TAN lines, dorsal side	Nesprin-2 (SR11-13)	TAN line assembly in 2D migration Behaves as a capping protein that inhibits polymerization	[20,105]
Filamin A	Actin cap	RefilinB	Actin crosslinker Organizes actin cap in fibroblasts	[36]
	Nurse cells	Villin, fascin, MSP-300	(Cheerio in *Drosophila*) Crosslinks perinuclear actin to actin cables	[14]
INF2	ER, ONM		Calcium-dependent perinuclear actin polymerization	[57,58]
IQGAP1	Perinuclear ring		Not yet known	[106]
	NE, NPC	MT	IQGAP1 bundles and caps actin filaments	[80]
mDia2	NPC, nuclear localization sequence (NLS) targets it to the cytoplasmic side of the nucleus	Importin B	No clear function	[92]
myo18A	Subnuclear	MRCK, LRAP35a	Subnuclear actomyosin network assembly	[40]
MyoIIb	Stress fibers around nucleus	Probably Nesprin-2	Squeezing of the nucleus during 3D migration; drives directional actin flow in polarizing fibroblasts	[53]
Shot	Nuclear periphery of *Drosophila* larval wall cells	MSP-300 and EB-1	Actin–microtubule crosslinker	[107]
STEF	ONM	Rac1	Phosphorylates RAC1 to recruit Refilin at bundling actin filaments	[38]

Box 2. The NE

One common feature among eukaryotes is the presence of a double lipid bilayer encapsulating the genome. Continuous with the ER, the NE is evenly punctured with large protein assemblies known as NPCs, allowing the nucleocytoplasmic shuttling of proteins. Close to the inner surface of the NE, a meshwork of intermediate filaments, the lamins, bind to chromatin and NE proteins and provide a physical scaffold that is partially responsible for nuclear shape and stiffness.

While its role was initially thought to be solely as a separation between DNA and the cytoplasm, several embedded proteins confer additional roles on the NE. A complex of proteins bridges the NE: the LINC complex, comprising two transmembrane proteins, SUN proteins at the INM and KASH proteins at the ONM. SUN proteins interact with lamins and chromatin-binding proteins inside the nucleus and connect to KASH proteins in the luminal space. These in turn bind cytoskeletal filaments. This complex is decisive for the transfer of mechanical cues from the exterior of the cell to the nucleus interior. The *SUN* and *SYNE* (encoding KASH proteins) genes are able to generate different splicing variants in a cell-type-dependent manner, thus fine-tuning their ability to transmit forces to the nuclear interior. The KASH proteins Nesprin-1 and -2, can bind actin filaments through calponin homology domains or through other intermediary proteins. Nesprins can indirectly bind to microtubules, while plectin links Nesprin-3 to intermediate filaments. Nesprins contain multiple spectrin repeats that may act as springs to buffer mechanical forces. This diversity in Nesprin isoforms contributes to the differences observed in the response to mechanical stress by cells and tissues.

---

as abolishing the actin-binding domain of ANC-1 is not necessary for nucleus anchorage [13]. It now remains to be determined how these giant actin-binding KASH proteins anchor the nucleus and the rest of the cellular organelles in place. In *Drosophila* nurse cells, nuclei are maintained in place by actin. This prevents the nuclei from clogging ring canals when nurse cells contract and expel their nutrient-rich cytoplasm to feed the growing oocyte. Actin filaments emerge from the ring canals and crosslink perinuclear actin via Cheerio, the *Drosophila* ortholog of filamin A that appears at the NE before dumping [14]. This mechanism is independent of LINC complex proteins. Mesenchymal stem cells and epithelial cells position their nucleus in concave areas below the cell, releasing strain on the nucleus in a mechanism that is dependent on **cell division cycle 42 (Cdc42)**, the **actin-related protein 2/3 complex (Arp2/3)**, A-type lamins, and LINC complex proteins [15].

Cell polarization prior to migration is characterized by the positioning of the nucleus behind the centrosome respective to the direction of migration. In a tissue-culture cell-based assay in which actin stress fibers are abolished and allowed to form again, actomyosin contraction at the cell front is transmitted toward the nucleus through actin retrograde flow [16,17]. Steered by a Cdc42/**myotonic dystrophy kinase-related Cdc42-binding kinase (MRCK)** pathway, nuclear movement is then driven by transverse actin cables bound to Nesprin-2, forming **transmembrane actin-associated nuclear (TAN) lines**, which undergo retrograde flow. These rearward-traveling actin fibers drag the nucleus toward the back of the cell, behind the centrosome [18], in concert with TorsinA, Emerin, Samp1, SUNs, lamins, **lamin-associated polypeptide 1 (LAP1)**, **formin homology 2 domain-containing 1 (FHOD1)**, fascin, and **nuclear pore complexes (NPCs)** (Figure 2) [19–24]. TorsinA, in the perinuclear space, interacts with LAP1, which spans the **inner nuclear membrane (INM)**, to assemble TAN lines. Emerin, a NE-associated protein known to be present on both nuclear membranes, is involved in the directionality of the retrograde flow [24]. Samp1, a component of TAN lines, is crucial for rearward nuclear movement [19]. FHOD1 and fascin are localized at the cytoplasmic side of the NE and crosslink Nesprin-2 to actin [20,21]. This TAN line assay, coupled with centrifugation to displace the nucleus away from its natural position in the cell, was used to demonstrate that nucleus movement toward the front of the cell is SUN1 and microtubule dependent, while rearward movement is actin and SUN2 dependent [25]. It is unclear how cells differentiate between these two mechanisms, as both use Nesprin-2G as the central element linking SUN1 to microtubules and SUN2 to actin, respectively. However, this mechanism has potential implications in a disease context: the mutant form of lamin A that causes progeria, an extremely rare disorder
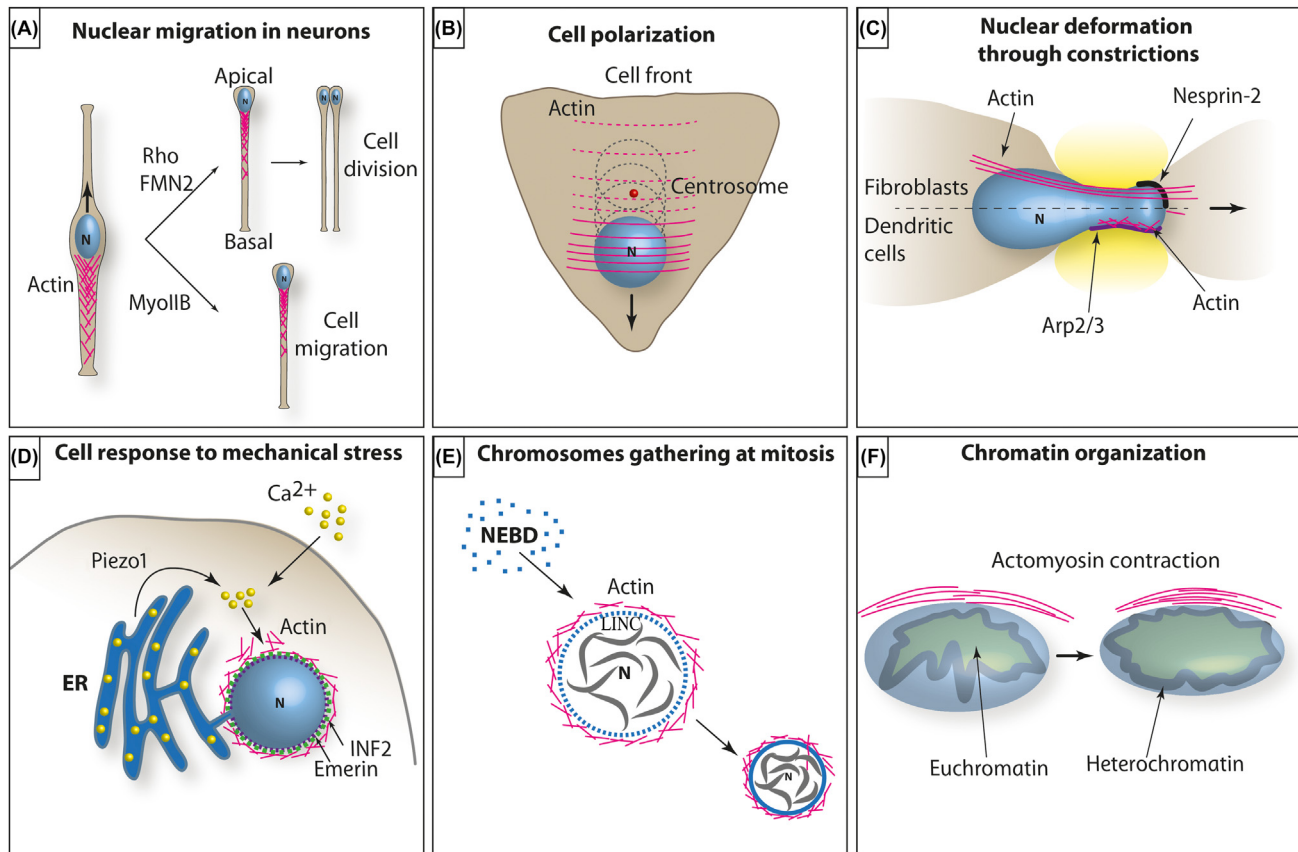
Figure 3. Nuclear Envelope–Actin Interactions Have Been Observed in Several Important Cellular Processes. (A) Actin-dependent nuclear migration in neurons is decisive during development for cell division and cell migration. The interkinetic nuclear movement preceding cell division is driven by Rho and formin-2 (FMN2) and actin polymerization at the nucleus rear. For neuronal migration, saltatory nuclear movement is driven by myosin IIB (MYOIIB) and actin polymerization at the nucleus rear. (B) During cell polarization, using actin retrograde flow, transmembrane actin-associated nuclear lines move the nucleus toward the back of the cell. (C) Actin polymerization is required to displace the nucleus through a constriction in fibroblasts and dendritic cells. In fibroblasts, nuclei are pulled through constrictions as Nesprin-2 accumulates at the front of the nucleus (orange). Actin is organized in bundles around the nucleus parallel to the direction of migration. In dendritic cells, actin-related protein 2/3 complex (Arp2/3) along the nucleus (purple) creates an actin sleeve to squeeze the nucleus through the constriction. (D) On mechanical stress, calcium (yellow) release into the cytoplasm [from the cells' exterior or endoplasmic reticulum (ER) stores] induces actin polymerization around the nucleus in an inverted formin-2- (INF2) and Emerin-dependent manner. (E) Immediately after nuclear envelope breakdown (NEBD), actin surrounds the chromosomes and contracts, preventing them from dispersing and thus reducing mitotic errors. (F) Actomyosin contraction induces nuclear deformation and chromatin organization changes in the nucleus.

characterized by premature aging symptoms, induces accumulation of SUN1 at the NE, reducing the potential for actin-based nuclear movements [26] (Figure 3B).

Actin around the Nucleus during Cell Migration

In vivo, nuclear movement is particularly important during the formation of the brain, when neuronal progenitors migrate across long distances. This movement is saltatory due to decoupling of the growth cone and the nucleus: extension of the leading process occurs through actin polymerization in the growth cone followed by nuclear movement, often initiated by myosin IIB-dependent actomyosin contraction at the nucleus rear [27]. Although lack of Nesprin-1 and -2 results in morphological defects in the mouse brain, it remains to be established whether this intermittent nuclear movement is dependent on a direct connection between actin and the NE [28]. It is, however, likely to involve drebrin, a microtubule–actin crosslinking protein [29].

In fibroblasts, actin filaments above the nucleus, termed the perinuclear actin cap, orient the nucleus in the direction of migration [30,31]. These dynamic structures align with the long axis of the cell, contain phosphorylated myosin II and α-actinin-1, and terminate at vinculin-containing focal adhesions [30]. Unlike ventral actin fibers, the actin cap is connected to the nucleus through Nesprin-2, is involved in nuclear shape, and controls mechanotransduction [30,32]. Actin fibers of the perinuclear actin cap connect to 30% of focal adhesions and can thus exert higher tension than other actin structures, potentially increasing their responsiveness to mechanical stress [33,34]. In a similar manner, actin connects cell adhesion complexes with the NE of human breast epithelial cells in 3D culture [35].

Many proteins participate in linking the nucleus to actin and help to organize the actin cap. Cells that do not assemble perinuclear actin caps, such as cancer cells or cells lacking α-actinin-1, do not orient their nucleus in the direction of migration even if dorsal and transverse actin fibers are intact. At the nuclear periphery, the actin branching protein filamin A is converted into an actin bundler by RefilinB to organize the actin structures above the nucleus [36] and is also involved in mechanotransduction [37]. Interestingly, depletion of the Rac1-selective guanine exchange factor (GEF) **Sif and Tiam1-like exchange factor (STEF)**, localized at the NE and colocalizing with Nesprin-2, leads to a decrease of perinuclear actin caps [38]. Lamin A/C is also required for the formation of the actin cap, suggesting feedback from the nuclear interior that dictates the architecture of the actin network [39]. The actin structures that exist below the nucleus in HeLa and Cos7 cells are not organized in the same direction as the actin cap and colocalize with MRCK and **leucine repeat adaptor protein 35 (LRAP35)** [40]. The role of these subnuclear structures is not clear yet, but they may be involved in contact guidance, characterized by cellular adaptation and cytoskeletal organization along topographical cues [41].

TAN lines and the perinuclear cap share many similarities (Figure 2), although TAN lines have not yet been shown to connect to focal adhesions nor has their role in mechanotransduction been demonstrated [18]. Recently, Hoffman *et al.* [23] described TAN lines formation upon cyclic stretching of cells. However, in a previous report Kim *et al.*, using the same cell-based assay, showed that the actin lines formed upon stretch are perinuclear actin caps instead of TAN lines, as they are connected to focal adhesions [32]. Several partners of TAN lines have been associated with multiple diseases where mechanical load is known to occur, such as laminopathies [42–44], Emery–Dreifuss muscular dystrophy [45–47], and cancer [48,49], thus indicating a potential role of this structure in transmitting mechanical cues to the nucleus interior. Further studies are required to determine whether TAN lines and the perinuclear cap could be specialized structures emanating from the same mechanism and whether they share partner proteins. Furthermore, it remains unclear whether these structures are found *in vivo*.

Actin around the Mechanically Deformed Nucleus

The deformability of the cell nucleus is a limiting factor for cell migration through narrow constrictions. In some cell types, actin-based mechanisms facilitate nuclear deformation. Dendritic cells squeeze their nuclei during entry into a narrow channel using an Arp2/3-nucleated actin sleeve to facilitate ingression [50]. This LINC complex-independent mechanism relies on the size of the object to be pushed through the constriction, as demonstrated using beads of different sizes injected in the cytoplasm: beads larger than the constriction are surrounded by actin when the cell attempts to transfer them through the constriction, but smaller beads are not. Actomyosin contractility, observed at the back of the cell indicating that the nuclei are pushed through the constriction from the rear, is not necessary for the formation of this actin sleeve. In a contrasting mechanism, murine fibroblasts deform their nucleus through constrictions via actomyosin contractility at the front of the cell [51], reminiscent of the nuclear movement observed when actomyosin contraction is induced at the

cell front on 2D substrates [52]. Fibroblasts lacking Nesprin-2G and fascin have defects in nuclear translocation through constrictions [21,53]. In these cells, actin filaments run parallel to the axis of migration, myosin IIB accumulates along these filaments [53], and Nesprin-2G accumulates at the front of the nucleus in an actin-dependent manner, implying that Nesprin-2G participates in pulling the nucleus through the constriction [51]. Primary human fibroblasts undergoing lobopodial migration through the extracellular matrix display a similar mechanism. (Lobopodia are blunt, cylindrical protrusions forming when fibroblasts migrate in 3D matrices [54].) In these cells, the confined nucleus is pulled forward via actin, vimentin, Nesprin-3, and myosin II at the cell front, resulting in increased pressure at the front of the cell and the formation of lobopodia in a piston-like mechanism [55]. It remains to be determined whether these similar mechanisms are related (Figure 3C).

Actin around the Nucleus in Response to Mechanical Stimuli

Actin structures around the nucleus can protect it from mechanical damage. The nuclei of stretched cells devoid of lamins A/C (that do not assemble a perinuclear actin cap) are more deformed than their wild-type counterparts, suggesting that the actin cap protects the nucleus from mechanical deformation [32]. Conversely, mechanical confinement exerted by actin on the nucleus is the force behind spontaneous NE rupture on 2D substrates [56].

Application of force to the cell, by direct probing, cell stretching, or shear, triggers an accumulation of actin in a ring around the nucleus that is dependent on calcium and **inverted formin 2 (INF2)** [57,58]. This rapid response (under 2 min), termed **'calcium-mediated actin reset' (CaAR)**, is observed in epithelial, mesenchymal, endothelial, and immune cells. It can be triggered by the import of extracellular calcium into the cytoplasm or the release of calcium from the **endoplasmic reticulum (ER)** in a Piezo-1-dependent mechanism [58,59]. In endothelial cells, actin accumulation around the nucleus in response to stretch is Emerin dependent and triggers the displacement of Emerin from the INM to the **ONM** [60]. This rapid, force-dependent response induces nuclear softening by reducing heterochromatin levels, thereby protecting the genome [59]. In mesenchymal stem cells, high-frequency cell stretching (above 5 Hz) results in decoupling of the nucleus from the cytoskeleton in a SUN2-dependent manner [61]. This is consistent with nucleus rounding observed in response to high-amplitude stretch in endothelial cells [59] and calcium/Piezo-1-dependent nuclear shrinkage in sheared epithelial cells [62]. Sustained force application leads to tissue-level reorganization into a cobblestone pattern [59], but changing the direction of the force exertion rapidly triggers a new actin ring around the nucleus. It is not yet clear how this calcium-mediated mechanism triggers changes inside the nucleus, although the pivotal role of the formin INF2 is a strong indicator that actin polymerization is involved (Figure 3D).

Actin around the Nucleus during Mitosis and Meiosis

During meiosis, actin plays roles immediately before and during NEBD and moves the nucleus and the spindle in mouse oocytes. Actin also forms filaments at centrosomes and in the spindle during mitosis and contributes to NE reassembly [63].

While microtubules are responsible for tearing down the NE in many systems [64], they are dispensable in some systems, where actin may play the starring role instead. Transient actin shells appear immediately before NEBD in echinoderms, cnidaria, and polychaetes [65]. In starfish oocytes, actin spikes, nucleated by Arp2/3 at the nuclear lamina, tear the INM between NPCs [65]. This mechanism may allow NPCs to remain intact in nucleoplasmic bodies throughout meiosis, thereby reducing the energy necessary to reform these NPCs when the NE is reassembled.

In mouse oocytes, nuclear movements during meiosis to the center of the cell and back to the cortex are actin dependent. Before meiosis I, actin polymerization creates a pressure gradient that nonspecifically centers large objects, thereby moving the largest organelle, the nucleus, to the cell center [66–69]. After this nucleus-centering step, the spindle is formed and it is then moved back to the cortex. Both of these movements depend on actin and its nucleator formin-2 [66,70].

At the start of mitosis, a contractile actin network reduces the volume taken up by chromosomes to ensure efficient chromosome capture by spindle microtubules. This serves to reduce the dispersion of individual chromosomes after NEBD. Removing LINC complexes from the NE or reducing myosin II contractility increases chromosome congression time and chromosome mislocalization, resulting in inefficient mitosis [71]. This actin network was not found in HeLa cells, suggesting that loss of this nonessential mechanism could be a source of mitotic errors in malignant cells (Figure 3E).

Actin interacts with centrosomes and the spindle *in vitro* and during mitosis [72–74]. Inhibition of Arp2/3-dependent branched actin nucleation reduces this spindle-associated pool of actin and results in disorganized chromosome congression and mitotic defects [75]. Similarly, centrosome separation and positioning around the cell centroid are orchestrated by transient perinuclear actin and the LINC complex [76]. Actin filaments nucleated by formin-2 can even be found in the spindle itself during mitosis, working with microtubules to ensure faithful chromosome segregation [77]. Actomyosin plays indirect roles during cell mitosis by exerting forces that flatten the cell. In HeLa cells, compressing the cells is sufficient to rescue mitosis when myosin II contractility is inhibited [78]. After mitosis, actin contributes to the reassembly of the NE; transient perinuclear F-actin rings have been reported in reforming nuclei (late telophase) in murine fibroblast and epidermal cell cultures, as well as insect epidermis [79]. The actin-regulator **IQ motif-containing GTPase activating protein 1 (IQGAP1)** coordinates NPC reassembly after mitosis [80].

Taken together, these results indicate that actin plays important roles during mitosis and meiosis, alongside microtubules. Actin plays important roles in setting up the nucleus for mitosis, reducing chromosomal segregation errors, and NE reassembly after mitosis. Whether these two cytoskeletal components work in parallel or together remains to be investigated.

Actin around the Nucleus and Gene Expression

Actomyosin contraction around the nucleus can affect the organization of chromatin. One striking example is the inversion of genomic architecture in rod photoreceptor cells caused by actomyosin-mediated nuclear deformation [81,82]. Actin contraction around the nucleus reduces nuclear volume and chromatin accessibility, resulting in poor reprogramming of fibroblasts to pluripotent stem cells [83]. It can also reduce telomere and heterochromatin dynamics [81] in a mechanism that is dependent on SUN2 [83], Nesprin-2G and lamin A/C [84]. Similarly, pulling on the LINC complex results in nucleus stiffening and altered gene expression [85,86]. This modulation of gene expression is well described in cells harboring high actomyosin contractility, such as cardiac and skeletal muscle cells [87]. In agreement with this, mutations in proteins associated with the LINC complex affect tissues subject to high mechanical forces. Actomyosin contractility increases SUN2's association with lamins in vascular smooth muscle cells, thus remodeling interactions at the INM and altering the balance between actin and microtubule associations with the ONM [88]. Downregulation of Nesprin-2 or non-muscle myosin II, both involved in the formation and maintenance of TAN lines and actin perinuclear caps, results in similar alterations of the expression of genes associated with the epithelial-to-mesenchymal transition [18,24,89,90]. Overall, actomyosin contractility around the nucleus results in alteration of gene expression by reducing the nuclear

volume and via LINC complex-dependent mechanisms (i.e., mechanotransduction). These mechanisms may explain in part the disease phenotypes observed in nuclear envelopathies [91] (Figure 3F).

Preventing monomeric actin from entering the nucleus is a promising strategy to modulate the expression of genes that are regulated by nuclear actin or to reduce the import of gene-regulating proteins that require actin to enter the nucleus [e.g., **myocardin-related transcription factor A (MRTF-A)**]. Actin polymerization at the NE reduces stores of actin at the cell periphery [58] and depletes nuclear actin [60]. The formin mDia2 shuttles between the nucleoplasm and cytoplasm and accumulates at the outer NE due to importin beta, colocalizing with NPCs [92]. These mechanisms could explain how actin polymerization around the NE (e.g., during CaAR) can result in downstream signaling.

In Vitro Reconstitution of Actin around the Nucleus

To better understand the factors that regulate actin assembly around the nucleus, the interaction between actin and the ONM is investigated by injecting fluorescent actin into cells, extracting nuclei out of the cell to observe actin structures present on the ONM, or observing the interaction of isolated nuclei with monomeric or polymerized actin. Injection or transient expression of fluorescent actin in HeLa cells results in accumulation of actin at the nuclear periphery, while isolated hepatocyte nuclei incubated in the presence of fluorescent actin monomers accumulate polymerized actin [93]. A similar accumulation of actin at the nuclear periphery was observed in nuclei isolated using non-ionic detergents [94]. Antibodies against NE proteins (Nesprin-2 and a NPC protein) reduce the accumulation of actin around the nucleus, but it is unclear whether this is due to a specific interaction with these specific proteins or whether the bulky antibodies mask the surface of the NE from actin. Precise studies are thus still required to determine whether actin filament accumulation around nuclei is due to the binding of one or several specific proteins. Nevertheless, this system presents exciting opportunities to study actin assembly at the NE.

To study force transmission between the cytoskeleton and the nucleus, beads coated with actin are brought into contact with nuclei using optical tweezers [95]. Jumps of a few nanometers were recorded upon retraction of the beads using forces up to 50 pN, likely indicating protein unfolding. The authors hypothesize that they are probing Nesprin-1 or -2, and that their transitions correspond to the unfolding of a helix (5–10 nm) or of a Nesprin spectrin repeat (15 nm) [95]. Further study is necessary to confirm that actin-coated beads are specifically probing Nesprins at the NE. Nevertheless, applying forces to Nesprins using antibody-coated beads triggers nuclear stiffening that is dependent on the nuclear lamina and Emerin [85].

Concluding Remarks

The diversity of architectures that actin can adopt and its wide variety of target proteins make it a versatile actor in the cell (Figure 3). Whereas actin was historically depicted as the cytoskeletal network in charge of cell shape and contractility, we now know that it has leading and supportive roles in many other cell processes. Careful examination of actin structures and associated proteins *in vivo* is likely to provide evidence for many more extraordinary ways that actin orchestrates functions in the cell.

Much work remains on many fronts to understand the roles that NE proteins play with actin. Many NE transmembrane (NET) proteins have yet to be described fully and overexpression or knockdown of some of these leads to cytoskeletal disruption. The results obtained *in vitro* or in cell-based assays to decipher the actin–nucleus connection are not always readily transferable *in vivo*. For example, the existence of TAN lines in tissues or even in 3D culture remains confirmed. The recent development of organoids, recapitulating organ structure and function, combined

with the latest improvements in super-resolution imaging could allow better visualization and comprehension of the mechanisms involved. Optogenetics to locally perturb protein conformation or localization, Förster resonance energy transfer (FRET) sensors inserted in proteins under mechanical stress, and microfluidics are some of the techniques to be applied to gain more insight into the nucleus–actin connection. A recent approach using mutually attracted magnetic beads on both sides of the plasma membrane has revealed the fluctuations of actomyosin contractions [96]. A similar approach using a single bead inside the cytoplasm revealed the elastic component of the NE [97]. In addition, exciting new tools are being developed that could be adapted to expand our understanding of actin around the NE: a technique to reveal actin that is in contact with the cytoplasmic membrane could be adapted to similarly reveal actin structures in contact with the NE [98]. *In vitro* models could help to elucidate the structures we observe in cells and *in vivo*: a recent publication, studying the interaction of actin with lipid membranes, strikingly recapitulated the membrane protrusions observed during NEBD in starfish oocytes [65,99].

We discussed previously the potential impact that the balance between perinuclear actin polymerization and the shuttling of monomeric actin across the nuclear membrane can have on gene expression and cell fate. Further research is necessary to determine whether this mechanism is used by the cell and whether it can explain the impact of actin accumulation around the nucleus on gene expression (e.g., during CaAR) (see Outstanding Questions). Many mechanisms discussed here, from mitosis to nuclear displacement during 3D migration, could play a particularly important role in tumor cell proliferation and metastatic dissemination, implying that actin binding partners could provide new therapeutic partners to investigate in the fight against cancer and metastatic disease. The link between actin and the NE may also be decisive in the mechanisms of nuclear envelopathies.

References

1. Crisp, M. *et al.* (2006) Coupling of the nucleus and cytoplasm: role of the LINC complex. *J. Cell Biol.* 172, 41–53
2. Sauer, F. (1935) Mitosis in the neural tube. *J. Comp. Neurol.* 62, 377–405
3. Strzyz, P.J. *et al.* (2016) Heterogeneity, cell biology and tissue mechanics of pseudostratified epithelia: coordination of cell divisions and growth in tightly packed tissues. *Int. Rev. Cell Mol. Biol.* 325, 89–118
4. Norden, C. *et al.* (2009) Actomyosin is the main driver of interkinetic nuclear migration in the retina. *Cell* 138, 1195–1208
5. Strzyz, P.J. *et al.* (2015) Interkinetic nuclear migration is centrosome independent and ensures apical cell division to maintain tissue integrity. *Dev. Cell* 32, 203–219
6. Yu, J. *et al.* (2011) KASH protein Syne-2/Nesprin-2 and SUN proteins SUN1/2 mediate nuclear migration during mammalian retinal development. *Hum. Mol. Genet.* 20, 1061–1073
7. Falk, N. *et al.* (2019) Lack of a retinal phenotype in a Syne-2/Nesprin-2 knockout mouse model. *Cells* 8, 1238
8. Yanakieva, I. *et al.* (2019) Cell and tissue morphology determine actin-dependent nuclear migration mechanisms in neuroepithelia. *J. Cell Biol.* 218, 3272–3289
9. Lahne, M. *et al.* (2015) Actin–cytoskeleton- and Rock-mediated INM are required for photoreceptor regeneration in the adult zebrafish retina. *J. Neurosci.* 35, 15612–15634
10. Kirkland, N.J. *et al.* (2020) Tissue mechanics regulate mitotic nuclear dynamics during epithelial development. *Curr. Biol.* 30, 2419–2432.e4
11. Roman, W. *et al.* (2017) Myofibril contraction and crosslinking drive nuclear movement to the periphery of skeletal muscle. *Nat. Cell Biol.* 19, 1189–1201
12. Starr, D.A. and Han, M. (2002) Role of ANC-1 in tethering nuclei to the actin cytoskeleton. *Science* 298, 406–409
13. Hao, H. *et al.* (2020) The Nesprin-1/-2 ortholog ANC-1 regulates organelle positioning in *C. elegans* without its KASH or actin-binding domains. *bioRxiv* Published online July 15, 2020. https://doi.org/10.1101/2020.07.14.202838
14. Huelsmann, S. *et al.* (2013) Filopodia-like actin cables position nuclei in association with perinuclear actin in *Drosophila* nurse cells. *Dev. Cell* 26, 604–615
15. Pieuchot, L. *et al.* (2018) Curvotaxis directs cell migration through cell-scale curvature landscapes. *Nat. Commun.* 9, 3995
16. Palazzo, A.F. *et al.* (2001) Cdc42, dynein, and dynactin regulate MTOC reorientation independent of Rho-regulated microtubule stabilization. *Curr. Biol.* 11, 1536–1541
17. Gomes, E.R. *et al.* (2005) Nuclear movement regulated by Cdc42, MRCK, myosin, and actin flow establishes MTOC polarization in migrating cells. *Cell* 121, 451–463
18. Luxton, G.W.G. *et al.* (2010) Linear arrays of nuclear envelope proteins harness retrograde actin flow for nuclear movement. *Science* 329, 956–959
19. Borrego-Pinto, J. *et al.* (2012) Samp1 is a component of TAN lines and is required for nuclear movement. *J. Cell Sci.* 125, 1099–1105
20. Kutscheidt, S. *et al.* (2014) FHOD1 interaction with Nesprin-2G mediates TAN line formation and nuclear movement. *Nat. Cell Biol.* 16, 708–715
21. Jayo, A. *et al.* (2016) Fascin regulates nuclear movement and deformation in migrating cells. *Dev. Cell* 38, 371–383
22. Saunders, C.A. *et al.* (2017) TorsinA controls TAN line assembly and the retrograde flow of dorsal perinuclear actin cables during rearward nuclear movement. *J. Cell Biol.* 216, 657–674

23. Hoffman, L.M. *et al.* (2020) Mechanical stress triggers nuclear remodeling and the formation of transmembrane actin nuclear lines with associated nuclear pore complexes. *Mol. Biol. Cell* 31, 1774–1784

24. Chang, W. *et al.* (2013) Emerin organizes actin flow for nuclear movement and centrosome orientation in migrating fibroblasts. *Mol. Biol. Cell* 24, 3869–3880

25. Zhu, R. *et al.* (2017) Centrifugal displacement of nuclei reveals multiple LINC complex mechanisms for homeostatic nuclear positioning. *Curr. Biol.* 27, 3097–3110.e5

26. Chang, W. *et al.* (2019) Imbalanced nucleocytoskeletal connections create common polarity defects in progeria and physiological aging. *Proc. Natl. Acad. Sci. U. S. A.* 116, 3578–3583

27. Nakazawa, N. and Kengaku, M. (2020) Mechanical regulation of nuclear translocation in migratory neurons. *Front. Cell Dev. Biol.* 8, 150

28. Zhang, X. *et al.* (2009) SUN1/2 and Syne/Nesprin-1/2 complexes connect centrosome to the nucleus during neurogenesis and neuronal migration in mice. *Neuron* 64, 173–187

29. Trivedi, N. *et al.* (2017) Drebrin-mediated microtubule–actomyosin coupling steers cerebellar granule neuron nucleokinesis and migration pathway selection. *Nat. Commun.* 8, 14484

30. Maninová, M. and Vomastek, T. (2016) Dorsal stress fibers, transverse actin arcs, and perinuclear actin fibers form an interconnected network that induces nuclear movement in polarizing fibroblasts. *FEBS J.* 283, 3676–3693

31. Khatau, S.B. *et al.* (2009) A perinuclear actin cap regulates nuclear shape. *Proc. Natl. Acad. Sci. U. S. A.* 106, 19017–19022

32. Kim, J.-K. *et al.* (2017) Nuclear lamin A/C harnesses the perinuclear apical actin cables to protect nuclear morphology. *Nat. Commun.* 8, 2123

33. Kim, D.-H. *et al.* (2012) Actin cap associated focal adhesions and their distinct role in cellular mechanosensing. *Sci. Rep.* 2, 555

34. Kim, D.-H. *et al.* (2013) The multi-faceted role of the actin cap in cellular mechanosensation and mechanotransduction. *Soft Matter* 9, 5516–5523

35. Jorgens, D.M. *et al.* (2017) Deep nuclear invaginations are linked to cytoskeletal filaments – integrated bioimaging of epithelial cells in 3D culture. *J. Cell Sci.* 130, 177–189

36. Gay, O. *et al.* (2011) Refilin holds the cap. *Commun. Integr. Biol.* 4, 791–795

37. Baudier, J. *et al.* (2018) The filamin-B–refilin axis – spatiotemporal regulators of the actin–cytoskeleton in development and disease. *J. Cell Sci.* 131, jcs213959

38. Woroniuk, A. *et al.* (2018) STEF/TIAM2-mediated Rac1 activity at the nuclear envelope regulates the perinuclear actin cap. *Nat. Commun.* 9, 2124

39. Kim, H.Y. *et al.* (2017) On the role of mechanics in driving mesenchymal-to-epithelial transitions. *Semin. Cell Dev. Biol.* 67, 113–122

40. Tan, I. *et al.* (2008) A tripartite complex containing MRCK modulates lamellar actomyosin retrograde flow. *Cell* 135, 123–136

41. Tamiello, C. *et al.* (2015) Competition between cap and basal actin fiber orientation in cells subjected to contact guidance and cyclic strain. *Sci. Rep.* 5, 8752

42. Antoku, S. *et al.* (2019) ERK1/2 phosphorylation of FHOD connects signaling and nuclear positioning alternations in cardiac laminopathy. *Dev. Cell* 51, 602–616.e12

43. Berk, J.M. *et al.* (2013) The nuclear envelope LEM-domain protein Emerin. *Nucleus* 4, 298–314

44. Zwerger, M. *et al.* (2013) Myopathic lamin mutations impair nuclear stability in cells and tissue and disrupt nucleo-cytoskeletal coupling. *Hum. Mol. Genet.* 22, 2335–2349

45. Meinke, P. *et al.* (2014) Muscular dystrophy-associated SUN1 and SUN2 variants disrupt nuclear-cytoskeletal connections and myonuclear organization. *PLoS Genet.* 10, e1004605

46. Taranum, S. *et al.* (2012) LINC complex alterations in DMD and EDMD/CMT fibroblasts. *Eur. J. Cell Biol.* 91, 614–628

47. Puckelwartz, M.J. *et al.* (2009) Disruption of Nesprin-1 produces an Emery Dreifuss muscular dystrophy-like phenotype in mice. *Hum. Mol. Genet.* 18, 607–620

48. Matsumoto, A. *et al.* (2015) Global loss of a nuclear lamina component, lamin A/C, and LINC complex components

49. Reis-Sobreiro, M. *et al.* (2018) Emerin deregulation links nuclear shape instability to metastatic potential. *Cancer Res.* 78, 6086–6097

50. Thiam, H.-R. *et al.* (2016) Perinuclear Arp2/3-driven actin polymerization enables nuclear deformation to facilitate cell migration through complex environments. *Nat. Commun.* 7, 10997

51. Davidson, P.M. *et al.* (2020) Nesprin-2 accumulates at the front of the nucleus during confined cell migration. *EMBO Rep.* 21, e49910

52. Wu, J. *et al.* (2014) Actomyosin pulls to advance the nucleus in a migrating tissue cell. *Biophys. J.* 106, 7–15

53. Thomas, D.G. *et al.* (2015) Non-muscle myosin IIB is critical for nuclear translocation during 3D invasion. *J. Cell Biol.* 210, 583–594

54. Petrie, R.J. and Yamada, K.M. (2012) At the leading edge of three-dimensional cell migration. *J. Cell Sci.* 125, 5917–5926

55. Petrie, R.J. *et al.* (2014) Generation of compartmentalized pressure by a nuclear piston governs cell motility in a 3D matrix. *Science* 345, 1062–1065

56. Hatch, E.M. and Hetzer, M.W. (2016) Nuclear envelope rupture is induced by actin-based nucleus confinement. *J. Cell Biol.* 215, 27–36

57. Shao, X. *et al.* (2015) Mechanical stimulation induces formin-dependent assembly of a perinuclear actin rim. *Proc. Natl. Acad. Sci. U. S. A.* 112, E2595–E2601

58. Wales, P. *et al.* (2016) Calcium-mediated actin reset (CaAR) mediates acute cell adaptations. *Elife* 5, e19850

59. Nava, M.M. *et al.* (2020) Heterochromatin-driven nuclear softening protects the genome against mechanical stress-induced damage. *Cell* 181, 800–817.e22

60. Le, H.Q. *et al.* (2016) Mechanical regulation of transcription controls Polycomb-mediated gene silencing during lineage commitment. *Nat. Cell Biol.* 18, 864–875

61. Gilbert, H.T.J. *et al.* (2019) Nuclear decoupling is part of a rapid protein-level cellular response to high-intensity mechanical loading. *Nat. Commun.* 10, 4149

62. Jetta, D. *et al.* (2019) Shear stress-induced nuclear shrinkage through activation of Piezo1 channels in epithelial cells. *J. Cell Sci.* 132, jcs226076

63. Kunda, P. and Baum, B. (2009) The actin cytoskeleton in spindle assembly and positioning. *Trends Cell Biol.* 19, 174–179

64. Beaudouin, J. *et al.* (2002) Nuclear envelope breakdown proceeds by microtubule-induced tearing of the lamina. *Cell* 108, 83–96

65. Wesolowska, N. *et al.* (2020) Actin assembly ruptures the nuclear envelope by prying the lamina away from nuclear pores and nuclear membranes in starfish oocytes. *Elife* 9, e49774

66. Almonacid, M. *et al.* (2015) Active diffusion positions the nucleus in mouse oocytes. *Nat. Cell Biol.* 17, 470

67. Almonacid, M. *et al.* (2019) Active fluctuations of the nuclear envelope shape the transcriptional dynamics in oocytes. *Dev. Cell* 51, 145–157.e10

68. Ahmed, W.W. *et al.* (2018) Active mechanics reveal molecular-scale force kinetics in living oocytes. *Biophys. J.* 114, 1667–1679

69. Colin, A. *et al.* (2020) Active diffusion in oocytes nonspecifically centers large objects during prophase I and meiosis I. *J. Cell Biol.* 219, e201908195

70. Duan, X. *et al.* (2020) Dynamic organelle distribution initiates actin-based spindle migration in mouse oocytes. *Nat. Commun.* 11, 277

71. Booth, A.J. *et al.* (2019) Contractile acto-myosin network on nuclear envelope remnants positions human chromosomes for mitosis. *Elife* 8, e46902

72. Blanchoin, L. *et al.* (2014) Actin dynamics, architecture, and mechanics in cell motility. *Physiol. Rev.* 94, 235–263

73. Inoue, D. *et al.* (2019) Actin filaments regulate microtubule growth at the centrosome. *EMBO J.* 38, e99630

74. Colin, A. *et al.* (2018) Actin-network architecture regulates microtubule dynamics. *Curr. Biol.* 28, 2647–2656.e4

75. Plessner, M. *et al.* (2019) Centrosomal actin assembly is required for proper mitotic spindle formation and chromosome congression. *iScience* 15, 274–281

76. Stiff, T. *et al.* (2020) Prophase-specific perinuclear actin coordinates centrosome separation and positioning to ensure accurate chromosome segregation. *Cell Rep.* 31, 107681

77. Mogessie, B. and Schuh, M. (2017) Actin protects mammalian eggs against chromosome segregation errors. *Science* 357, eaal1647

78. Aureille, J. *et al.* (2019) Nuclear envelope deformation controls cell cycle progression in response to mechanical force. *EMBO Rep.* 20, e48084

79. Clubb, B.H. and Locke, M. (1996) F-Actin forms transient perinuclear shells at the mitosis–interphase transition. *Cell Motil.* 33, 151–162

80. Lian, A.T.Y. *et al.* (2015) IQGAP1 is associated with nuclear envelope reformation and completion of abscission. *Cell Cycle* 14, 2058–2074

81. Makhija, E. *et al.* (2016) Nuclear deformability and telomere dynamics are regulated by cell geometric constraints. *Proc. Natl. Acad. Sci. U. S. A.* 113, E32–E40

82. Seirin-Lee, S. *et al.* (2019) Role of dynamic nuclear deformation on genomic architecture reorganization. *PLoS Comput. Biol.* 15, e1007289

83. Hu, X. *et al.* (2019) MKL1–actin pathway restricts chromatin accessibility and prevents mature pluripotency activation. *Nat. Commun.* 10, 1695

84. Jokhun, D.S. *et al.* (2018) Actin dynamics couples extracellular signals to the mobility and molecular stability of telomeres. *Biophys. J.* 115, 1166–1179

85. Guilluy, C. *et al.* (2014) Isolated nuclei adapt to force and reveal a mechanotransduction pathway in the nucleus. *Nat. Cell Biol.* 16, 376

86. Cho, S. *et al.* (2019) Mechanosensing by the lamina protects against nuclear rupture, DNA damage, and cell-cycle arrest. *Dev. Cell* 49, 920–935.e5

87. Piccus, R. and Brayson, D. (2020) The nuclear envelope: LINCing tissue mechanics to genome regulation in cardiac and skeletal muscle. *Biol. Lett.* 16, 20200302

88. Porter, L. *et al.* (2020) SUN1/2 are essential for RhoA/ROCK-regulated actomyosin activity in isolated vascular smooth muscle cells. *Cells* 9, 132

89. Halder, D. *et al.* (2019) Nonmuscle myosin IIA and IIB differentially modulate migration and alter gene expression in primary mouse tumorigenic cells. *Mol. Biol. Cell* 30, 1463–1476

90. Déjardin, T. *et al.* (2020) Nesprins are mechanotransducers that discriminate epithelial–mesenchymal transition programs. *J. Cell Biol.* 219, e201908036

91. Janin, A. *et al.* (2017) Nuclear envelopathies: a complex LINC between nuclear envelope and pathology. *Orphanet J. Rare Dis.* 12, 147

92. Shao, X. *et al.* (2015) Novel localization of formin mDia2: importin β-mediated delivery to and retention at the cytoplasmic side of the nuclear envelope. *Biol. Open* 4, 1569–1575

93. Münter, S. *et al.* (2006) Actin polymerisation at the cytoplasmic face of eukaryotic nuclei. *BMC Cell Biol.* 7, 23

94. Sardo, L. *et al.* (2017) Real-time visualization of chromatin modification in isolated nuclei. *J. Cell Sci.* 130, 2926–2940

95. Balikov, D.A. *et al.* (2017) The Nesprin–cytoskeleton interface probed directly on single nuclei is a mechanically rich system. *Nucleus* 8, 534–547

96. Laplaud, V. *et al.* (2020) Pinching the cortex of live cells reveals thickness instabilities caused by myosin II motors. *bioRxiv* Published online September 29, 2020. https://doi.org/10.1101/2020.09.28.316729

97. Venturini, V. *et al.* (2020) The nucleus measures shape changes for cellular proprioception to control dynamic cell behavior. *Science* 370, eaba2644

98. Bisaria, A. *et al.* (2020) Membrane-proximal F-actin restricts local membrane protrusions and directs cell migration. *Science* 368, 1205–1210

99. Simon, C. *et al.* (2019) Actin dynamics drive cell-like membrane deformation. *Nat. Phys.* 15, 602–609

100. Firat-Karalar, E.N. and Welch, M.D. (2011) New mechanisms and functions of actin nucleation. *Curr. Opin. Cell Biol.* 23, 4–13

101. Wheeler, M.A. *et al.* (2007) Distinct functional domains in Nesprin-1α and Nesprin-2β bind directly to Emerin and both interactions are disrupted in X-linked Emery–Dreifuss muscular dystrophy. *Exp. Cell Res.* 313, 2845–2857

102. Nastaly, P. *et al.* (2020) Role of the nuclear membrane protein Emerin in front–rear polarity of the nucleus. *Nat. Commun.* 11, 2122

103. Holaska, J. *et al.* (2004) Emerin caps the pointed end of actin filaments: evidence for an actin cortical network at the nuclear inner membrane. *PLoS Biol.* 2, e231

104. D'Alessandro, M. *et al.* (2015) Amphiphysin 2 orchestrates nucleus positioning and shape by linking the nuclear envelope to the actin and microtubule cytoskeleton. *Dev. Cell* 35, 186–198

105. Schönichen, A. *et al.* (2013) FHOD1 is a combined actin filament capping and bundling factor that selectively associates with actin arcs and stress fibers. *J. Cell Sci.* 126, 1891–1901

106. Johnson, M.A. and Henderson, B.R. (2012) The scaffolding protein IQGAP1 co-localizes with actin at the cytoplasmic face of the nuclear envelope: implications for cytoskeletal regulation. *Bioarchitecture* 2, 138–142

107. Wang, S. *et al.* (2015) Nesprin provides elastic properties to muscle nuclei by cooperating with spectraplakin and EB1. *J. Cell Biol.* 209, 529–538