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Mechanisms of Nuclear Actin in Chromatin Remodeling Complexes

Prabodh Kapoor and Xueting Shen

Department of Molecular Carcinogenesis, Science Park Research Division, The University of Texas M.D. Anderson Cancer Center, Smithville TX 78957, USA

Abstract

The mystery of nuclear actin has puzzled biologists for decades largely due to the lack of defined experimental systems. However, the development of actin-containing chromatin modifying complexes as a defined genetic and biochemical system in the past decade has provided an unprecedented opportunity to dissect the mechanism of actin in the nucleus. While the established functions of actin mostly rely on its dynamic polymerization, the novel finding of actin's mechanism in the INO80 chromatin remodeling complex suggests a conceptually distinct mode of actin that functions as a monomer. In this review, we highlight the new paradigm and discuss how actin's interaction with chromatin suggests a fundamental divergence between conventional cytoplasmic actin and nuclear actin. Furthermore, we provide how this framework could be applied to investigations of nuclear actin in other actin-containing chromatin modifying complexes.

Keywords

Nuclear actin; Chromatin remodeling; INO80; SWR1; NuA4

A role for actin in the nucleus

Actin is one of the most abundant and most conserved proteins in the cell, and plays central roles in a wide range of cellular activities involving cell motility¹⁻⁴. Although the mechanisms of actin in the cytoplasm are well established, the existence of actin within the nucleus has been a controversial matter for many decades⁵⁻⁸. With the number of studies indicating association of actin with multiple nuclear complexes⁹⁻¹⁷, the existence of nuclear actin is now gradually being accepted. Recognizing the potential roles of actin in the cell nucleus has opened new avenues for dissecting the mechanisms of nuclear actin in various nuclear events.

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It is still unclear how conventional actin such as β -actin shuttles in and out of the nucleus, and the molecular mechanism of nuclear transport of actin remains vague. Preliminary evidence suggests that without a nuclear localization signal (NLS) in its primary sequence, actin is transported into the nucleus in complex with actin binding proteins such as cofilin that contains a NLS^{18, 19}. Moreover, actin has nuclear export signals (NES1 and NES2) in its primary sequence, which were shown to be functional and used to remove excess actin rapidly from the nucleus by the export receptor CRM1 (chromosome region maintenance) in yeast, and by the exportin-6 family of nuclear membrane receptor proteins in mammalian somatic nuclei^{16, 20, 21}. Within the nucleus, the identification of actin in several nuclear complexes implicates it in diverse nuclear activities including transcription, chromatin remodeling, RNA metabolism and nucleocytoplasmic trafficking^{17, 22-27}. A striking observation of nuclear actin in contrast to cytoplasmic actin is that it does not form large filamentous structures and that it associates with many actin-related proteins that are exclusively present inside the nucleus in a number of nuclear complexes. Together, these observations support the notion that nuclear actin has distinct functions and that it may be utilized in a different fashion compared to cytoplasmic actin.

Despite this accumulating evidence, the mechanisms of nuclear actin have remained elusive, largely due to the lack of defined biochemical and genetic systems in which the function of nuclear actin can be unambiguously demonstrated. In this review, we discuss recent advances in the development of well-defined nuclear complexes to address the role of actin in chromatin modification. We focus on the novel mechanism associated with the monomeric function of nuclear actin within chromatin remodeling complexes in contrast to its polymeric cytoplasmic counterpart.

Nuclear actin states: monomer, oligomers and polymers

In cytoplasm, actin exists in dynamic equilibrium between its two major physical states: globular actin (G-actin), which is the monomeric state of actin, and polymerized filamentous actin (F-actin). A key feature of cytoplasmic G-actin is its ability to polymerize and form F-actin. Controversy regarding the presence of nuclear actin started decades ago when researchers failed to detect filamentous actin (F-actin) in the nucleus using classical actin stains that decorate the extensive actin cytoskeleton framework in cytoplasm. As a result early observations for the biochemical copurification of actin with nuclear proteins were dismissed and were considered as cytoplasmic contaminations because actin constitutes a major protein content in the cytoplasm. However, several subsequent studies strongly argued for the presence of nuclear actin, and demonstrated that at least a fraction of actin can be found in the cell nucleus^{10-17, 28}. The presence of substantially less actin in the nucleus compared to in the cytoplasm raises the question of its potential physical states. Whether actin is able to form F-actin in the nucleus as it does in cytoplasm has remained controversial. Many of the proposed functions of actin remain speculative because we do not yet understand the major existing states of actin in the nucleus, which is a major obstacle in defining the mechanisms related to nuclear actin. Some studies suggest that nuclear actin adopts a distinct conformation that is not typically present in the cytoplasm. First, certain monoclonal antibodies against actin preferentially recognize actin in the nucleus over the cytoplasm. Second, nuclear actin oligomers that are recognized by 2G2 in *X. laevis* oocytes

are not stained by the classical actin staining drug phalloidin^{11, 29}. These observations indicate that nuclear actin is either monomeric or forms new oligomeric structures that are distinct from cytoplasmic actin filamentous structures. Given that the 2G2 epitope is buried in the F-actin structure, the 2G2 results argue against the presence of F-actin in the nucleus. Moreover, the presence of actin as a monomer in chromatin modifying complexes also supports the argument for the existence of a monomeric state of nuclear actin³⁰.

Furthermore, there is evidence supporting the existence of polymeric forms of nuclear actin as well. Early studies in isolated salamander nuclei showed that anti-actin antibodies or proteins that are known to sever conventional actin filaments, affected the transcription in lampbrush chromosomes, which was comparable to known transcription inhibitors. Moreover, antibodies against nuclear myosin-I colocalize and coimmunoprecipitate with mammalian RNA polymerase II and have been shown to inhibit transcription under *in vitro* conditions³¹⁻³³. Since myosin-I isoforms are monomeric motor proteins and are directed to the barbed end of actin filaments, these results indicate the involvement of a polymeric state of actin in transcription. Furthermore, a recent report has also suggested a serum-stimulated assembly of nuclear actin in a formin dependent manner³⁴.

So far, the studies using different experimental approaches argue that actin is a versatile protein with a high degree of structural plasticity and can adopt a variety of structural states depending on the specific ionic conditions or its interactions with other actin interacting proteins. In cytoplasmic events, monomeric G-actin and filamentous F-actin are the prevalent forms³⁵. However, there might be other structural states of actin in cells that have not yet been identified and characterized. Likewise, some ‘unconventional’ actin conformations might contribute especially to the multitude of functions executed by actin in the nucleus.

There are three non-exclusive models for the form of nuclear actin. First, in complexes such as chromatin remodeling complexes, actin seems to be monomeric, in which the ATPase activity of actin may be used as ‘conformational switch’ to facilitate interaction with chromatin and “turn-on” the activities of the complexes. Second, for example at the nuclear periphery, actin might be present in short filaments that are sensitive to latrunculin A but are too short to be recognized by phalloidin. In this state, actin could 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 its formation is inhibited by the latrunculins. Clearly, testing these models or formulating 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.

Nuclear actin in chromatin modifying complexes

The presence of actin in chromatin modifying complexes is one of the strongest lines of evidence for the presence of actin in the nucleus. Chromatin research in the past two decades has opened a unique opportunity to study nuclear actin, with the identification of many nuclear actin-containing chromatin modifying complexes including INO80, SWR1, NuA4 (TIP60 in higher organisms), and BAF^{10, 12-15, 17}. The mammalian BAF and *Drosophila*

BAP chromatin remodeling complexes were initially identified as containing an actin subunit^{14, 17}. However, studies of nuclear actin in these chromatin modifying complexes in higher organisms is difficult due to two limitations. First, the presence of multiple actin isoforms coded by separate actin genes makes genetic studies difficult and also complicates the interpretation of existing results. Second, the limited availability and high complexity of these complexes make it challenging to biochemically dissect actin mechanisms in mammalian actin-containing nuclear complexes.

The constraints associated with nuclear actin studies in higher eukaryotes can be overcome by utilizing lower eukaryotes such as yeast. Yeast has only one actin gene (*ACT1*), which allows the facile genetic analysis of actin mutants affecting nuclear functions without the complication of gene redundancy. In addition, these complexes have been extensively characterized biochemically, allowing for a wide range of biochemical analyses of nuclear actin as well. In yeast, there are three known actin-containing chromatin modifying complexes: the INO80 and SWR1 chromatin remodeling complexes and the NuA4 histone acetyltransferase complex (Box 1). Given the high degree of conservation of actin from yeast to human, yeast nuclear actin containing chromatin modifying complexes are one of the best systems, both genetically and biochemically, to address the fundamental role of nuclear actin in chromatin modification.

Nuclear actin as a monomer in the INO80 complex

The INO80 chromatin remodeling complex was first identified as a co-activator of genes involved in inositol metabolism, and is now known to also have significant roles during DNA repair, replication and cell cycle checkpoint control^{15, 36-40}. Although the exact function of actin in regulating these INO80 roles is unclear, new studies are emerging that suggest actin may play an important role in chromatin remodeling. Nuclear actin has been shown to form a functional module along with other actin-related proteins (Arps) including Arp4 and Arp8 in the INO80 complex, and this module has been shown to interact with chromatin during INO80-chromatin interaction. More recently, to uncover specifically the role of actin in chromatin remodeling, the yeast actin-containing INO80 system has been analyzed by using a series of conditional point mutations in actin that negatively affect INO80 remodeling^{30, 41}. It was observed that one mutation in subdomain 2 of actin (*act1-2*) reduced the ability of INO80 to bind and mobilize nucleosomes, whereas another mutation (*act1-1*) that affects actin polymerization had no significant effect on INO80 activity³⁰. It had already been shown earlier that the *act1-1* mutant impairs the ability of actin to polymerize and form filaments⁴², but in recent observations it has not been observed to affect the ability of INO80 to facilitate repair caused by hydroxylurea-induced DNA damage or to activate *PHO5* under low-phosphate conditions³⁰. Since the *act1-2* mutant showed defects in *PHO5* activation, the normal activation of *PHO5* in the absence of actin polymerization in the *act1-1* mutant suggests that actin, but not its polymerization, is required in INO80-mediated chromatin remodeling at the *PHO5* promoter or during DNA repair. Together, these genetic studies of actin mutants suggest a role for monomeric actin in INO80 chromatin remodeling³⁰.

Another key observation in the same studies involved the utilization of classical actin biochemistry through the use of actin structural probes and dynamic measurements of actin. These biochemical analyses to probe the microenvironment of actin within chromatin modifying complexes explain how actin remains a monomer in the INO80 complex and unveil surprising molecular mechanisms regarding nuclear actin in chromatin remodeling. The barbed, or '+', end of actin in INO80 was found to be inaccessible as it does not interact with profilin, which binds the barbed end of monomeric actin and sequesters it from the pool of polymerizing actin that forms filaments. These observations suggested that the barbed or growing end of actin in the INO80 complex is masked by other subunits, which likely prevents it from polymerization and associating with actin filaments.

Despite the masking of the barbed end, the pointed end of actin could potentially allow actin polymerization. Probing the pointed end of actin in the INO80 complex with DNase I, which binds to subdomain 2 of actin at the pointed end, suggested that subdomain 2 of actin in the INO80 complex is exposed to the solvent. However, when the INO80 complex interacts with its natural substrate, chromatin, subdomain 2 is no longer exposed. Further study showed that the pointed end of actin in INO80 likely interacts with the linker region of chromatin as assessed by protease mapping experiments. These results suggest that actin remains as a monomer in the INO80 complex along with other Arps to act as a binding surface with chromatin. Further, in the same study, measurements of subunit stoichiometry revealed that actin is present in a 1:1 ratio relative to Ino80, Arp8 and Arp4, consistent with one monomer of actin being bound to each INO80 complex. INO80 with a mutation at the pointed end of actin (*act1-2*) binds free DNA and nucleosomes containing extranucleosomal DNA three times less efficiently than it did with the wildtype INO80 complex. Consequently, the ability of INO80 to mobilize nucleosomes is deficient in the complex purified from *act1-2* strains compared to wildtype cells.

A separate study also showed that INO80 requires linker or extranucleosomal DNA to efficiently bind and mobilize nucleosomes⁴³, which is consistent with the pointed end of actin being involved in binding extranucleosomal DNA. Although actin alone does not bind DNA, the actin/arp module containing the helicase-SANT-associated (HSA) domain from Ino80, Arp8, Arp4 and actin has a much higher affinity for DNA than do the individual subunits⁴⁴, which suggests that other subunits might be involved in actin binding to linker DNA. Given that the actin/arp module is highly conserved and found in many chromatin modifying complexes, it can be argued that this actin/arp module could be universally used by chromatin remodeling complexes to contact linker or nucleosomal DNA.

Notably, all subunits of this actin/arp subcomplex, including the N-terminal region of the Ino80 ATPase that recruits the actin/arp module, are evolutionarily conserved, suggesting that this subcomplex represents a unique and ancient module used for INO80 chromatin remodeling. Because actin and Arp4 are consistently present in several chromatin modifying complexes, including INO80, SWR1 and NuA4^{10, 13, 15}, and the loss of Arp8 in the INO80 complex results in the loss of actin and Arp4⁴¹, it is possible that actin and Arp4 may form a dimer and that this dimer may represent a basic module involving nuclear actin. This actin-Arp4 module may also be used in combination with other Arps and proteins in chromatin modifying complexes. For example, the actin-Arp4 dimer may associate with Arp8 and the

N-terminal region of the Ino80 ATPase, thus forming the actin/arp module observed in the INO80 complex (Fig. 1). Similarly, the actin-Arp4 dimer may associate with other proteins to form functional modules in the SWR1 and NuA4 complexes. In yeast, the actin-Arp4 module may also have evolved into the less-conserved Arp7-Arp9 dimer found in the SWI/SNF and RSC chromatin remodeling complexes⁴⁵. Based on these observations, it can be postulated that actin and nuclear Arps in chromatin modifying complexes are used in a combinatorial fashion to suit specific functions.

Mechanism of nuclear actin in chromatin remodeling

Although nuclear actin has been shown to be involved in many nuclear processes, there is a general lack of tangible molecular mechanisms for nuclear actin, and two basic and significant questions remain; (i) How does actin participate in nuclear events mechanistically? (ii) Does actin polymerize inside the nucleus and use the dynamics of its assembly and disassembly to govern nuclear processes, as it does in most of the cellular processes in the cytoplasm?

Mechanism of nuclear actin in BAF and INO80 complex

Two, nonexclusive models of the mechanisms of nuclear actin in chromatin modifications exist. *In vitro* studies of the BAF chromatin remodeling complex suggest a model whereby nuclear actin-containing chromatin modifying complexes are anchored to actin filaments in a phosphoinositide-regulated fashion, and can move along these filaments by employing the dynamic assembly and disassembly of actin in these filaments⁴⁶. This model is reminiscent of the actin nucleation or branching mechanism of the Arp2/3 complex⁴⁷; however, its *in vivo* relevance remains to be demonstrated. Another model can be proposed from recent studies of the INO80 complex, in which monomeric actin serves as a functional subunit in chromatin modifying complexes and participates in chromatin modification by interacting directly with chromatin. This model does not involve the polymeric form of actin in the nucleus; instead, it requires a direct interaction between monomeric actin and the linker region of chromatin (Fig. 2). This model is also supported by recent biochemical and structural studies of subunits present in the actin/arp module of the INO80 complex^{44, 48, 49}. The studies of nuclear actin in INO80 mediated chromatin remodeling do not exclude the possibility that some aspects of nuclear actin function still require polymeric actin in the form of short oligomers or unconventional filaments. These observations support the hypothesis that nuclear actin may have differential mechanisms in distinct actin-containing chromatin modifying complexes.

Given that the Arp2/3 complex structurally mimics the actin dimer in a filament with the free barbed end to facilitate actin polymerization, it is plausible that the actin/arp subunits in chromatin modifying complexes could also mimic the function of Arp2/3 dimers in initiating actin polymerization⁵⁰. However, the orientation of nuclear actin in the INO80 complex differs from the orientation of cytoplasmic actin in the Arp2/3 complex. In the INO80 complex, the barbed end of actin is blocked by other INO80 subunits, preventing actin polymerization. The other pointed end of actin is exposed and could potentially be used for actin polymerization, but instead, it associates with chromatin through subdomain 2. We suggest actin acts as a chaperone to induce a conformational change in the INO80

complex upon its interaction with chromatin. Indeed, Arps such as Arp4 and Arp8 can bind to histones and prevent actin from polymerizing^{41, 51} suggesting that actin-containing chromatin modifying complexes such as INO80 may interact directly with chromatin at various points and locations during ATP-dependent chromatin remodeling. In this model, the actin/arp modules may serve as interaction surfaces or chaperones for chromatin. Because actin and Arps form distinct functional modules, it can be postulated that specific combinations of actin and Arps in the chromatin modifying complexes are involved in the direct binding of specific features of chromatin such as DNA, combinations of histones and histone variants or histone modifications (Fig. 1).

In ATP dependent chromatin remodeling complexes such as INO80, the binding of ATP with actin brings forth a conformational change⁵²⁻⁶⁰, suggesting that the interaction of ATP or chromatin with the actin/arp module could induce a 'conformational switch' in the structure of the INO80 complex required for INO80 chromatin remodeling. With the availability of the actin/arp module of the INO80 complex, probing a conformational change in the module upon interaction with substrates like ATP and DNA would help to explain the structure-function relationship of the actin/arp module in chromatin remodeling. Given that chromatin is also highly conserved evolutionarily, it can be proposed that a previously unrecognized yet fundamental function of actin is to interact directly with chromatin in the nucleus. Taken together, these new studies reveal fundamental mechanisms of actin in regulating chromatin and epigenetics and suggest that conventional actin has a separate chromatin regulation role as one of its fundamental functions since the emergence of eukaryotes.

Potential mechanism of nuclear actin in other chromatin remodeling complexes

Apart from ATP-dependent chromatin remodeling complexes such as INO80 and SWR1, actin is also a subunit of key histone acetyltransferase complexes such as NuA4¹⁰. Although the exact role of nuclear actin in SWR1 and NuA4 function remains undefined, since each complex contains actin and Arp4 subunits, it is plausible that they share the same actin mechanism. However, different actin mutations (*act1-2* vs. *act1-136*) show distinct effects on INO80 and NuA4³⁰: the *act1-2* mutation at subdomain 2 of actin affected INO80 function; however, the effect of *act1-2* on NuA4 function was relatively small. Interestingly, the *act1-136* mutation at subdomain 1 of actin, appears to affect NuA4 function³⁰. These results raise the interesting possibility that the mechanism of actin in NuA4 may be different from that of INO80 complex. As actin has a tendency to polymerize and form filaments, it is unknown whether actin dynamics is involved in NuA4 function or whether it participates as a monomer, as in the INO80 complex. Recent studies have shown that similar to Ino80, the HSA domain at the N-terminal region (residues 340–411) of Swr1, is sufficient to incorporate actin and Arp4, and thus can be considered as a binding platform for actin and Arp4⁴⁵. Since Arp4 is known to interact with histones or nucleosomes directly^{10, 61}, and actin has been implicated in interacting with the linker region of chromatin in INO80-chromatin complex³⁰, this module, like the INO80 complex, may also be involved in binding the conventional nucleosome.

In the case of SWR1, given that the actin/arp module of INO80 complex contains Arp8 as well, which is absent in SWR1, there may be some other subunits of SWR1 like Swc4 or Arp6 which may associate with actin and arp4 in the actin/arp module of SWR1. Moreover, there are some functional similarities between the *S. cerevisiae* SWR1 and INO80 complexes in that the *in vitro* remodeling activity of both complexes is dependent on their actin and Arps subunits^{30, 41, 62}. Therefore, both common and distinct mechanisms of actin/arp module in chromatin remodeling may exist among the different members of the INO80 subfamily.

Potential role of actin in chromatin remodeling dependent processes

Nuclear actin has been shown to be involved in many nuclear processes including transcription (Box 2), cell cycle and DNA damage repair. Recent evidence suggests that actin within chromatin remodeling complexes may play a role in some of these various cellular processes. During the initiation of transcription, nucleosome movements at the promoter require the activity of ATP dependent chromatin remodeling complexes⁶³⁻⁶⁸. However, how these complexes are targeted to specific genes is still a matter of investigation. Nonetheless, the present studies support the view that ATP dependent chromatin remodeling complexes utilize the energy of ATP hydrolysis to form a bulge of DNA on the surface of the nucleosome. This bulge of DNA can be extended by translocation to form a larger loop, which upon dissipation, can result in reverse translocation, a jump in the position of the nucleosome, or nucleosome sliding^{69, 70}. Although the mechanistic details for different remodelers may vary among the different classes of enzymes, such remodeling activity influences the accessibility of DNA at promoters during transcription initiation and in some cases suppresses cryptic initiation sites within the gene⁷¹. Chromatin remodeling complexes can positively and negatively regulate transcription⁶⁸, and the role of actin in transcription could be related to actin-containing chromatin modifying complexes.

In addition to nuclear actin, Arp4 has roles in DNA damage repair, DNA replication, transcriptional regulation, and chromatin organization⁷²⁻⁷⁴. Furthermore, temperature-sensitive alleles of arp4 cause defects in the G2-M phase transition⁷⁵. To better understand overlapping phenotypes and specific contributions of the shared module, a comprehensive genetic interaction network map of SWC4, YAF9, ARP4, and ACT1 has been constructed using both positive (suppression) and negative (synthetic sick or synthetic lethal) genetic interactions identified from high-throughput genetic interaction screens. The genetic interaction map revealed that the majority of interaction partners of the four-shared subunits could be categorized into three main biological functions: chromatin remodeling, transcription regulation, and ubiquitin dependent catabolic process⁷⁶⁻⁸¹. This corroborates the functions of SWR1 and NuA4 in chromatin modification and suggests that these four-shared subunits may play a central role in this process. Taken together, these genetic interactions provide important insights into the functional relationships between the shared subunits including actin and arps.

Concluding remarks

A long debate on the existence of actin in the nucleus for the past several decades has essentially concluded that a small fraction of cytoplasmic actin can access the nuclear compartment of the cell in a highly regulated fashion. Although nuclear actin has defined nuclear functions, the distinctive mechanisms of nuclear actin are still poorly understood and need to be investigated. Nonetheless, emerging evidence at least suggests that the physical state and perhaps conformation of nuclear actin might be different from cytoplasmic actin, owing to distinct solvent conditions and proteins with which nuclear actin is associated. Moreover, in the context of chromatin modifying complexes, recent findings suggest that in contrast to cytoplasmic actin, which relies on dynamic polymerization for functions, nuclear actin can participate as a monomer in INO80-mediated chromatin remodeling inside the nucleus. These observations provide key evidence for the differential mechanisms of nuclear actin in contrast to cytoplasmic actin.

Since actin and arps form a key functional module in various actin containing nuclear complexes and that this module can interact with DNA and histones in the chromatin, it can thus be postulated that binding of chromatin with the actin/arp module may induce a conformational change in the overall conformation of the complex required for its functional activity. As such, the study of the actin/arp module from various actin containing nuclear complexes concerning its association with chromatin may reveal the mechanistic role of nuclear actin and arps in chromatin modification. These studies will ultimately uncover the fundamental and highly conserved mechanisms of nuclear actin and Arps. In summary, defining the distinct mechanisms of nuclear actin in different nuclear complexes is needed to establish a new paradigm for nuclear actin as it has been established for its cytoplasmic counterpart.

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INO80 complex, SWR1 complex, and NuA4 complex

Among yeast chromatin remodeling complexes, three contain actin – INO80, SWR1, and NuA4 complex. The purified INO80 complex contains 15 subunits (Table 1, Fig. I), while the purified human INO80 complex (hINO80) contains orthologs of Ino80, actin, Rvb1, Rvb2, Arp4, Arp5, Arp8, Ies2 and Ies6, as well as five unique subunits⁸² (Table 1). Similar to its yeast counterpart, hINO80 complex exhibits DNA- and nucleosome-activated ATPase activity and ATP-dependent nucleosome remodeling activity^{15, 82}. The ATPase subunits of the INO80 subfamily are distinguished from other ATPases in the ISWI, SWI/SNF and CHD subfamilies owing to the presence of a spacer region (1018–1299) that splits the conserved ATPase domain (698–1450)⁸³. Alteration of the lysine to arginine (K737R) in the conserved GXGKT motif for nucleotide binding results in a non-functional INO80,⁸³. Moreover, INO80 complex purified from a strain carrying a K737A substitution also failed to show ATPase activity, DNA helicase activity, and the ability to rescue the *ino80* mutant phenotypes¹⁵ suggesting ATP-binding is essential for Ino80 function *in vivo*. Interestingly, INO80 complex appears to contain two specific modules. The actin/arp module containing actin, Arp4, Arp8, and Taf14 associates with the HSA domain at the N-terminus of core Ino80, whereas, the helicase module containing Rvb1, Rvb2, an Arp5 binds to the insertion region of split ATPase domain of Ino80. Conventional actin and Arps have been identified as highly stable subunits of the INO80 complex. The INO80 complex contains actin, Arp4, Arp5 and Arp8¹⁵, whereas Arp5 and Arp8 have so far only been found in the INO80 complex. Arp5 appears to associate with the complex independently of any other subunit, while Arp8 is necessary for the inclusion of actin and Arp4⁴¹. The functions of Arp5 and Arp8 appear to be important for the process of chromatin remodeling, since it has been shown that the phenotypes of *arp5* and *arp8* are similar to that of *ino80*.

The *S. cerevisiae* SWR1 complex co-purifies with the histone variant Htz1 (H2AZ in mammals), and has been found to specifically exchange histone H2A in nucleosomes for its variant H2AZ^{13, 80, 84}. The purified yeast SWR1 complex contains 14 subunits^{13, 85} (Table 1, Fig. Box1). Interestingly, actin, Arp4, Rvb1 and Rvb2 are shared subunits with INO80 complex, whereas actin, Arp4, Swc4 and Yaf9 are also shared with NuA4 complex^{15, 86}. Swr1 is the Swi2/Snf2-related core ATPase subunit with a split conserved ATPase domain, characteristic of the core ATPases of the INO80 subfamily. Similar to the INO80 complex, the SWR1 complex exhibits nucleosome stimulated ATPase activity¹³. Swr1 is the key catalytic subunit in the complex and is crucial for its function since the catalytic site mutant (K727G) of Swr1 fails to rescue the *swr1* null phenotype, and the SWR1 complex containing the Swr1 K727G mutation fails to catalyze replacement of H2A with H2AZ *in vitro*¹³. It has been shown that an N-terminal region (N2) ending just before the ATPase domain of Swr1 is responsible for the binding of actin, Arp4, Swc4, Swc5 and Yaf9, whereas, the conserved ATPase domain, including the insert region, is crucial for the association of other components, such as Swc2, Swc3, Rvb1, Rvb2, Arp6 and Swc6^{13, 85}. Arp4 has been shown to play a key structural role in SWR1 complex integrity. Arp4 is required for the association of several subunits, including actin, Bdf1, Yaf9, Swc4, Arp6, and Swc2. Arp4 is required for functional

H2AZ incorporation both *in vitro* and *in vivo*, and is therefore important part of histone replacement machinery of the SWR1 complex⁶².

The NuA4 complex is a major histone acetyltransferase linked to the global and targeted acetylation of histone tails⁸⁷⁻⁸⁹. The yeast NuA4 complex contains 13 stably associated proteins⁸⁹⁻⁹¹ (Table 1, Fig. Box1). Strikingly, out of the 13 components of yeast NuA4, 12 homologous proteins are found in the human complex Tip60^{86, 92} (Table 1). However, *ruvB*-like helicases (RUVBL1/2, Tip48/49, pontin/reptin) are proteins found in the human complex with no apparent equivalent in the yeast complex (Table 1). Among the set of stable stoichiometric subunits, the essential Esa1 protein was found as the catalytic HAT component⁹³. One attractive model for the close cooperation of SWR1 and NuA4 in H2A.Z deposition and acetylation involves the association of unique subunits of the two complexes with the four shared subunits acting as a docking platform to chromatin^{62, 84}. These subunits include actin, Arp4, Swc4, and Yaf9. Arp4, along with other nuclear actin-related proteins, and has been suggested to bind histones and may be implicated in the association of NuA4 to DNA-damage sites *in vivo*^{10, 41, 94}.

Figure I. Figure showing actin-containing chromatin modifying complexes in yeast comprising INO80, SWR1, and NuA4 complex. Act1 and Arp4 are the most common and shared subunits among all the three complexes.

Nuclear actin in transcription

Research on nuclear actin from the past decade has provided convincing evidence for the significant role of actin in transcription and regulation of gene expression. First, actin binds directly to all three classes of RNA polymerase, and is required for their full transcriptional activity^{22, 23, 27}. It has been found that actin is associated with actively transcribed genes and has an essential role in the initiation of transcription through participation in the formation of pre initiation complexes (PICs)⁹⁵. Actin appears to activate transcription by all three RNA polymerases present in eukaryotic cells, and has been suggested to play an integral part of both initiating and elongating polymerases. It has been proposed that actin interacts with one of the common subunits, RPABC2 or RPABC3, as well as indirectly associates with the C-terminal domain of RNA polymerase II²³. Actin participates not only in transcription bound to RNA polymerases, but it also recruits histone acetyltransferases such as, P2D10, during transcriptional elongation when bound directly or indirectly to the growing RNA⁹⁶.

Second, actin can bind and affect the activity of transcription factors by regulating their subcellular localization^{24, 97-99}. In this context, two mechanisms have been proposed: Monomeric actin might promote the cytoplasmic retention of transcriptional regulators by occluding their nuclear localization sequences. This is supported by a study showing G-actin binding to the MAL RPEL motifs that surround a nuclear localization signal²⁴. Alternatively, G-actin interacts with transcription factors in the nucleus and either renders the complex competent for nuclear exclusion or causes a conformational change that exposes nuclear export signals^{24, 98}.

Finally, actin associates with nascent mRNPs and participates in the recruitment of histone modifiers to transcribed genes¹⁰⁰⁻¹⁰³. Chromatin remodeling during transcriptional activation and the control of the nucleocytoplasmic distribution of transcription factors are regulatory mechanisms that operate on specific genes in response to extracellular stimuli. In contrast, the proposed role of actin in direct association with RNA polymerases, as well as its role in nascent pre-mRNPs, may be basal roles that are necessary for all transcription. The basal role of actin could be particularly important for certain types of genes, while it could be dispensable for others. It has been shown that actin can adopt different conformations when bound to ATP or ADP, or in association with actin-binding proteins, which suggests that the major function of actin at the molecular level is to act as an allosteric regulator in the remodeling of large multimolecular assemblies such as chromatin remodeling factors or transcription complexes^{96, 104}.

Highlights

1. Chromatin modifying complexes as a well-defined system to study nuclear actin.
2. In contrast to cytosolic actin, nuclear actin in INO80 complex functions as a monomer.
3. Nuclear actin with actin related proteins forms modules to interact with chromatin.
4. New insights into nuclear actin suggest a distinct paradigm from cytosolic actin.

Figure 1.

Figure showing actin/arp module of actin containing chromatin modifying complexes. The actin/arp module of INO80 complex comprises Act1, Arp4, Arp8, Taf14, and N-terminal region of Ino80. This functional module of INO80 complex interacts with nucleosomes in the chromatin, placing actin towards the linker region of chromatin, whereas Arp4 and Arp8 interact with canonical histones. However, the actin/arp module of SWR1 and NuA4 complexes are not completely characterized yet but seems to contain functionally complementing subunits as of INO80 complex. The flags on histones represent the modification on histone tails, which may be required for the interaction of actin/arp module with chromatin.

Figure 2.

Figure showing the model of actin mechanism in INO80 complex inside the nucleus, which is distinct from actin mechanism in Arp2/3 complex in the cytoplasm of cell. The barbed end (+) of actin in INO80 complex is masked by other subunits of the complex, which prevents its polymerization from the growing end while the pointed end (-) interacts with chromatin. This mechanism of actin inside nucleus allows it to function as a monomer in chromatin modification.

Table 1

Subunit composition of the actin-containing chromatin modifying complexes in yeast and human.

INO80 complex		SWR1 complex		NuA4 complex	
<i>S. cerevisiae</i>	<i>Homo sapiens</i>	<i>S. cerevisiae</i>	<i>Homo sapiens</i> (SRCAP)	<i>S. cerevisiae</i>	<i>Homo sapiens</i> (TIP60)
Ino80	Ino80	Swr1	SRCAP	Esa1	Tip60
Actin (Act1)	□-actin	Actin (Act1)	□-actin	Actin (Act1)	□-actin
Arp4	BAF53a	Arp4	BAF53a	Arp4	BAF53a
Taf14, Arp5, Arp8	Arp5, Arp8	Yaf9, Arp6, Swc4	GAS41, Arp6	Yaf9, Swc4	GAS41
Rvb1, Rvb2	RUVBL1, RUVBL2	Rvb1, Rvb2	Tip49a, Tip49b,	Tra1	TRRAP
Ies1, Ies2, Ies3, Ies4, Ies5, Ies6, Nhp10	Amida, CCDC95, FLJ20309, IES6,	Htz1, Bdf1, Swc2, Swc3, Swc5, Swc6, Swc7	H2A.Z, YL1, ZnF-HIT1, DMAP1	Yng2, Epl1, Eaf1, Eaf3, Eaf5, Eaf6, Eaf7	ING3, EPC1, MRG15, hEaf6, MRGBP, DMAP1