ISSN 0026-8933, Molecular Biology, 2024. © Pleiades Publishing, Ltd., 2024.

REVIEWS

UDC 576.315

What Actin and Myosin Do in the Nucleus: New Functions of the Well-Known Proteins

A. A. Saidova[a], * and I. A. Vorobjev[b]

[a] *Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, Moscow, 119991 Russia*

[b] *Faculty of Biology, Lomonosov Moscow State University, Moscow, 119991 Russia*

**e-mail: saidova@mail.bio.msu.ru*

Received October 27, 2023; revised December 8, 2023; accepted December 11, 2023

Abstract—The functions of actin and its motor proteins myosins in the cytoplasm have been the subject of research for more than 100 years, but the existence and function of these proteins in the nucleus has been a matter of debate until recently. Recent data has clarified the role of actin and myosin molecules in controlling the dynamics of processes in the cell nucleus, chromatin organization and genome integrity. New microscopy techniques and the use of modified actin-binding probes have made it possible for the first time to directly visualize the polymerization of actin filaments in the nucleus of living cells. Here we discuss the processes that control the dynamic balance of actin and myosins between the nucleus and the cytoplasm, as well as the role of these proteins in the regulation of transcription, DNA repair, chromatin reorganization, tumor transformation and cell differentiation.

Keywords: actin, myosin 1C, myosin VI, transcription, DNA repair

DOI: 10.1134/S002689332470002X

INTRODUCTION

Actin is one of the most conserved proteins of eukaryotic cells. Six actin isoforms in humans (α-skeletal, α-cardiac, α-smooth muscle, γ-smooth muscle, γ-cytoplasmic and β-cytoplasmic) are encoded by separate genes [1]. The monomeric form (G-actin) can reversibly assemble into long microfilaments (F-actin) under the control of multiple actin-binding proteins [2]. Actin filaments are one of the three major components of the cytoskeleton. Together with the motor proteins myosins actin filaments play the key role in the control of cell shape and motility, intracellular transport, muscle contraction and organelle dynamics. It is well known that monomeric actin, as well as some of the myosins and actin-binding proteins, rapidly shuttles between the cytoplasm and the nucleus [3, 4], but the functions of these proteins in the nucleus only became unraveled in the early twenty-first century when reliable methods to visualize and study the dynamics of nuclear actin and myosin fractions became available [5]. Cytoplasmic β-actin is the only isoform that is present not only in the cytoplasm but also in the cell nucleus [6]. Among myosins, the main proteins present in the nucleus are myosin I (three isoforms), non-muscle myosins IIa, IIB, myosins V, X, XVI and XVIIIB [7, 8].

Recent data have shown that actin and myosins of the nucleus usually do not usually form actomyosin complexes as in the cytoplasm [9], but play an important role in all fundamental nuclear processes, from gene expression to DNA repair [10–12]. The dynamic spatial organization of the cell nucleus has now become a key issue in cell biology [13]. The actin filaments and myosins of the nucleus are considered to be ideal candidates for the role of key players of the dynamic nuclear matrix that control the topology of nuclear domains and their movement within the nucleus. Actin monomers in the nucleus, as well as individual myosin molecules play important roles as signaling molecules or cofactors [14, 15] (e.g. in the allosteric control of chromatin remodeling complexes). Actin polymers in the nucleus, together with non-muscle myosins, are involved in the movement of chromosomes over relatively long (over 500 nm) distances [16], which is essential for the correct spatial organization of DNA repair processes [17]. They are also involved in cell cycle control [10] and determine the gene expression profile during mammalian ontogenesis [18] (Fig. 1).

Actin filaments located in the cytoplasm around the nucleus also play an important role in determining the gene expression profile. These structures are one of the key components of the mechanotransduction cascade, which transfers signals from the cytoskeleton to the cell nucleus and changes the expression of genes controlling differentiation, proliferation and pro-

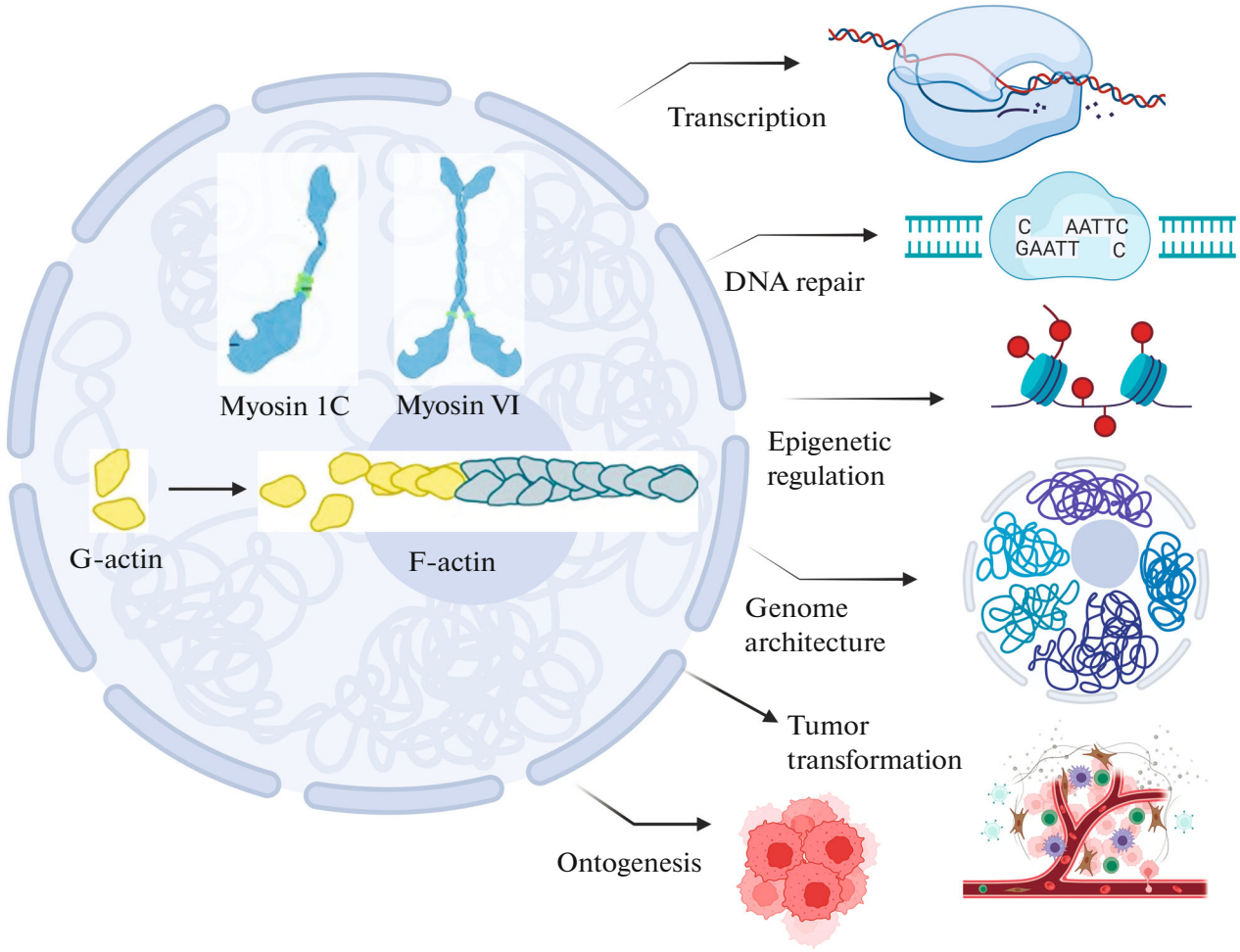

Fig. 1. Functions of actin and myosins in the cell nucleus. Myosin 1C and myosin VI are depicted as the example of nuclear myosins, β-actin is the major isoform of actin in the nucleus.

grammed death in response to external stimuli. The transmission of signals from the cytoplasm to the nucleus occurs through the LINC complexes (linker of nucleoskeleton to cytoskeleton), which mechanically connect the cytoskeleton and chromatin through the nuclear envelope [19]. Altered gene expression after nucleus deformation and disruption of the LINC complex are critical for many diseases associated with defects in nuclear envelope structure [20]. Here we review the role of actin and myosin molecules in transcription, chromatin dynamics, DNA repair, response to mechanical stimuli, cell cycle, and provide some data on the role of nuclear actin and myosins in tumor transformation (Table 1).

NUCLEAR-CYTOPLASMIC TRANSPORT OF ACTIN AND MYOSINS

The pool of actin monomers shuttles in dynamic equilibrium between the nucleus and cytoplasm. In the classical model of nuclear-cytoplasmic transport dependent on the GTP/GDP gradient and the Ran GTPase, import of actin monomers into the nucleus occurs mainly via importin 9 and export via exportin 6 [3, 21, 22].

In order to enter the nucleus, actin binds to cofilin, as actin itself lacks a nuclear localization signal [23, 24]. Numerous proteins that can interact with cofilin determine its ability to bind to actin and the rate at which actin nuclear import [25].

Recently, it was reported that several importins (Ipo9, Cadmus, Moleskin, RanBP11, Tnpo, Tnpo-SR) are simultaneously responsible for actin import. To significantly reduce the concentration of nuclear actin, which affects the viability of developing Drosophila larvae, it is necessary to simultaneously insert an effective nuclear export signal into actin molecules and switch off the expression of at least one importin (Ipo9 or RanBP9) [26]. Increased actin concentration in the nucleus is generally associated with high levels of transcription [27]. Moreover, in direct experiments, β-actin itself has been shown to be an effective regula-

Table 1. Major functions of actin and myosins in the nucleus

Function	Polymer/monomer, isoform	References
Interaction with RNA polymerases	Isoform B of myosin 1C, myosin VI/β-actin monomers, possible oligomers of β-actin	[1] [9] [44–48]
Control of nuclear domain motility	Myosin 1C isoform B/Possible β-actin polymers	[49–52]
Epigenetic regulation of gene expression	Polymers of β-actin/isoform B of myosin 1C	[53] [54]
DNA repair	Polymers of β-actin/myosin V, myosin 1C, myosin 1A	[12] [55] [56]
Cell cycle regulation	Polymers of β-actin/isoform B of myosin 1C	[10] [57] [58]
Tumor transformation	Myosin 1C, myosin V, myosin X	[59–62]

tor of its transcription in response to serum stimulation [28].

Actin export from the nucleus is also controlled by several mechanisms. Although the amino acid sequence of actin contains a signal to exit the nucleus (NES), the formation of a complex with profilin is necessary for efficient actin export [22]. Another important regulator of nuclear actin is isoform A of the Ras association domain family 1 (RASSF1A) [29], a tumor suppressor that localizes to the nuclear envelope and is required for nuclear actin export in complex with exportin 6 and profilin. RASSF1A expression is decreased in many solid tumors, and RASSF1A downregulation correlates with increased nuclear β-actin concentration and slowed MRTF/SRF transcription [29].

In general, actin concentration in the nucleus is many times lower than in the cytoplasm цитоплазме [3, 22, 30, 31], and its polymerization in the nucleus depends on actin-binding proteins [31].

The mechanisms of myosin import into the nucleus depend on its class. The mechanisms of nuclear-cytoplasmic transport for myosin 1C are most well studied. Myosin 1C has a common for all its isoforms NLS-sequence in the "neck" (second IQ motif). Importins 5, 7 and β1 are presumably involved in the canonical nuclear transport of myosin 1C; however, most of the transport of this protein is independent of Ran GTPase and occurs through a non-canonical pathway [32]. Calcium plays a crucial role in the regulation of intracellular localization of myosin 1C, an increase in calcium concentration leads to the activation of myosin 1C import into the nucleus [33]. At the same time, calmodulin, to which myosin neck binds at low calcium ions concentration [34], inhibits nuclear transport of the protein [32]. The authors suggest that increasing $[Ca^{2+}]$ concentration causes the dissociation of calmodulin from myosin neck 1C, not only increasing the activity of the protein as an ATPase and inhibiting its mobility [32], but also stimulating the transport of this protein into the nucleus, probably through the exposure of NLS required for binding to importins. Since calmodulin alters the motor activity of myosin 1C [35] and is itself imported into the nucleus via a facilitated pathway [36], analysis of the role of $[Ca^{2+}]$ in the regulation of intranuclear myosins seems to be an extremely promising perspective.

Myosin 1C binds to the membrane through the PH domain (pleckstrin homology domain), i.e. it acts as a peripheral membrane protein. Binding to the membrane is regulated through phosphatidylinositol 4,5-biphosphate [37]. It has been suggested that this form of myosin uses a non-canonical pathway for import through the fusion of nuclear envelope with ER, which is common feature of inner nuclear membrane proteins [38], and mutations in the NLS-sequence result in impaired nuclear import not through nuclear pores but through impaired interaction with membrane phospholipids. Finally, using point amino acid substitutions, it was shown that the import of myosin 1C into the nucleus really depends solely on its binding to phosphoinositol, and the nuclear localization signal just facilitates this interaction but does not affects import itself [39].

FRAP experiments demonstrated that myosin import proceeds slower than actin import, which depends on cofilin and importins [39]. Given that active transport is insensitive to the molecular mass of the transported proteins, the difference in speed can be explained by different mechanisms of intranuclear import. The same authors, using the FLIP method showed that there is a nuclear fraction of myosin 1C immobilized on chromatin (up to 50% of the molecules) that does not escape into the cytoplasm.

Миозины VI and XVI, apparently, are transported to the nucleus by canonical mechanism using NLS. In

myosin VI, several predicted NLSs in different domains have been described. One of these sequences is located in the IQ motif, suggesting a Ca^{2+}-dependent transport mechanism for this myosin [40]. Accumulation of myosin VI occurs in the nucleus in response to potassium ion (K^+) stimulation in pheochromocytoma cells [40], or serum stimulation in HeLa cells [41]. Transport of myosin VI into neuronal cell nuclei requires the formation of its complex with the regulatory protein muskelin and transport to the perinuclear region via microtubules by dynein (minus-end motor) [42]. Myosin XVI has NLS in the tail domain and shuttles to the nucleus by the canonical Ran-dependent mechanism, and colocalizes in the nucleus with actin and cofilin [43]. For other myosins, the mechanisms of nuclear-cytoplasmic transport still have to be elucidated.

ACTIN AND MYOSINS IN THE NUCLEUS

Nucleus contains about 20% of all cellular actin, and the nuclear and cytoplasmic actin fractions are in dynamic equilibrium.

The volume of the nuclear actin fraction is directly related to the rate of transcription [3, 22]. The ratio of nuclear to cytoplasmic actin is evaluated using the monomeric actin sensor MRTF-A (also known as MKL1 or MAL) [63]. In its normal state, this molecule is bound to the actin monomer in the cytoplasm, which screens its NLS and prohibits entry into the nucleus [64]. Under serum stimulation or when mechanical tension is applied to stimulate actin polymerization in the cytoplasm, the amount of monomeric actin in the cytoplasm is reduced, resulting in increase of free MRTF-A molecules [65]. Unbound MRTF-A molecules accumulate in the nucleus where they bind to the SRF transcription factor and trigger transcription of MRTF/SRF-dependent early response genes associated with cytoskeletal rearrangements [66]. Whole-genome analysis has shown that SRF has approximately 3100 binding regions in mammalian cells and triggers the transcription of 960 early response genes [67]. These genes include genes encoding different actin isoforms.

Monomeric actin in the nucleus is a part of DNA-remodeling complexes such as PBAF [68, 69] INO80 [70] and SWR1 [71]. Intranuclear actin is required for transcription and mRNA processing [72] and, along with the actin-related proteins (ARF) family, is involved in post-translational modification of histones [73, 74]. Knockout of β-actin in mouse fibroblasts leads to an increase in the fraction of trimethylated histones H3 (H3K9Me3 and H3K4Me3 variants), their redistribution from the nuclear envelope to the interior of the nucleus, and an overall increase in nucleus size [75].

For quite a long time, actin was thought to be present in the nucleus only in the form of monomers, either in a specific conformation or polymerizing only under specific conditions [31, 76]. The use of new probes has allowed to show that actin is indeed able to polymerize in the nucleus. Using a probe based on the known actin-binding protein utrophin UTR230-EN, short actin polymers were visualized in chromatin-depleted regions of the nucleus [11]. The use of a peptide probe to nuclear actin (nuclear-targeted LifeAct) and nanoantibodies allowed to visualize short-term actin polymerization in the nucleus that occurs in response to cell stimulation with serum [53], or in response to integrin binding during cell spreading [77]. In both cases, actin polymerization occurs under the control of mDia1/2 formins and requires the involvement of MRTF-A, which in turn regulates the activity of the SRF transcription factor [63]. The activation of the LINC complex and nuclear lamina components is also required for actin polymerization in the nucleus during cell spreading, i.e. in this case the nuclear actin polymerization is the last component of the mechanotransduction cascade triggered by focal adhesions in response to cell stretching on the substrate. Interestingly, short-term polymerization of nuclear actin in the form of long filaments without increasing its concentration in the nucleoplasm can be observed in the early G1 phase of the cell cycle, which seems to be required for chromatin decondensation after mitosis [10], or for the possible involvement of actin filaments in the initial stages of preparation for DNA replication [57]. It is still unclear whether actin monomers or polymers in the nucleus interact with myosins.

TRANSCRIPTION

Actin can interact with all three eukaryotic RNA polymerases, and this interaction involves the conserved subunits Rbp6 and Rbp8 [78]. Actin activates RNA polymerases in order to maintain basal level of transcription [79] and is also required for RNA polymerase II to function at various stages of transcription [44, 46, 72, 80, 81]. Direct binding of actin to RNA polymerase complexes has been shown in a large number of studies [9, 44–46, 82]. Interestingly, in the case of RNA polymerase II, actin can bind to both active and inactive variants of the complex [44, 46].

Intranuclear actin binds to RNA polymerases through different cofactors [83], which allows its effective concentration to be kept relatively low. The interaction of non-muscle myosin 1C with actin in complex with RNA polymerase II is thought to be required for transcription activation [84]. The synthesis of β-actin in response to extracellular stimuli is also a key link in the assembly and regulation of the transcription factor complexes. Using the method of selective depolymerization of actin in the nucleus (the dominant active mutant form of actin G13 was conjugated to the nuclear localization signal and overexpressed), it was shown that nuclear actin is required for the rapid formation of short-lived RNA polymerase II

clusters, which provide explosive activation of transcription [79].

The function of actin oligomers could be also related to the assembly and disassembly of RNPs at translation sites [47]. Mass spectrometry data demonstrating that actin dynamically binds to proteins involved in pre-initiation and elongation processes as well as pre-mRNA processing, support this hypothesis [85].

To date, it remains unclear whether actin participates in transcription processes as a monomer or whether it requires polymerization. In cells with reduced concentration of nuclear actin, the rate of transcription is reduced and can be restored not only by wild-type actin but also by mutant actin-R62D, which cannot polymerize [86]. This result is opposite to the experiments on MEF cells with β-actin knockout, where actin-R62D does not restore rRNA synthesis, in contrast to wild-type actin [87]. Interestingly, the interaction with transcription factors has also been described for regulatory proteins that control actin polymerization, such as Arp2/3 [88] and its activators N-WASP [89], WAVE1 [90] and WASH [91]. In addition to actin, nuclear myosins, in particular myosin IC and myosin VI, are required for all steps of transcription. Myosin IC is a part of complexes with all three RNA polymerases [44], whereas myosin VI interacts only with RNA polymerase II [1]. Myosin IC is also a part of the chromatin-remodelling SNF2h/WSTF complex, which is involved in nucleosome relocation required for the initiation of transcription by RNA polymerase I [92] and RNA polymerase II [93]. In addition, myosin 1C is involved in the binding of histone acetyltransferase PCAF and methyltransferase Set1/Ash2 which support acetylation of H3K9a and trimethylation of H3K4 required for active transcription [93].

Myosin VI, together with the cofactor NDP52, is a part of complexes with RNA polymerase II and participates in mRNA transcription [94, 95]. When myosin VI is inhibited in in vitro and in vivo systems, transcription levels of a number of genes drop fourfold or more [96]. Myosin VI has several specific functions, for example, in in TH1 cells, where it mediates the transition of the RNA polymerase II complex from pausing to elongation through re-stimulation of TNF allele expression [97]. Recent work by Gupta et al. [48] has directly demonstrated that myosin VI in the nucleus functions as a molecular anchor that keeps RNA polymerase II in region of active transcription, and inactivation or repression of myosin VI expression leads to changes in RNA polymerase II localization and total chromatin rearrangement. These data suggest that myosin VI starts to function when the gene expression profile changes, which is indirectly confirmed by the overexpression of this protein in some tumor types, where it triggers the expression of tumor-specific genes [98, 99].

Given that myosin IC and myosin VI bind to RNA polymerase II complexes, the interesting question is whether these proteins are complementary or competing. In experiments with alteration of the expression level of nuclear myosins, myosin IC knockdown was shown to have no effect on the rate of transcription in U2OS cells [94]. Myosin VI knockdown also does not completely stop transcription [100], which suggests at least partial interchangeability of myosins for different stages of the transcription process.

CHROMATIN DYNAMICS

Chromatin in the nucleus permanently moves on short (less than 0.2 μm) and less frequently long (greater than 0.5 μm) distances [16]. Large chromatin movements are associated with global chromatin reorganization during cell differentiation and also precede DNA repair [101, 102]. In addition to their direct involvement in transcription regulation, actin filaments and myosin molecules also maintain the overall genome architecture by moving chromatin regions and even entire chromosomes over distances of up to several microns. Examples include the migration of chromosomes from the periphery to the center of the nucleus upon activation of transcription at their sites [52]; movement of the U2 snRNA locus to Cajal's bodies [49], movement of the hsp70 protein to nuclear speckles upon induction of heat shock [51] and chromosome relocalization upon serum starvation [50]. Immunoprecipitation and deep sequencing experiments have shown that actin binding sites are scattered throughout the human and drosophila genome [87, 103].

The involvement of nuclear actin polymerization in long-distance chromatin transport is supported by a number of experiments using inhibitors of actin polymerization [52], as well as by the expression of polymerization-incapable mutant forms of this protein [49, 51, 52, 66].

In fibroblasts with knock-out of β-actin gene, the overall architecture of heterochromatin is disrupted, the size of the nucleus is reduced, and the gene expression profile is altered [75]. Later studies have directly demonstrated the involvement of actin and myosin 1C in chromosome rearrangements in the interphase nucleus. Upon transcription activation in *S. cerevisiae* cells, the INO1 locus moves from the center of the nucleus to the periphery by directional movement over relatively long distances (over 500 nm). This movement depends on the chromatin-remodeling proteins INO80 and SWR, as well as on proteins that trigger actin polymerization, such as the formin homologue Bnr1, which are probably required for the creation of a pool of short actin filaments in the nucleus [16].

DNA DAMAGE REPAIR

DNA damage repair is another process where nuclear actin and myosins are involved. In this case actin and myosins enable chromosomes to move relatively long distances to form "repair factories" [101, 103].

The first evidence for the potential involvement of F-actin in the repair of DNA double-strand breaks was obtained in vitro in co-precipitation experiments of nuclear extracts with purified polymeric actin, where DNA repair proteins including Ku80, Mre11 and Rad51 were shown to bind to actin [104, 105].

In *Drosophila melanogaster* cells actin polymerization in the nucleus was visualized upon the induction of DNA double-strand breaks. In this case, chromatin with DSBs moves directionally towards repair sites, and this movement occurs through a network of actin filaments that are assembled by Arp 2/3 in the vicinity of repair complexes [56]. The motors that move chromatin are nuclear myosins 1A, 1B and myosin V together with its activator Unc45, which arrives at repair sites via the chromosome structural support protein Smc5/6 [56].

In mammalian cells, the mechanism of actin participation in DNA repair processes is much more complicated. If double-strand breaks occur in actively transcribed genes, they are first assembled into clusters, and repair only occurs by the mechanism of homologous recombination. This process occurs predominantly in G1 phase and depends on the activity of the MRN complex, formin 2 (FMN2) and LINC complex [55]. In the case of breaks in the G2 phase, an Arp 2/3-dependent actin polymerization process is activated, which promotes the movement of damaged DNA into clusters, which also ensures their repair by the mechanism of homologous recombination (HDR) instead of the more common mechanism of non-homologous end joining (NHEJ) [106].

Induction of DNA double-strand breaks by cisplatin leads to myosin 1C overexpression and its binding to chromatin, and knockdown of all three myosin 1C isoforms results in chromosome movement arrest [107]. Myosin 1C also acts as a motor in repairing double-stranded breaks by homology-directed DNA repair (HDR), when homologous chromosomes need to come into contact to create a template for repair [108]. Thus, nuclear actin and myosins play an important role in inducing a homologous recombination mechanism to repair DNA double-strand breaks by inhibiting non-homologous joining of DNA ends, ensuring greater fidelity in the repair process.

TUMOR TRANSFORMATION

Overexpression of nuclear myosins is known to be a characteristic feature of some tumor types [109]. The main model where overexpression of nuclear myosins has been described is prostate cancer cells, which are characterized by both hyperexpression of myosin VI and hyperexpression of myosin 1C isoform A. Nuclear myosin VI in prostate cancer cells controls androgen receptor expression [110]. Knockdown of myosin VI results in decreased expression levels of a number of androgen-dependent genes, and the same pattern holds true for breast cancer cells, where knockdown of the MYOVI gene resulted in reduced expression levels of estrogen receptor-dependent genes [94].

Isoform A of myosin 1C, which, unlike the other two isoforms of this protein, is tissue-specific, is expressed in normal kidney, adrenal, pancreatic and ovarian tissue [111]. We have showed that it is possible to detect an increase in the mRNA expression level of this isoform even at a ratio of normal and tumor prostate cells of 1 : 1000, which allows makes it a promising diagnostic marker of prostate cancer even in samples with a small number of cells or in samples with a large amount of stromal component [102]. We have also shown that the expression level of isoform A is elevated in clinical prostate cancer samples and allows us to reliably distinguish not only tumor from reactive benign prostatic hyperplasia, but also tumor stages from each other, which opens new perspectives in the use of this isoform as a diagnostic and prognostic marker [59]. Other nuclear myosins are also involved in oncogenesis: for example, myosin V (MYO5A) overexpression has been shown to be associated with colorectal cancer [60], and myosin X overexpression is characteristic of breast cancer cells [61, 62]. On the other hand, nuclear myosins may, on the contrary, act as tumor suppressors. This phenomenon has been described for myosin XVIII in colorectal cancer [112] and non-muscle myosin IIA in various squamous cell carcinomas [113].

The processes occurring inside the nucleus also depend on its morphology and position in the cell. Examples of this interaction include epithelial cell division, which can only occur after translocation of the nucleus to the apical surface of the cell, and various differentiation processes in which changes in gene expression profile occur in response to changes in the morphology of the nucleus. The morphology and position of the nucleus in the cell also depends on actin filaments, which form special perinuclear structures—perinuclear cap and TAN lines.

MORPHOLOGY OF PERINUCLEAR ACTIN

A special network of actin filaments around the nucleus is organized into structures that link the cytoskeleton in the cytoplasm and chromatin in the nucleus. The first structure is transmembrane actin-associated nuclear lines (TAN lines). These are thin, non-contractile actin filaments around the nucleus that are connected to the inner nuclear membrane via the LINC complex. TAN lines interact with many proteins, including torsin A, emerin, Samp1, SUN1, lamins, LAP1, fascin and nuclear pore proteins [114–

117]. Torzin A and LAP1 bind lamins, SUN1 and nesprin-2G on the nucleus side, whereas FHOD1 and fascin localize to the cytoplasmic side of the nuclear envelope and work as adaptors for binding nesprin-2G to actin [115, 118].

The second structure formed by perinuclear actin is the perinuclear actin cap. The actin cap differs from TAN-lines by the presence of phosphorylated myosin and its ability to contract. In fibroblasts and endothelial cells, perinuclear actin cap filaments extend along the long axis of the cell and orient the nucleus towards the direction of cell migration. Such filaments are connected to the nuclear envelope via nesprin-2 and are associated with focal adhesions at each end [119–121]. The perinuclear actin cap can also be seen in 3D culture, such as in mammary epithelial cells, where nuclei have deep invaginations at sites where actin filaments attach to the nuclear envelope [122]. The organization of the perinuclear actin cap requires the coordinated interaction of multiple proteins, the key ones being filamin A and refilin B [123]. The filamin-refilin axis is particularly important for signaling pathway leading to cell shape change during skeletal tissue formation [124]. The interaction of its adaptor proteins with nuclear laminin proteins also appears to be required for actin cap formation, as cells with laminin A/C knockout do not form an actin cap [121]. The perinuclear actin cap appears to play a key role in mechanochemical pathways. It remains unclear whether TAN-lines and the perinuclear actin cap are derived from the same structure and whether they share common regulatory proteins.

PERINUCLEAR ACTIN STRUCTURES ARE INVOLVED IN THE DETERMINATION OF FORM AND LOCALIZATION OF THE CELL NUCLEUS

During migration within the organism cells often have to change their shape to elongate and contract. Common examples of cells forced to migrate in a narrow space are neutrophils crawling through endothelial and epithelial barriers and tumor cells in the process of metastasis. If a cell needs to migrate in a narrow channel, its nucleus must be deformed. There are two mechanisms of nucleus pushing: in the LINC-dependent mechanism, fibroblasts compress their nucleus by actomyosin contraction at the leading edge of the cell, pushing it through the narrow site. In this case, nesprin 2 accumulates in front of the nucleus and coordinates the formation of a barrel-like structure of actin filaments that compresses the nucleus and pushes it through [125]. In the case of the LINC-independent mechanism, actomyosin contraction occurs at the posterior edge of the cell, resulting in the nucleus also being pushed forward, but in this case, there is no contraction of actin structures around the nucleus [126].

If a local force in the form of stretching or shearing is applied to the cell, a very rapid reorganization of the perinuclear actin forming the ring can be seen in response. This process, described at least in epithelial cells, depends on the operation of the inf2 (inverted formin2) protein and is called CAAR (calcium-mediated actin reset) [127, 128]. It can be triggered through the release of calcium ions from the ER into the cytoplasm via a Piezo-1 dependent mechanism [128]. In endothelial cells, the rearrangement of actin around the nucleus depends on emerin and is initiated by the redeployment of this protein from the inner nuclear membrane to the outer membrane [129]. This cellular response leads to a reduction in the amount of heterochromatin and a rapid decrease in nucleus rigidity, which can be seen as a way to protect the genome from mechanical damage [128]. On the other hand, rapid cyclic stretch-compression of mesenchymal stem cells, in contrast, leads to dissociation of the nucleus and cytoplasmic cytoskeleton through suppression of transcription and phosphorylation of SUN2, a key component of the LINC complex [130]. It is still difficult analyze all the processes that occur in the nucleus itself in response to mechanical stretching/compression, but it is clear that most of them involve rearrangement of actomyosin complexes.

Another important function of the actin filament network is to determine the correct position of the cell nucleus according to the current physiological state. A striking example of this function is the movement of nuclei in pseudostratified epithelial cells, where mitosis is possible only if the nucleus moves from the basal part of the cell to the apical part with the help of stress fibrils. Another example of cells in which the position of the nucleus depends on actomyosin contraction are retinal photoreceptors and *Danio rerio* hindbrain cells [131, 132]. Nucleus movement in hindbrain cells depends on activation of the RhoA-ROCK-kinase cascade, whereas in the retina, nucleation of actin filaments by formin-like protein 3 (formin 3) plays a leading role [133, 134]. In both cases, a network of polymerizing actin filaments pushes the nucleus towards the apical surface of the cell. A similar mechanism drives nucleus movement in wing embryo cells in *D. melanogaster*, where Diaphanos (an orthologue of the mDia protein) and ROK (myosin activator) proteins participate in pushing the nucleus towards the apical surface [135]. Oscillation of nuclei between the apical and basal cell surface has also been described in a mouse retinal photocyte model [136].

In multinucleated muscle cells in the process of myofibril formation there is movement of nuclei from the center of the cell to the periphery. In this case, actin filaments stimulate the formation of desmin cross-links, which constrict myofibrils and help pushing the nuclei towards the cell periphery [137, 138]. In *Drosophila melanogaster* "nurse" cells of the growing oocyte, actin stress fibrils bind to perinuclear actin structures and, with the help of the Cheerio protein

(an orthologue of filamin A), anchor the nucleus, preventing it from blocking the ring channels that feed the oocyte [139].

Nucleus positioning in cells is an active process, and is regulated through a system of microtubules and microfilaments. The nuclear envelope is linked to microtubules by dynein and to microfilaments by the LINC complex, which includes SUN proteins (or their orthologues) bound to the inner nuclear membrane and KASH proteins bound to the outer nuclear membrane [140].

In fibroblasts spread on the substrate, nucleus displacement is associated with retrograde actin flow, and nucleus backward displacement is achieved through stimulation of actomyosin contraction by cdc42/MRCK. Interestingly, during the mutual reorientation of the nucleus and centrosome, the latter must remain sedentary with the help of microtubule system [141]. The process of nucleus displacement starts with the tension of transmembrane actin-associated filaments (TANs) that ensure retrograde displacement of the nucleus [114–117]. Thus, a scheme has been proposed for fibroblasts whereby components of the TAN-line complex, together with the inner nuclear membrane protein SUN2, are responsible for backward movement of the nucleus, whereas forward movement of the nucleus along the direction of cell movement depends on the operation of microtubule motors and the SUN1 protein [141]. In both cases, the nesprin-2G protein acts as a central adaptor element to link the cytoskeleton to the inner nuclear membrane (with SUN proteins).

PROBLEMS AND PERSPECTIVES

Over the last 20 years, the new data on actin and myosins in the cell nucleus, their localizations and functions in normal and tumor cells has been accumulated. Summarizing the state of art, it should be noted that the functions of actin and myosin molecules in the nucleus appear to be quite different from those of these proteins in the cytoplasm and are often not related to mechanical work. The question of whether the interaction of actin filaments and myosin motors is necessary for specific nuclear functions is of great interest. So far, there are no direct observations proving the presence of actomyosin complexes in the nucleus similar to those formed in the cytoplasm. It remains unclear whether myosin molecules, without the participation of polymeric and monomeric actin, can perform specific functions in transcription and chromosome movement, and whether myosins in the nucleus can function as signalling molecules.

Another problem to be solved is to find new methods to elucidate the functions of nuclear myosins. In this case, genetic knockdown and knockout methods do not provide definite results because the different forms of myosins in the nucleus at least partially compensate for each other. In addition, knockdown/knockout or inhibition of myosin molecules only in the nucleus without affecting the cytoplasmic fraction of the protein has not yet been possible.

Mutations associated with abnormalities in the structure and function of intranuclear actin/myosins underlie some hereditary myopathies and neuropathies. In particular, the appearance of long filamentous filaments in the nucleus has been shown for nemaline myopathy [142] and Hungtington's disease, where abnormal expression of huntingtin appears to stabilize such filaments [143]. In addition, the appearance of stable actin filaments in the nucleus has been described for aging neurons [144]. It is unclear whether the appearance of such structures is related to the cause of diseases or is rather a consequence of them, but in this case it is obvious that the functions of actin filaments in the nucleus are not related to cell contractility but to transcription and chromatin dynamics, and the study of the mechanisms of their formation and role in the cell will help to shed light on the pathogenesis of many diseases.

Therefore, a detailed analysis of the dynamic equilibrium of these proteins between the nucleus and cytoplasm in normal and pathological processes remains the most promising direction for the study of actin and myosin functions.

ABBREVIATIONS

LINC, linker of nucleoskeleton to cytoskeleton; NLS, nuclear localization signal; NES, nuclear export signal; CAAR, calcium-mediated actin reset; FRAP, fluorescence recovery after photobleaching; FLIP, fluorescence loss in photobleaching; TANs, transmembrane actin-associated filaments.

FUNDING

The work was supported by the Russian Science Foundation (grant no. 22-24-00714).

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This work does not contain any studies involving human and animal subjects.

CONFLICT OF INTEREST

The authors of this work declare that they have no conflicts of interest.

REFERENCES

1. Vreugde S., Ferrai C., Miluzio A., Hauben E., Marchisio P.C., Crippa M.P., Bussi M., Biffo S. 2006. Nuclear myosin VI enhances RNA polymerase ii-dependent transcription. *Mol. Cell.* **23** (5), 749–755.

2. Pollard T.D. 2016. Actin and actin-binding proteins. *Cold Spring. Harb. Perspect. Biol.* **8** (8), a018226.
3. Dopie J., Skarp K.P., Kaisa Rajakylä E., Tanhuanpää K., Vartiainen M.K. 2012. Active maintenance of nuclear actin by importin 9 supports transcription. *Proc. Natl. Acad. Sci. U. S. A.* **109** (9), E544–E552.
4. Hyrskyluoto A., Vartiainen M.K. 2020. Regulation of nuclear actin dynamics in development and disease. *Curr. Opin. Cell. Biol.* **64**, 18–24.
5. Plessner M., Grosse R. 2019. Dynamizing nuclear actin filaments. *Curr. Opin. Cell. Biol.* **56**, 1–6.
6. Olave I.A., Reck-Peterson S.L., Crabtree G.R. 2002. Nuclear actin and actin-related proteins in chromatin remodeling. *Annu. Rev. Biochem.* **71** (1), 755–781.
7. Cook A.W., Gough R.E., Toseland C.P. 2020. Nuclear myosins—roles for molecular transporters and anchors. *J. Cell. Sci.* **133** (11), jcs242420.
8. de Lanerolle P. 2012. Nuclear actin and myosins at a glance. *J. Cell. Sci.* **125** (21), 4945–4949.
9. Fomproix N., Percipalle P. 2004. An actin-myosin complex on actively transcribing genes. *Exp. Cell. Res.* **294** (1), 140–148.
10. Baarlink C., Plessner M., Sherrard A., Morita K., Misu S., Virant D., Kleinschnitz E.-M., Harniman R., Alibhai D., Baumeister S., Miyamoto K., Endesfelder U., Kaidi A., Grosse R. 2017. A transient pool of nuclear F-actin at mitotic exit controls chromatin organization. *Nat. Cell. Biol.* **19** (12), 1389–1399.
11. Belin B.J., Cimini B.A., Blackburn E.H., Mullins R.D. 2013. Visualization of actin filaments and monomers in somatic cell nuclei. *Mol. Biol. Cell.* **24** (7), 982–994.
12. Belin B.J., Lee T., Mullins R.D. 2015. DNA damage induces nuclear actin filament assembly by formin-2 and spire-1/2 that promotes efficient DNA repair. *Elife.* **4**, e11935
13. Barth R., Bystricky K., Shaban H.A. 2020. Coupling chromatin structure and dynamics by live super-resolution imaging. *Sci. Adv.* **6** (27), eaaz2196.
14. Maly I.V., Hofmann W.A. 2020. Myosins in the nucleus. In: *Myosins.* Ed. Coluccio L. Springer, Cham., pp. 199–231.
15. Venit T., El Said N.H., Mahmood S.R., Percipalle P. 2021. A dynamic actin-dependent nucleoskeleton and cell identity. *J. Biochem.* **169** (3), 243–257.
16. Wang A., Kolhe J.A., Gioacchini N., Baade I., Brieher W.M., Peterson C.L., Freeman B.C. 2020. Mechanism of long-range chromosome motion triggered by gene activation. *Dev. Cell.* **52** (3), 309–320.
17. Chatterjee N., Walker G.C. 2017. Mechanisms of DNA damage, repair, and mutagenesis. *Environ. Mol. Mutagen.* **58** (5), 235–263.
18. Mahmood S.R., El Said N.H., Percipalle P. 2022. The role of nuclear actin in genome organization and gene expression regulation during differentiation. *Results Probl. Cell Differ.* **70**, 607–624.
19. Wong X., Loo T.H., Stewart C.L. 2021. LINC complex regulation of genome organization and function. *Curr. Opin. Genet. Dev.* **67**, 130–141.
20. Janin A., Bauer D., Ratti F., Millat G., Méjat A. 2017. Nuclear envelopathies: A complex LINC between nuclear envelope and pathology. *Orphanet J. Rare Dis.* **12** (1), 147.
21. Fiore A.P.Z.P., Spencer V.A., Mori H., Carvalho H.F., Bissell M. J., Bruni-Cardoso A. 2017. Laminin-111 and the level of nuclear actin regulate epithelial quiescence via exportin-6. *Cell. Rep.* **19** (10), 2102–2115.
22. Stuven T. 2003. Exportin 6: A novel nuclear export receptor that is specific for profilin-actin complexes. *EMBO J.* **22** (21), 5928–5940.
23. Bamburg J.R., Wiggan O.P. 2002. ADF/cofilin and actin dynamics in disease. *Trends Cell Biol.* **12** (12), 598–605.
24. Pendleton A., Pope B., Weeds A., Koffer A. 2003. Latrunculin B or ATP depletion induces cofilin-dependent translocation of actin into nuclei of mast cells. *J. Biol. Chem.* **278** (16), 14394–14400.
25. Dopie J., Rajakylä E.K., Joensuu M.S., Huet G., Ferrantelli E., Xie T., Jäälinoja H., Jokitalo E., Vartiainen M.K. 2015. Genome-wide RNAi screen for nuclear actin reveals a network of cofilin regulators. *J. Cell Sci.* **128** (13), 2388–2400.
26. Borkúti P., Kristó I., Szabó A., Bajusz C., Kovács Z., Réthi-Nagy Z., Lipinszki Z., Lukácsovich T., Bogdan S., Vilmos P. 2022. Parallel import mechanisms ensure the robust nuclear localization of actin in *Drosophila*. *Front. Mol. Biosci.* **9**, 963635.
27. Misu S., Takebayashi M., Miyamoto K. 2017. Nuclear actin in development and transcriptional reprogramming. *Front. Genet.* **8**, 27.
28. Kalo A., Kanter I., Shraga A., Sheinberger J., Tzemach H., Kinor N., Singer R.H., Lionnet T., Shav-Tal Y. 2015. Cellular levels of signaling factors are sensed by β-actin alleles to modulate transcriptional pulse intensity. *Cell Rep.* **11** (3), 419–432.
29. Chatzifrangkeskou M., Pefani D., Eyres M., Vendrell I., Fischer R., Pankova D., O'Neill E. 2019. RASSF 1A is required for the maintenance of nuclear actin levels. *EMBO J.* **38** (16), e101168.
30. Görlich D., Seewald M.J., Ribbeck K. 2003. Characterization of Ran-driven cargo transport and the RanGTPase system by kinetic measurements and computer simulation. *EMBO J.* **22** (5), 1088–1100.
31. Vartiainen M.K. 2008. Nuclear actin dynamics—from form to function. *FEBS Lett.* **582** (14), 2033–2040.
32. Dzijak R., Yildirim S., Kahle M., Novák P., Hnilicova J., Venit T., Hozák P. 2012. Specific nuclear localizing sequence directs two myosin isoforms to the cell nucleus in calmodulin-sensitive manner. *PLoS One.* **7** (1), e30529.
33. Maly I.V., Hofmann W.A. 2016. Calcium-regulated import of myosin IC into the nucleus. *Cytoskeleton.* **73** (7), 341–350.
34. Gillespie P.G., Cyr J.L. 2002. Calmodulin binding to recombinant myosin-1c and myosin-1c IQ peptides. *BMC Biochem.* **3** (1), 31.
35. Lu Q., Li J., Ye F., Zhang M. 2015. Structure of myosin-1c tail bound to calmodulin provides insights into calcium-mediated conformational coupling. *Nat. Struct. Mol. Biol.* **22** (1), 81–88.

36. Pruschy M., Ju Y., Spitz L., Carafoli E., Goldfarb D.S. 1994. Facilitated nuclear transport of calmodulin in tissue culture cells. *J. Cell Biol.* **127** (6), 1527–1536.

37. Hokanson D.E., Laakso J.M., Lin T., Sept D., Ostap E.M. 2006. Myo1c binds phosphoinositides through a putative pleckstrin homology domain. *Mol. Biol. Cell.* **17** (11), 4856–4865.

38. Ungricht R., Kutay U. 2015. Establishment of NE asymmetry-targeting of membrane proteins to the inner nuclear membrane. *Curr. Opin. Cell Biol.* **34**, 135–141.

39. Nevzorov I., Sidorenko E., Wang W., Zhao H., Vartiainen M.K. 2018. Myosin-1C uses a novel phosphoinositide-dependent pathway for nuclear localization. *EMBO Rep.* **19** (2), 290–304.

40. Majewski L., Nowak J., Sobczak M., Karatsai O., Havrylov S., Lenartowski R., Suszek M., Lenartowska M., Redowicz M.J. 2018. Myosin VI in the nucleus of neurosecretory PC12 cells: Stimulation-dependent nuclear translocation and interaction with nuclear proteins. *Nucleus.* **9** (1), 125–141.

41. Hari-Gupta Y., Fili N., Dos Santos Á., Cook A.W., Gough R.E., Reed H.C.W., Wang L., Aaron J., Venit T., Wait E., Grosse-Berkenbusch A., Christof J., Gebhardt M., Percipalle P., Chew T.L., Martin-Fernandez M., Toseland C.P. 2020. Nuclear myosin VI regulates the spatial organization of mammalian transcription initiation. *Nat. Commun.* **13** (1), 1346.

42. Kneussel M., Sánchez-Rodríguez N., Mischak M., Heisler F.F. 2021. Dynein and muskelin control myosin VI delivery towards the neuronal nucleus. *iScience*. **24** (5), 102416.

43. Cameron R.S., Liu C., Mixon A.S., Pihkala J.P.S., Rahn R.J., Cameron P.L. 2007. Myosin16b: The COOH-tail region directs localization to the nucleus and overexpression delays S-phase progression. *Cell Motil. Cytoskeleton*. **64** (1), 19–48.

44. Hofmann W.A., Stojiljkovic L., Fuchsova B., Vargas G.M., Mavrommatis E., Philimonenko V., Kysela K., Goodrich J.A., Lessard J.L., Hope T.J., Hozak P., de Lanerolle P. 2004. Actin is part of pre-initiation complexes and is necessary for transcription by RNA polymerase II. *Nat. Cell. Biol.* **6** (11), 1094–1101.

45. Hu P., Wu S., Hernandez N. 2004. A role for β-actin in RNA polymerase III transcription. *Gen. Dev.* **18** (24), 3010–3015.

46. Kukalev A., Nord Y., Palmberg C., Bergman T., Percipalle P. 2005. Actin and hnRNP U cooperate for productive transcription by RNA polymerase II. *Nat. Struct. Mol. Biol.* **12** (3), 238–244.

47. Kotani T., Yasuda K., Ota R., Yamashita M. 2013. Cyclin B1 mRNA translation is temporally controlled through formation and disassembly of RNA granules. *J. Cell Biol.* **202** (7), 1041–1055.

48. Hari-Gupta Y., Fili N., dos Santos Á., Cook A.W., Gough R.E., Reed H.C.W., Wang L., Aaron J., Venit T., Wait E., Grosse-Berkenbusch A., Gebhardt J.C.M., Percipalle P., Chew T.L., Martin-Fernandez M., Toseland C.P. 2022. Myosin VI regulates the spatial organisation of mammalian transcription initiation. *Nat. Commun.* **13** (1), 1346.

49. Dundr M., Ospina J.K., Sung, M.H., John S., Upender M., Ried T., Hager G.L., Matera A.G. 2007. Actin-dependent intranuclear repositioning of an active gene locus in vivo. *J. Cell Biol.* **179** (6), 1095–1103.

50. Mehta I.S., Amira M., Harvey A.J., Bridger J.M. 2010. Rapid chromosome territory relocation by nuclear motor activity in response to serum removal in primary human fibroblasts. *Genome Biol.* **11** (1), R5.

51. Khanna N., Hu Y., Belmont A.S. 2014. HSP70 Transgene directed motion to nuclear speckles facilitates heat shock activation. *Curr. Biol.* **24** (10), 1138–1144.

52. Chuang C.H., Carpenter A.E., Fuchsova B., Johnson T., de Lanerolle P., Belmont A.S. 2006. Long-range directional movement of an interphase chromosome site. *Curr. Biol.* **16** (8), 825–831.

53. Baarlink C., Wang H., Grosse R. 2013. Nuclear actin network assembly by formins regulates the SRF coactivator MAL. *Science*. **340** (6134), 864–867.

54. Percipalle P., Fomproix N., Cavellán E., Voit R., Reimer G., Krüger T., Thyberg J., Scheer U., Grummt I., Östlund Farrants A. 2006. The chromatin remodelling complex WSTF–SNF2h interacts with nuclear myosin 1 and has a role in RNA polymerase I transcription. *EMBO Rep.* **7** (5), 525–530.

55. Aymard F., Aguirrebengoa M., Guillou E., Javierre B.M., Bugler B., Arnould C., Rocher V., Iacovoni J. S., Biernacka A., Skrzypczak M., Ginalski K., Rowicka M., Fraser P., Legube G. 2017. Genome-wide mapping of long-range contacts unveils clustering of DNA double-strand breaks at damaged active genes. *Nat. Struct. Mol. Biol.* **24** (4), 353–361.

56. Caridi C.P., D'Agostino C., Ryu T., Zapotoczny G., Delabaere L., Li X., Khodaverdian V.Y., Amaral N., Lin E., Rau A.R., Chiolo I. 2018. Nuclear F-actin and myosins drive relocalization of heterochromatic breaks. *Nature*. **559** (7712), 54–60.

57. Parisis N., Krasinska L., Harker B., Urbach S., Rossignol M., Camasses A., Dewar J., Morin N., Fisher D. 2017. Initiation of DNA replication requires actin dynamics and formin activity. *EMBO J.* **36** (21), 3212–3231.

58. Sarshad A., Sadeghifar F., Louvet E., Mori R., Böhm S., Al-Muzzaini B., Vintermist A., Fomproix N., Östlund A.K., Percipalle P. 2013. Nuclear myosin 1c facilitates the chromatin modifications required to activate rRNA gene transcription and cell cycle progression. *PLoS Genet.* **9** (3), e1003397.

59. Saidova A.A., Potashnikova D. M., Tvorogova A.V., Paklina O.V., Veliev E.I., Knyshinsky G.V., Setdikova G.R., Rotin D.L., Maly I.V., Hofmann W.A., Vorobjev I.A. 2021. Myosin 1C isoform A is a novel candidate diagnostic marker for prostate cancer. *PLoS One*. **16** (5), e0251961.

60. Lan L., Han H., Zuo H., Chen Z., Du Y., Zhao W., Gu J., Zhang Z. 2010. Upregulation of myosin Va by Snail is involved in cancer cell migration and metastasis. *Int. J. Cancer.* **126** (1), 53–64.

61. Arjonen A., Kaukonen R., Ivaska J. 2011. Filopodia and adhesion in cancer cell motility. *Cell Adh. Migr.* **5** (5), 421–430.

62. Cao R., Chen J., Zhang X., Zhai Y., Qing X., Xing W., Zhang L., Malik Y.S., Yu H., Zhu X. 2014. Elevated expression of myosin X in tumours contributes to breast cancer aggressiveness and metastasis. *Br. J. Cancer.* **111** (3), 539–550.

63. Vartiainen M.K., Guettler S., Larijani B., Treisman R. 2007. Nuclear actin regulates dynamic subcellular localization and activity of the SRF cofactor MAL. *Science*. **316** (5832), 1749–1752.

64. Pawłowski R., Rajakylä E.K., Vartiainen M.K., Treisman R. 2010. An actin-regulated importin α/β-dependent extended bipartite NLS directs nuclear import of MRTF-A. *EMBO J.* **29** (20), 3448–3458.

65. Mouilleron S., Langer C.A., Guettler S., McDonald N.Q., Treisman R. 2011. Structure of a pentavalent G-actin·MRTF-A complex reveals how G-actin controls nucleocytoplasmic shuttling of a transcriptional coactivator. *Sci. Signal.* **4** (177), ra40.

66. Posern G., Treisman R. 2006. Actin' together: Serum response factor, its cofactors and the link to signal transduction. *Trends Cell Biol.* **16** (11), 588–596.

67. Esnault C., Stewart A., Gualdrini F., East P., Horswell S., Matthews N., Treisman R. 2014. Rho-actin signaling to the MRTF coactivators dominates the immediate transcriptional response to serum in fibroblasts. *Gen Dev.* **28** (9), 943–958.

68. Nishimoto N., Watanabe M., Watanabe S., Sugimoto N., Yugawa T., Ikura T., Koiwai O., Kiyono T., Fujita M. 2012. Heterocomplex formation by Arp4 and β-actin involved in integrity of the Brg1 chromatin remodeling complex. *J. Cell Sci.* **125** (16), 3870–3882.

69. Zhao K., Wang W., Rando O. J., Xue Y., Swiderek K., Kuo A., Crabtree G.R. 1998. Rapid and phosphoinositol-dependent binding of the SWI/SNF-like BAF complex to chromatin after T lymphocyte receptor signaling. *Cell*. **95** (5), 625–636.

70. Kapoor P., Chen M., Winkler D.D., Luger K., Shen X. 2013. Evidence for monomeric actin function in INO80 chromatin remodeling. *Nat. Struct. Mol. Biol.* **20** (4), 426–432.

71. Kapoor P., Shen X. 2014. Mechanisms of nuclear actin in chromatin-remodeling complexes. *Trends Cell Biol.* **24** (4), 238–246.

72. Qi T., Tang W., Wang L., Zhai L., Guo L., Zeng X. 2011. G-actin participates in RNA polymerase ii-dependent transcription elongation by recruiting positive transcription elongation factor b (P-TEFb). *J. Biol. Chem.* **286** (17), 15171–15181.

73. Galarneau L., Nourani A., Boudreault A.A., Zhang Y., Héliot L., Allard S., Savard J., Lane W.S., Stillman D.J., Côté J. 2000. Multiple links between the NuA4 histone acetyltransferase complex and epigenetic control of transcription. *Mol. Cell.* **5** (6), 927–937.

74. Serebryannyy L.A., Cruz, C.M., de Lanerolle P. 2016. A role for nuclear actin in HDAC 1 and 2 regulation. *Sci. Rep.* **6** (1), 28460.

75. Xie X., Almuzzaini B., Drou N., Kremb S., Yousif A., Farrants A. Ö., Gunsalus K., Percipalle P. 2018. β-Actin-dependent global chromatin organization and gene expression programs control cellular identity. *FASEB J.* **32** (3), 1296–1314.

76. Grosse R., Vartiainen M.K. 2013. To be or not to be assembled: Progressing into nuclear actin filaments. *Nat. Rev. Mol. Cell. Biol.* **14** (11), 693–697.

77. Plessner M., Melak M., Chinchilla P., Baarlink C., Grosse R. 2015. Nuclear F-actin formation and reorganization upon cell spreading. *J. Biol. Chem.* **290** (18), 11209–11216.

78. Percipalle P. 2013. Co-transcriptional nuclear actin dynamics. *Nucleus*. **4** (1), 43–52.

79. Wei M., Fan X., Ding M., Li R., Shao S., Hou Y., Meng S., Tang F., Li C., Sun, Y. 2020. Nuclear actin regulates inducible transcription by enhancing RNA polymerase II clustering. *Sci. Adv.* **6** (16), eaay6515.

80. Percipalle P., Fomproix N., Kylberg K., Miralles F., Björkroth B., Daneholt B., Visa N. 2003. An actin–ribonucleoprotein interaction is involved in transcription by RNA polymerase II. *Proc. Natl. Acad. Sci. U. S. A.* **100** (11), 6475–6480.

81. Sjölinder M., Björk P., Söderberg E., Sabri N., Östlund Farrants A.K., Visa N. 2005. The growing pre-mRNA recruits actin and chromatin-modifying factors to transcriptionally active genes. *Gen. Dev.* **19** (16), 1871–1884.

82. Philimonenko V.V., Zhao J., Iben S., Dingová H., Kyselá K., Kahle M., Zentgraf H., Hofmann W.A., de Lanerolle P., Hozák P., Grummt I. 2004). Nuclear actin and myosin I are required for RNA polymerase I transcription. *Nat. Cell. Biol.* **6** (12), 1165–1172.

83. Xie X., Percipalle P. 2018. An actin-based nucleoskeleton involved in gene regulation and genome organization. *Biochem. Biophys. Res. Commun.* **506** (2), 378–386.

84. Sarshad A.A., Corcoran M., Al-Muzzaini B., Borgonovo-Brandter L., Von Euler A., Lamont D., Visa N., Percipalle P. 2014. Glycogen synthase kinase (GSK) 3β phosphorylates and protects nuclear myosin 1c from proteasome-mediated degradation to activate rDNA transcription in early G1 cells. *PLoS Genet.* **10** (6), e1004390.

85. Viita T., Kyheröinen S., Prajapati B., Virtanen J., Frilander M.J., Varjosalo M., Vartiainen M.K. 2019. Nuclear actin interactome analysis links actin to KAT14 histone acetyl transferase and mRNA splicing. *J. Cell Sci.* **132** (8), jcs226852.

86. Spencer V.A., Costes S., Inman J.L., Xu R., Chen J., Hendzel M.J., Bissell M.J. 2011. Depletion of nuclear actin is a key mediator of quiescence in epithelial cells. *J. Cell Sci.* **124** (1), 123–132.

87. Almuzzaini B., Sarshad A.A., Rahmanto A.S., Hansson M.L., Von Euler A., Sangfelt O., Visa N., Farrants A.Ö., Percipalle P. 2016. In β-actin knockouts, epigenetic reprogramming and rDNA transcription inactivation lead to growth and proliferation defects. *FASEB J.* **30** (8), 2860–2873.

88. Yoo Y., Wu X., Guan J.L. 2007. A novel role of the actin-nucleating Arp2/3 complex in the regulation of RNA polymerase II-dependent transcription. *J. Biol. Chem.* **282** (10), 7616–7623.

89. Wu X., Yoo Y., Okuhama N.N., Tucker P.W., Liu G., Guan J.L. 2006. Regulation of RNA-polymerase-II-

dependent transcription by N-WASP and its nuclear-binding partners. *Nat. Cell. Biol.* **8** (7), 756–763.

90. Miyamoto K., Teperek M., Yusa K., Allen G.E., Bradshaw C.R., Gurdon J.B. 2013. Nuclear Wave1 is required for reprogramming transcription in oocytes and for normal development. *Science*. **341** (6149), 1002–1005.
91. Xia P., Wang S., Huang G., Zhu P., Li M., Ye B., Du Y., Fan Z. 2014. WASH is required for the differentiation commitment of hematopoietic stem cells in a c-Myc–dependent manner. *J. Exp. Med.* **211** (10), 2119–2134.
92. Vintermist A., Böhm S., Sadeghifar F., Louvet E., Mansén A., Percipalle P., Östlund Farrants A.K. 2011. The chromatin remodelling complex B-WICH changes the chromatin structure and recruits histone acetyltransferases to active rRNA genes. *PLoS One*. **6** (4), e19184.
93. Almuzzaini B., Sarshad A.A., Farrants A.K.Ö., Percipalle P. 2015. Nuclear myosin 1 contributes to a chromatin landscape compatible with RNA polymerase II transcription activation. *BMC Biol.* **13** (1), 35.
94. Fili N., Hari-Gupta Y., dos Santos Á., Cook A., Poland S., Ameer-Beg S.M., Parsons M., Toseland C.P. 2017. NDP52 activates nuclear myosin VI to enhance RNA polymerase II transcription. *Nat. Commun.* **8** (1), 1871.
95. Fili N., Hari-Gupta Y., Aston B., dos Santos Á., Gough R.E., Alamad B., Wang L., Martin-Fernandez M.L., Toseland C.P. 2020. Competition between two high- and low-affinity protein-binding sites in myosin VI controls its cellular function. *J. Biol. Chem.* **295** (2), 337–347.
96. Cook A., Hari-Gupta Y., Toseland C.P. 2018. Application of the SSB biosensor to study in vitro transcription. *Biochem. Biophys. Res. Comm.* **496** (3), 820–825.
97. Zorca C.E., Kim L.K., Kim Y.J., Krause M.R., Zenklusen D., Spilianakis C.G., Flavell R.A. 2015. Myosin VI regulates gene pairing and transcriptional pause release in T cells. *Proc. Natl. Acad. Sci. U. S. A.* **112** (13), E1587–E1593
98. Puri C., Chibalina M.V., Arden S.D., Kruppa A.J., Kendrick-Jones J., Buss F. 2010. Overexpression of myosin VI in prostate cancer cells enhances PSA and VEGF secretion, but has no effect on endocytosis. *Oncogene*. **29** (2), 188–200.
99. Loikkanen I., Toljamo K., Hirvikoski P., Väisänen T., Paavonen T.K., Vaarala M.H. 2009. Myosin VI is a modulator of androgen-dependent gene expression. *Oncol. Rep.* **22** (5), 991–995.
100. Venit T., Dzijak R., Kalendová A., Kahle M., Rohožková J., Schmidt V., Rülicke T., Rathkolb B., Hans W., Bohla A., Eickelberg O., Stoeger T., Wolf E., Yildirim A.Ö., Gailus-Durner V., Fuchs H., de Angelis M.H., Hozák P. 2013. Mouse nuclear myosin I knock-out shows interchangeability and redundancy of myosin isoforms in the cell nucleus. *PLoS One.* **8** (4), e61406.
101. Mehta I. S., Kulashreshtha M., Chakraborty S., Kolthur-Seetharam U., Rao B.J. 2013. Chromosome territories reposition during DNA damage-repair response. *Genome Biol.* **14** (12), R135.
102. Saidova A.A., Potashnikova D.M., Tvorogova A.V., Maly I.V., Hofmann W.A., Vorobjev I.A. 2018. Specific and reliable detection of myosin 1C isoform A by RTqPCR in prostate cancer cells. *Peer J.* **6**, e5970.
103. Fatakia S.N., Kulashreshtha M., Mehta I.S., Rao B.J. 2017. Chromosome territory relocation paradigm during DNA damage response: Some insights from molecular biology to physics. *Nucleus.* **8** (5), 449–460.
104. Sokolova M., Moore H.M., Prajapati B., Dopie J., Meriläinen L., Honkanen M., Matos R.C., Poukkula M., Hietakangas V., Vartiainen M.K. 2018. Nuclear actin is required for transcription during *Drosophila* oogenesis. *iScience*. **9**, 63–70.
105. Andrin C., McDonald D., Attwood K.M., Rodrigue A., Ghosh S., Mirzayans R., Masson J.Y., Dellaire G., Hendzel M.J. 2012. A requirement for polymerized actin in DNA double-strand break repair. *Nucleus.* **3** (4), 384–395.
106. Schrank B.R., Aparicio T., Li Y., Chang W., Chait B.T., Gundersen G.G., Gottesman M.E., Gautier J. 2018. Nuclear ARP2/3 drives DNA break clustering for homology-directed repair. *Nature*. **559** (7712), 61–66.
107. Kulashreshtha M., Mehta I.S., Kumar P., Rao B.J. 2016. Chromosome territory relocation during DNA repair requires nuclear myosin 1 recruitment to chromatin mediated by γ-H2AX signaling. *Nucleic Acids Res.* **44** (17), 8272–8291.
108. Evdokimova V.N., Gandhi M., Nikitski A.V., Bakkenist C.J., Nikiforov Y.E. 2018. Nuclear myosin/actin-motored contact between homologous chromosomes is initiated by ATM kinase and homology-directed repair proteins at double-strand DNA breaks to suppress chromosome rearrangements. *Oncotarget.* **9** (17), 13612–13622.
109. Li Y.R., Yang W.X. 2016. Myosins as fundamental components during tumorigenesis: Diverse and indispensable. *Oncotarget.* **7** (29), 46785–46812.
110. Dunn T. A., Chen S., Fait D. A., Hicks J.L., Platz E.A., Chen Y., Ewing C.M., Sauvageot J., Isaacs W.B., De Marzo A.M., Luo J. 2006. A novel role of myosin VI in human prostate cancer. *Am. J. Pathol.* **169** (5), 1843–1854.
111. Ihnatovych I., Sielski N.L., Hofmann, W.A. 2014. Selective expression of Myosin IC isoform A in mouse and human cell lines and mouse prostate cancer tissues. *PLoS One.* **9** (9), e108609.
112. Nakano T., Tani M., Nishioka M., Kohno T., Otsuka A., Ohwada S., Yokota J. 2005. Genetic and epigenetic alterations of the candidate tumor-suppressor gene MYO18B, on chromosome arm 22q, in colorectal cancer. *Genes Chromosomes Cancer.* **43** (2), 162–171.
113. Schramek D., Sendoel A., Segal J.P., Beronja S., Heller E., Oristian D., Reva B., Fuchs E. 2014. Direct in vivo RNAi screen unveils myosin IIa as a tumor suppressor of squamous cell carcinomas. *Science*. **343** (6168), 309–313.
114. Borrego-Pinto J., Jegou T., Osorio D.S., Auradé F., Gorjánácz M., Koch B., Mattaj I.W., Gomes E.R. 2012. Samp1 is a component of TAN lines and is re-

quired for nuclear movement. *J. Cell Sci.* **125** (5), 1099–1105.

115. Jayo A., Malboubi M., Antoku S., Chang W., Ortiz-Zapater E., Groen C., Pfisterer K., Tootle T., Charras G., Gundersen G.G., Parsons M. 2016. Fascin regulates nuclear movement and deformation in migrating cells. *Dev. Cell.* **38** (4), 371–383.
116. Saunders C.A., Harris N.J., Willey P.T., Woolums B.M., Wang Y., McQuown A.J., Schoenhofen A., Worman H.J., Dauer W.T., Gundersen G.G., Luxton G.W.G. 2017. Torsin A controls TAN line assembly and the retrograde flow of dorsal perinuclear actin cables during rearward nuclear movement. *J. Cell Biol.* **216** (3), 657–674.
117. Chang W., Folker E.S., Worman H.J., Gundersen G.G. 2013. Emerin organizes actin flow for nuclear movement and centrosome orientation in migrating fibroblasts. *Mol. Biol. Cell.* **24** (24), 3869–3880.
118. Kutscheidt S., Zhu R., Antoku S., Luxton G.W.G., Stagljar I., Fackler O.T., Gundersen G.G. 2014. FHOD1 interaction with nesprin-2G mediates TAN line formation and nuclear movement. *Nat. Cell Biol.* **16** (7), 708–715.
119. Maninová M., 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**20), 3676–3693.
120. Khatau S.B., Hale C.M., Stewart-Hutchinson P.J., Patel M.S., Stewart C.L., Searson P.C., Hodzic D., Wirtz, D. 2009. A perinuclear actin cap regulates nuclear shape. *Proc. Natl. Acad. Sci. U. S. A.* **106** (45), 19017–19022.
121. Kim J.K., Louhghalam A., Lee G., Schafer B.W., Wirtz D., Kim D.H. 2017. Nuclear lamin A/C harnesses the perinuclear apical actin cables to protect nuclear morphology. *Nat. Commun.* **8** (1), 2123.
122. Jorgens D.M., Inman J.L., Wojcik M., Robertson C., Palsdottir H., Tsai W.T., Huang H., Bruni-Cardoso A., López C.S., Bissell M.J., Xu K., Auer M. 2016. Deep nuclear invaginations linked to cytoskeletal filaments: Integrated bioimaging of epithelial cells in 3D culture. *J. Cell Sci.* **130** (1), 177–189.
123. Gay O., Nakamura F., Baudier J. 2011. Refilin holds the cap. *Commun. Integr Biol.* **4** (6), 791–795.
124. Baudier J., Jenkins Z.A., Robertson S.P. 2018. The filamin-B–refilin axis—spatiotemporal regulators of the actin-cytoskeleton in development and disease. *J. Cell Sci.* **131** (8), jcs213959.
125. Wu J., Kent I.A., Shekhar N., Chancellor T.J., Mendonca A., Dickinson R.B., Lele T.P. 2014. Actomyosin pulls to advance the nucleus in a migrating tissue cell. *Biophys. J.* **106** (1), 7–15.
126. Thiam H.R., Vargas P., Carpi N., Crespo C.L., Raab M., Terriac E., King M.C., Jacobelli J., Alberts A.S., Stradal T., Lennon-Dumenil A.M., Piel M. 2016. Perinuclear Arp2/3-driven actin polymerization enables nuclear deformation to facilitate cell migration through complex environments. *Nat. Commun.* **7** (1), 10997.
127. Shao X., Li Q., Mogilner A., Bershadsky A.D. Shivashankar G.V. 2015. Mechanical stimulation induces formin-dependent assembly of a perinuclear actin rim. *Proc. Natl. Acad. Sci. U. S. A.* **112** (20), E2595–E2601.
128. Wales P., Schuberth C.E., Aufschnaiter R., Fels J., García-Aguilar I., Janning A., Dlugos C.P., Schäfer-Herte M., Klingner C., Wälte M., Kuhlmann J., Menis E., Hockaday Kang L., Maier K.C., Hou W., Russo A., Higgs H.N., Pavenstädt H., Vogl T., Wedlich-Söldner R. 2016. Calcium-mediated actin reset (CaAR) mediates acute cell adaptations. *Elife.* **5**, e19850.
129. Le H.Q., Ghatak S., Yeung C.Y.C., Tellkamp F., Günschmann C., Dieterich C., Yeroslaviz A., Habermann B., Pombo A., Niessen C.M., Wickström S.A. 2016. Mechanical regulation of transcription controls Polycomb-mediated gene silencing during lineage commitment. *Nat. Cell. Biol.* **18** (8), 864–875.
130. Gilbert H.T.J., Mallikarjun V., Dobre O., Jackson M.R., Pedley R., Gilmore A.P., Richardson S.M., Swift J. 2019. Nuclear decoupling is part of a rapid protein-level cellular response to high-intensity mechanical loading. *Nat. Commun.* **10** (1), 4149.
131. Norden C., Young S., Link B.A., Harris W.A. 2009. Actomyosin is the main driver of interkinetic nuclear migration in the retina. *Cell.* **138** (6), 1195–1208.
132. Strzyz P.J., Lee H.O., Sidhaye J., Weber I.P., Leung L.C., Norden C. 2015. Interkinetic nuclear migration is centrosome independent and ensures apical cell division to maintain tissue integrity. *Dev. Cell.* **32** (2), 203–219.
133. Yanakieva I., Erzberger A., Matejčić M., Modes C.D., Norden C. 2019. Cell and tissue morphology determine actin-dependent nuclear migration mechanisms in neuroepithelia. *J. Cell Biol.* **218** (10), 3272–3289.
134. Lahne M., Li J., Marton R.M., Hyde D.R. 2015. Actin-cytoskeleton- and rock-mediated INM are required for photoreceptor regeneration in the adult zebrafish retina. *J. Neurosci.* **35** (47), 15612–15634.
135. Kirkland N.J., Yuen A.C., Tozluoglu M., Hui N., Paluch E.K., Mao Y. 2020. Tissue mechanics regulate mitotic nuclear dynamics during epithelial development. *Curr. Biol.* **30** (13), 2419–2432.e4.
136. Yu J., Lei K., Zhou M., Craft C.M., Xu G., Xu T., Zhuang Y., Xu R., Han M. 2011. KASH protein Syne-2/Nesprin-2 and SUN proteins SUN1/2 mediate nuclear migration during mammalian retinal development. *Hum. Mol. Genet.* **20** (6), 1061–1073.
137. Roman W., Martins J.P., Carvalho F. A., Voituriez R., Abella J.V.G., Santos N.C., Cadot B., Way M., Gomes E.R. 2017. Myofibril contraction and crosslinking drive nuclear movement to the periphery of skeletal muscle. *Nat. Cell. Biol.* **19** (10), 1189–1201.
138. Huelsmann S., Ylänne J., Brown, N.H. 2013. Filopodia-like actin cables position nuclei in association with perinuclear actin in *Drosophila* nurse cells. *Dev. Cell.* **26** (6), 604–615.
139. Burke B. 2019. Chain reaction: LINC complexes and nuclear positioning. *F1000Res.* **8**, 136.
140. Luxton G.W.G., Gomes E.R., Folker E.S., Vintinner E., Gundersen G.G. 2010. Linear arrays of nuclear envelope proteins harness retrograde actin flow for nuclear movement. *Science.* **329** (5994), 956–959.

141. Zhu R., Antoku S., Gundersen G.G. 2017. Centrifugal displacement of nuclei reveals multiple LINC complex mechanisms for homeostatic nuclear positioning. *Curr. Biol.* **27** (20), 3097–3110.e5.

142. Stenzel W., Preusse C., Allenbach Y., Pehl D., Junckerstorff R., Heppner F. L., Nolte K, Aronica E., Kana V., Rushing E., Schneider U., Claeys K.G., Benveniste O., Weis J., Goebel H.H. 2015. Nuclear actin aggregation is a hallmark of anti-synthetase syndrome-induced dysimmune myopathy. *Neurology.* **84**, 1346–1354.

143. Munsie L., Caron N., Atwal R.S., Marsden I., Wild E.J., Bamburg J.R., Tabrizi S.J., Truant R. 2011. Mutant huntingtin causes defective actin remodeling during stress: Defining a new role for transglutaminase 2 in neurodegenerative disease. *Hum. Mol. Genet.* **20**, 1937–1951.

144. Bamburg J.R., Wiggan O.P. 2002. ADF/cofilin and actin dynamics in disease. *Trends Cell. Biol.* **12**, 598–605.