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Competing interests statement

The authors declare that they have no competing financial interests

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DATABASES

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OPINION

Actin up in the nucleus

Blaine T. Bettinger, David M. Gilbert and David C. Amberg

Scepticism regarding the existence of actin in the nucleus is finally giving way to the productive investigation of its functional roles. The identification of actin in several nuclear complexes implicates it in diverse nuclear activities including transcription, chromatin remodelling and nucleocytoplasmic trafficking. A major challenge is that actin does not seem to form large filamentous structures in the nucleus and might adopt unique conformations, the elucidation of which would greatly assist our understanding of its functions.

For more than 30 years, scores of reports have provided evidence for the presence of actin in the nucleus, but until recently the functional significance and even the validity of these findings was in doubt. As actin is one of the most abundant cellular proteins, the identification of actin in preparations of nuclei or in isolated nuclear protein complexes could not rule out cytoplasmic actin contamination. In addition, actin has many binding partners and a high potential for nonspecific interactions, so even findings of direct interactions of actin with nuclear proteins have been questioned. Experiments that identified essential roles for actin in stimulating *in vitro* activities did not convincingly demonstrate physiological significance. To make matters worse, many of the reagents that are typically used to localize actin in intact cells did not stain the nucleus.

At present, it could still be argued that there is no single seminal study that unequivocally identifies a physiological role for actin in the nucleus, and this has undoubtedly impeded further work on nuclear actin. Here, we briefly summarize evidence for the presence of conventional β-actin in the nucleus and its role in diverse nuclear activities, such as transcription, mRNA export and chromatin remodelling. We also discuss evidence that nuclear actin adopts a novel conformation or is present as short polymers that escape detection by reagents that are typically used to stain cytoskeletal actin. Taken together, the evidence leaves little doubt that actin has some function in the nucleus.

Actin and ARPs in the nucleus

Speculation on the potential role of actin in the nucleus derives largely from its known functions as a cytoskeletal protein[1] (BOX 1). Within the cytoplasm, actin is known to have a key role in organizing the cell cortex to facilitate both intracellular traffic at the plasma membrane and to drive cell-shape changes that are involved in cytokinesis, cell motility and cell adhesion. These complicated activities are coordinated with the assistance of many actin-binding proteins; some that regulate actin dynamics, others that organize actin filaments into distinct networks, and still more that use the actin filaments to generate force or move cargo along actin filaments (for example, using myosin motors). So, it has been anticipated that actin will have many binding partners (TABLE 1) and roles in the nucleus.

A superfamily of proteins with similarity to actin, which are known as actin-related proteins (ARPs), are also found in the nucleus and

Box 1 | Conventional actin

Actin is a globular protein that is separated into two lobes by a cleft that forms the ATP-binding site. ATP-bound actin monomers (globular or G-actin) can assemble into filaments (filamentous or F-actin), which results in the hydrolysis of ATP. Actin filaments are composed of two strands that twist around one another to form a double right-handed helix. These filaments are further organized by accessory proteins into diverse structures that carry out actin's cytoplasmic functions. There are three isoforms of actin in higher eukaryotes; α-actin is muscle specific, whereas β- and γ-actin are found in all cell types. Conventional β-actin is highly conserved (Physarum and yeast actin are 95% and 89% identical to human actin[52]) and is the form of actin for which a role in the nucleus has been so hotly debated.

have recently been shown to have important roles in chromatin remodelling[2]. Although the nuclear functions of ARPs are often cited as evidence for the presence of conventional actin in the nucleus, ARPs share only 17–60% identity with conventional actin[3], and most ARPs (with the exception of the closely related ARP1 family) are unable to interact with known actin-binding proteins or form long polymers, although they can form short filaments. So, even though the nuclear functions of ARPs are interesting in their own right, they neither support nor deny a role for conventional actin in the nucleus.

A long history of healthy scepticism

Early studies identified actin as a component of isolated nuclei, first with the large and easily purified nuclei of amphibians[4,5], and later with mammalian nuclei[6] and purified preparations of human nucleoli[7]. Isolated nuclear matrices were also found to contain actin[6,8], which fuelled speculation that actin might be part of a 'nucleoskeleton'. Unfortunately, actin is such an abundant cellular protein that the possibility of cytoplasmic contamination complicated the definitive identification of actin as a nuclear protein. Even *in vivo* crosslinking studies that identified actin as a major component (20% of total DNA-bound protein) of DNA–protein adducts[9] were discounted, because actin is small enough to diffuse into the nucleus. Moreover, given that we now know that actin can accumulate in the nucleus in response to cellular stress (see below), it is possible that long incubations with chemical crosslinking agents can induce the translocation of actin into the nucleus.

Among the many reasons for doubting the existence of actin in the nucleus was that fluorescently tagged phalloidin, which specifically binds filamentous (F)-actin, uniquely stains the cytoplasm. This criticism was alleviated when immunofluorescence studies with a particular anti-actin monoclonal antibody (2G2) revealed a punctate staining pattern in formaldehyde-fixed cells that was restricted almost entirely to the nuclei of several cultured cell lines as well as *Xenopus laevis* oocytes[10]. When these same cells were fixed with methanol to denature cytoplasmic actin, 2G2 stained the cytoplasm in patterns that were identical to those seen with the fluorescently tagged phalloidin, which indicates that 2G2 recognizes a specific epitope within actin that is present in the nucleus but is masked in cytoplasmic actin filaments. Although fixation artefacts and antibody crossreactivity are always a concern when interpreting immunofluorescence studies, this finding provides a logical explanation for why nuclear actin might not stain with phalloidin, and indicates that nuclear actin is present in a different form to cytoplasmic actin.

Although it is still uncertain how much actin is normally present in the nucleus, several recent studies leave little doubt that actin can shuttle into and out of the nucleus. It has been known for some time that stresses such as dimethyl sulphoxide (DMSO) treatment and heat shock induce the nuclear translocation of actin in various eukaryotic cells[11]. Nuclear translocation that is induced by heat shock is reversible, which indicates that there is a means of shuttling actin between the cytoplasm and the nucleus. Recently, cofilin was shown to be an active carrier of actin into the nucleus[12]. This small globular (G)- and F-actin-binding phosphoprotein translocates to the nucleus after dephosphorylation in response to heat shock or DMSO[13], and was found to colocalize with actin inside the nucleus[12]. Cofilin, unlike actin, contains a nuclear localization sequence (NLS) that is responsible for its translocation to the nucleus[13]. Interestingly, when cells were treated with latrunculin B (which causes the disassembly of F-actin in the cytoplasm) or depleted for ATP, actin was translocated to the nucleus in a cofilin-dependent manner.

Once inside the nucleus, actin can be exported via two highly conserved and functional nuclear export signals (NESs), which are found in α-, β- and γ-actin[14]. Mutant forms of transfected actin that lack NESs accumulate in the nucleus, and leptomycin B, a drug that specifically inhibits nuclear export of leucine-rich NESs by the exportin protein CRM1, causes endogenous actin to accumulate in nuclei[14]. Recently, a new mechanism for the export of actin from the nucleus was described[15]. Exportin-6, which is a member of the importin-β family, forms a stable export complex with actin, but only if profilin is present. Profilin is a small actin-binding protein that is known to localize to both the cytoplasm and nucleus[15,16], and that catalyses ADP exchange on G-actin and facilitates F-actin assembly. The depletion of exportin-6 by RNA interference resulted in the nuclear accumulation of actin and the formation of large actin paracrystals that resemble those seen after DMSO treatment. The presence of two NESs and a profilin–actin export protein indicates that actin concentrations in the nucleus are tightly regulated. These

Table 1 | Recently identified actin-binding proteins in the nucleus*

Protein	Function	References
Profilin	A monomer-binding protein that promotes nucleotide exchange	15,16
CapG	An abundant protein in macrophages, which binds pointed ends of F-actin	53,54
Zyxin	Zyxin organizes the actin-polymerization machinery and has actin-polymerization-promoting activity	55,56
Myopodin	A filamentous (F)-actin-bundling protein	57
Nrf2	On oxidative stress, Nrf2 forms a complex with actin that translocates to the nucleus	58
NDHII	A helicase that seems to bind a form of F-actin in the nucleus	24
hrp36, DBP40, hrp65	Proteins that associate with pre-mRNA to form ribonucleoprotein complexes	25–27
Emerin	A nuclear-envelope protein that interacts with lamin A and actin	44,59‡
Lamin A	A major protein of the nuclear lamina, which binds nuclear actin	43,60
Exportin-6	A nuclear-export receptor that specifically exports profilin-bound actin	15

*For a list of previously identified proteins, see REF. 61. ‡J. M. Holaska and K. L. Wilson, personal communication. DBP, DNA-binding protein; hrp, heterogeneous nuclear ribonucleoprotein; NDHII, nuclear DNA helicase-II; Nrf, NF-E2-related factor.

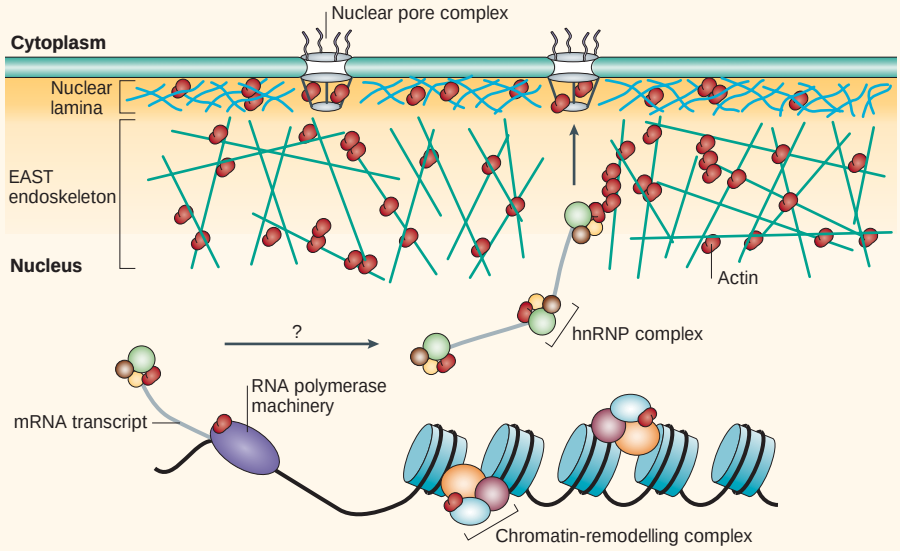

Figure 1 | **Functions of actin in the nucleus.** Actin is thought to have a structural and/or regulatory role within chromatin-remodelling complexes and/or the RNA polymerase machinery. Once an mRNA transcript has been produced, actin associates with these transcripts through interactions with heterogeneous ribonucleoprotein (hnRNP) complexes. And at the nuclear pore complex (NPC), actin might participate in the export of the mRNA transcripts. Finally, actin could have a role in establishing and/or maintaining nuclear structure through interactions with the nuclear lamina and the enhanced adult sensory threshold (EAST) endoskeleton. Although actin could be involved individually in each of these processes, it is possible that actin has a coupling role between transcription, movement towards the nuclear periphery and mRNA export, possibly by using cargo transport mechanisms.

experiments show definitively that actin regularly enters the intranuclear environment. However, it can still be argued that actin only accumulates in the nucleus under conditions of stress, and that these export mechanisms are normally present to ensure that actin is excluded from the nucleus. It is tempting to speculate that actin has an active role in the stress response; by translocating to the nucleus after stress it might be part of a stress-sensing and/or stress-response pathway, as has recently been shown for osmotic stress and cytoplasmic actin[17,18]. The only way to settle these debates is to elucidate what functional roles actin has in nuclear processes.

Functions of actin in the nucleus

RNA transcription, processing and export. In developing amphibian oocytes, paired chromosomes form highly de-condensed lampbrush chromosomes with numerous lateral loops that are indicative of active transcription; inhibitors of transcription cause immediate loop retraction. Early studies in isolated *Pleurodeles waltlii* (salamander) nuclei found that anti-actin antibodies stained the condensed portions of these chromosomes but were absent from the transcriptionally active loops[19], which indicated that actin is involved in the formation of the lampbrush structure. Later, it was shown that the injection of anti-actin antibodies, or proteins that are known to sever conventional actin filaments, into salamander nuclei resulted in a retraction of the lateral loops that was similar to the effect observed with transcriptional inhibitors, which implied that actin has a direct role in transcription[20]. Moreover, antibodies against nuclear myosin-I (REF. 21) colocalize and co-immunoprecipitate with mammalian RNA polymerase II and have been shown to inhibit *in vitro* transcription assays[22]. As myosin-I isoforms are monomeric, barbed-end-directed actin-filament motor proteins, these results also indicate that there might be a role for actin filaments in transcription.

A role for actin in RNA export surfaced unexpectedly from studies of retroviral RNA export[23]. Rev, which is a well-characterized HIV-1 mRNA export factor, contains a leucine-rich hydrophobic NES that is similar to the NESs of actin. The NES of Rev binds to eukaryotic initiation factor-5A (eIF5A), which is a protein that interacts with a known export receptor and accumulates at nuclear pore complexes (NPCs). Actin was found to co-purify with eIF5A in glutathione-*S*-transferase (GST)–eIF5A pull-down assays. Anti-actin antibodies inhibited Rev-mediated mRNA export from *X. laevis* oocyte nuclei, and electron microscopy localized actin specifically to the nucleoplasmic filaments of the NPC (FIG. 1).

Actin also has been shown to be present in a small nuclear ribonucleoprotein (snRNP)-associated protein complex, apparently through an interaction with nuclear DNA helicase-II (NDHII), a protein that facilitates the shuttling of this snRNP complex through the NPC[24]. This interaction led to the speculation that NDHII might mediate shuttling by its attachment to a hypothetical actin nucleoskeleton, similar to cargo transport along the cytoskeleton (FIG. 2C).

Actin has also been found to associate with Balbiani ring mRNA from the site of transcription in the nucleus to polyribosomes in the cytoplasm[25–27]. Balbiani rings are sites of active transcription in the salivary glands of the fly *Chironomus tentans*, in which RNA products can be easily visualized. DNase-I –actin affinity chromatography was used to investigate the presence of actin-associated proteins in salivary glands, and this identified hrp36 (REF. 25) and hrp65 (REF. 27). Heterogeneous nuclear ribonucleoproteins (hnRNPs) such as hrp36 and hrp65 associate with pre-mRNA to form hnRNP complexes and package the RNA for stability and/or transport[25]. These interactions were confirmed *in vitro* using purified recombinant hrp36, hrp65 and β-actin, and *in vivo* with the use of a chemical crosslinker[25,27]. The introduction of a small peptide that contains part of the actin-binding site of hrp65 disrupted the actin–hrp65 interaction and caused a decrease in transcription from Balbiani rings, which further supports a role for actin not only in RNA transport but also directly in maintaining active transcription by RNA polymerase II[27].

Actin in chromatin-remodelling complexes. The identification of actin as a component of chromatin-remodelling complexes (BOX 2) is arguably the strongest evidence for a functional role of actin in the nucleus[2]. Since the identification of actin in the mammalian BAF (BRG-associated factor) complex[28], actin has been purified from the *Drosophila melanogaster* BAP (Brm-associated protein) complex[29], the *Saccharomyces cerevisiae* Ino80 (REF. 30) and histone acetyltransferase NuA4 (REF. 31) complexes, and the mammalian TIP60 (REF.32), PBAF[33] (containing a different composition of BRG1-associated factors compared with the BAF complex mentioned above) and p400 (REF. 34) complexes. Interestingly, there seems to be one actin molecule per mammalian BAF complex[28]. This association is highly specific and indicates that actin might have an important role in chromatin-remodelling complexes.

Recent work has shown that the binding of phosphatidylinositol 4,5-bisphosphate

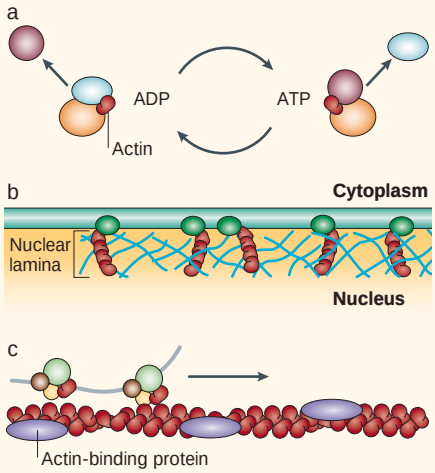

Figure 2 | **Possible forms of nuclear actin.** There are at least three possible forms that actin could adopt within the nucleus. Importantly, actin could be present in all three forms within the nucleus. **a** | Actin could be monomeric. Complexes such as chromatin-remodelling complexes could use the conformation changes of actin (through actin's ATPase activity) to regulate subunit composition or function. **b** | Alternatively, actin could be found in short filaments (similar to those that are found associated with protein 4.1 in erythrocytes) that are too short or diffuse to be visualized by phalloidin. Short filaments of actin would probably have a structural role, such as interacting with the lamin nucleoskeleton at the nuclear periphery. **c** | Finally, actin could adopt a novel oligomeric form, which can not be recognized by phalloidin but the formation of which is inhibited by the latrunculins. In this form, actin is likely to be involved in structural and/or trafficking roles.

($PtdIns(4,5)P_2$), which is a regulator of the actin cytoskeleton, to the BAF complex induces the purified complex to associate with the pointed ends and branch points of actin filaments *in vitro*[35]. As the authors point out, the BAF complex might be binding to actin branch points (similar to the ARP2/3 complex in migrating cells) to alter or maintain the chromatin structure.

Actin as part of a nucleoskeleton. It is tempting to see actin as a component of a nucleoskeleton that is analogous to the cytoskeleton. A recently discovered structural protein of the nucleus, EAST (enhances adult sensory threshold), shows remarkable colocalization with nuclear actin[36]. EAST is an essential, ubiquitous nuclear protein that was first described in *D. melanogaster* and that forms a network throughout the nucleus, excluding the chromosomes and the nucleolus. The amount of EAST that is present changes as the extra-chromosomal compartment of the nucleus expands in response to heat shock. The overproduction of EAST results in an expansion of the extra-chromosomal compartment and the nuclear accumulation of actin, which indicates that EAST could be retaining and/or regulating actin in the nucleus to reorganize the nucleoskeleton in response to stress. Interestingly, the nuclei in these studies could not be stained by phalloidin, which again indicates that nuclear actin is not filamentous or is so diffuse that it escapes detection.

Protein 4.1, a member of a family of spectrin- and actin-binding structural proteins, is a key component of the junctional complex that links actin and spectrin to the plasma membrane of erythrocytes through interactions with glycoproteins[37]. In nucleated cells, protein 4.1 is found throughout the cell including inside the nucleus[38]. It has recently been shown that protein 4.1 is required for the proper assembly of nuclei in *in vitro* assays[39]. Demembranated sperm, when added to interphasic *X. laevis* egg extracts, formed pronuclei. The addition of protein 4.1 domain fragments, however, disrupted this process and caused morphologically altered nuclei to form. Interestingly, when two amino acids within the actin-binding domain of one of these dominant-negative fragments were deleted, the peptide had no effect and the assembled nuclei were morphologically normal.

In a related study[40], the role of actin in nuclear assembly was examined. Fluorescently labelled actin was added to *X. laevis* egg extracts and nuclear assembly was initiated. As the chromatin assembled, actin accumulated and formed what appeared to be an actin network in the mature nuclei. Furthermore, when the actin inhibitor latrunculin A was added to the *X. laevis* egg extracts, nuclear assembly was completely inhibited. As latrunculin A binds to G-actin and blocks F-actin assembly, this result indicates that the assembly of F-actin is essential for nuclear assembly[40]. In the erythrocyte membrane cytoskeleton, protein 4.1 is associated with short actin filaments that are only 13 subunits long[41,42]. Perhaps similarly short nuclear actin filaments associate with nuclear protein 4.1 to stabilize the nuclear envelope. If so, these nuclear filaments would have to be in low abundance to escape detection by phalloidin staining as the erythrocyte cytoskeletal filaments can be visualized with phalloidin.

Anti-actin antibodies have also shown that actin is present along the fibrogranular structures in nuclear matrix preparations[8]. The nuclear lamina is a meshwork of mixed intermediate filaments that are assembled from three lamin proteins A, B and C. Lamin A binds actin directly[43], and also binds emerin, which is a nuclear envelope protein that itself binds to actin[44]. Interestingly, a recent study has shown that emerin increases actin polymerization *in vitro* by stabilizing the pointed end of actin filaments (J. M. Holaska and K. L. Wilson, personal communication). The interactions between actin, emerin and lamin A indicate that an actin-containing structural network is involved in the structure and function of the nuclear periphery, perhaps connecting the periphery to an internal skeleton. It is tempting to speculate further that protein 4.1 could be part of the mechanism that anchors these actin fibrogranular structures to the inner nuclear envelope in conjunction with the membrane-anchored lamin proteins.

Actin and DNase I. Interestingly, G-actin binds with high affinity to DNase I in a 1:1 complex. In fact, actin was originally crystallized in association with DNase I to prevent actin polymerization under the high concentrations that are required to crystallize the protein[45]. Also, the binding of actin to DNase I inhibits its activity[46], which indicates that there could be two functions for this interaction in the nucleus: the prevention of actin polymerization or the inhibition of DNase I. In fact, an early report that actin stimulates transcription *in vitro*[47] was later shown to be due to the inhibition of template degradation. Therefore, although the relevance of this interaction is still unknown, the activities of DNase I should be considered when interpreting the results of experiments with actin.

From form will come function

Many of the proposed functions of actin remain speculative because we do not yet understand which form of actin is in the nucleus[48]. This is undoubtedly the most difficult obstacle that the field faces. Two particular characteristics of nuclear actin indicate that it adopts a conformation that is not typically encountered in the cytosol. First, some monoclonal antibodies against actin preferentially stain the nucleus over the cytoplasm. The 2G2 antibody (described above) was not the first to preferentially stain nuclear actin. In 1993, an antibody to sarcomeric α-actin was shown to have clear nuclear staining but poor cytoplasmic staining in neuron and PC12 (rat pheochromocytoma) cells[49]. Conversely, in the same study an antibody to smooth-muscle α-actin stained the cytoplasm but was never seen to stain the nucleus. The fact that three antibodies differentially recognize nuclear versus cytoplasmic actin strongly suggests that

Box 2 | Nuclear complexes that contain actin

In recent years, many nuclear complexes have been shown to contain actin as a constituent.

Pre-mRNP particles
As they are transcribed, pre-mRNA molecules associate with heterogeneous nuclear ribonucleoproteins (hnRNPs) to form ribonucleoprotein complexes that are known as pre-mRNP particles. Actin binds to the hnRNP proteins hrp36 (REF. 25), DBP40 (REF. 26) and hrp65 (REF. 27).

Nuclear DNA helicase-II
Nuclear DNA helicase-II (NDHII) unwinds double-stranded DNA and has been seen to stimulate translation and have a role in RNA transport. Interestingly, NDHII binds actin and hnRNP C[24].

BAF complex
The BAF (BRG-associated factor) complex is a mammalian chromatin-remodelling complex that is related to the yeast SWI/SNF complex. Actin is required for the optimal ATPase activity of its binding partner BRG1 (REF. 28).

BAP complex
The BAP (Brm-associated protein) complex is a *Drosophila melanogaster* chromatin-remodelling complex. Actin co-purifies with Brm, a SWI2/SNF2-related helicase that functions as the catalytic subunit of the BAP complex[29].

Ino80 complex
The Ino80 complex is a *Saccharomyces cerevisiae* SWI/SNF-like complex that is involved in transcription and DNA processing. Actin co-purifies with INO80, which is the ATPase subunit of the complex[30].

NuA4 complex
Actin co-purifies with the NuA4 (nucleosomal acetyltransferase of H4) complex, which modifies histones H4 and H2A[31].

TIP60 complex
Actin co-purifies with TIP60, a histone acetylase of the mammalian TIP60 complex, which also has ATPase and DNA-helicase activity[32].

p400 complex
The mammalian SWI/SNF-like p400 complex binds to the adenovirus E1A oncoprotein, and is involved in the oncogenic transformation of cells by E1A. Actin co-purifies with p400, a protein that is also found in the TIP60 complex[34].

PBAF complex
The mammalian PBAF (polybromo BRG1-associated factors) complex localizes to the kinetochores of mitotic chromosomes. Actin co-purifies with BAF180, a protein that is found in the PBAF complex[33].

there are important conformational differences between the two, although these epitopes could be differentially masked by actin-binding proteins. Second, nuclear actin in *D. melanogaster* cells[36], myogenic cells and the filamentous network that is recognized by 2G2 in *X. laevis* oocytes[10] is not stained by the small molecule phalloidin, the binding of which would not be readily masked by actin-binding proteins (as could be the case with antibodies). This indicates that nuclear actin is either monomeric or forms a new oligomeric structure. In either case, the 2G2 results argue against the presence of F-actin in the nucleus because the 2G2 epitope is predicted to be buried in the F-actin structure[10].

So far, the data argue that there are three non-mutually exclusive hypotheses for the form of nuclear actin (FIG. 2). First, in some complexes, such as chromatin-remodelling complexes, actin could be monomeric, in which case the ATPase activity of actin could be used to regulate cycles of complex formation or configuration (FIG. 2a). From structural studies it is known that ATP hydrolysis produces substantial changes in actin structure[50] and ATP hydrolysis in F-actin changes its affinity for F-actin-binding proteins. Second, for example at the nuclear periphery, actin might be present in short filaments that are sensitive to latrunculin A but are too short or diffuse to be recognized by phalloidin (FIG. 2b). In this situation actin would probably have a structural role. Finally, actin could be adopting a new oligomeric form in which the 2G2 epitope is exposed, which is not recognizable by phalloidin, but whose formation is inhibited by the latrunculins (FIG. 2c). Such a hypothetical structure could be consistent with a structural and/or an intranuclear trafficking role. Clearly, the testing of these models and/or the formulating of new models of nuclear actin function will require the elucidation of the actual structures of nuclear actin complexes, where they are located and with which proteins they are associated.

Concluding remarks

The body of evidence that is summarized above indicates that actin is present in the nucleus and implicates it in diverse functions, including transcription, nucleocytoplasmic transport, and chromatin and nuclear structure. Although quality-control issues regarding the potential for contamination and nonspecific binding of actin will, and should, remain a concern, it is important to continue to address the structure and function of actin in the nucleus. The generation of other monoclonal antibodies, such as 2G2, that specifically recognize nuclear actin and the identification of their epitopes should help to unravel the structural differences between nuclear and cytoplasmic actin that are so crucial to hypotheses about function. Such reagents might also be useful to 'fish out' other nuclear-specific actin-binding partners, a more complete catalogue of which would help to reveal the breadth of functions that actin might have in the nucleus. Identifying nuclear-specific actin-binding proteins *in vivo* will also lead to a better understanding of the structure of nuclear actin.

One surprisingly unexploited tool is the vast array of actin mutants that have been constructed, particularly in *S. cerevisiae*[51]. Although actin has been found in two chromatin-remodelling complexes in *S. cerevisiae*[30,31], there have been no reports in which the power of yeast genetics has been applied to the problem of nuclear actin, or that evaluated whether existing actin mutants have defects in yeast nuclear functions. For example, it might be possible to isolate actin mutants that carry out cytoplasmic but not nuclear functions and to examine their physical association with the relevant nuclear protein complexes.

In any case, what is most important is that moving away from the debate on whether nuclear actin exists should stimulate robust interactions between investigators who have traditionally seen themselves as separated by more than just a nuclear envelope. The future of actin in the nucleus might lie in the hands of those individuals who tap into the enormous body of intellectual and practical resources that have been accumulated over many decades of cytoplasmic actin investigation.

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Competing Interests Statement

The authors declare that they have no competing financial interests.

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