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Nuclear actin and actin-related proteins in chromatin dynamics

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Conventional actin and actin-related proteins (Arps) are members of the actin superfamily and are conserved throughout evolution. Although the cytoskeletal functions of cytoplasmic actin and Arps have been characterized extensively, the functions and mechanisms of nuclear actin and Arps are not yet well understood. Emerging evidence suggest that nuclear actin and Arps are involved in many nuclear processes, such as transcription and chromatin remodeling. Actin and Arps are subunits of multiple chromatin modifying complexes, and functionally contribute to chromatin modifications. Recent progress has been made in understanding nuclear actin and Arps in the context of chromatin regulation, suggesting potential mechanisms for their functions.

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The actin superfamily

Conventional actin and Arps represent an evolutionarily ancient and highly conserved group of proteins — the actin superfamily. Muller and colleagues have recently reunified and extended the identification and classification of Arps on the basis of a comparative genomic analysis of ~700 protein sequences. 11 Arp subfamilies have been identified and classified according to their sequence identity and similarity with conventional actin, with Arp1 being the most closely related to actin and Arp10 and Arp11 the least similar [1••].

Conventional actin is one of the major components of the cytoskeleton and its roles in the cytoplasm are well established. In addition to actin, at least eight Arp subfamilies are conserved from humans to yeast (Table 1). Arp1–Arp3, Arp10 and Arp11 encode cytoplasmic Arp proteins. Arp1, Arp10 and Arp11 are components of the dynein complex, which helps the dynein motor to

transport vesicles along the microtubule. Notably, Arp1 in the dynein complex is the only known Arp protein that is shown to form short actin-like filament. Arp2 and Arp3 can form a stable dimer in the Arp2/3 complex, which has been shown to function in actin filament nucleation and branching by mimicking the plus end of an actin filament [2,3]. Arp4–Arp9 are predominantly localized in the nucleus [4]. Recently, conventional actin and Arp4–Arp9 have been identified as stoichiometric subunits of multiple chromatin-modifying complexes. They are involved in chromatin modification, transcription regulation and DNA repair. Arp4, Arp5, Arp6 and Arp8 are present in several chromatin modifying complexes and are conserved evolutionarily. However, Arp7 and 9 appear to be specific to fungi, and may represent a duplication of the actin and Arp4 proteins [1]. Arp7 and Arp9 form a stable heterodimer that regulates the activity of the RSC and SWI/SNF complexes [5,6].

High sequence identity and similarity between Arps and actin suggest that the Arps are likely to have a common tertiary structure centered around a highly conserved ATPase domain: an ATP/ADP-binding pocket, known as the ‘actin fold’. In addition, all nuclear Arps contain internal insertions and/or N- or C-terminal extensions as subfamily determination signatures [1••]. These specific sequences may exhibit divergent surface features and confer additional specialized functions to each nuclear Arp. For instance, insertion II in yeast Arp4 appears to be responsible for binding to core histones [7]. The functions of these unique insertions in the Arps are likely to be key to the function of each nuclear Arp subfamily.

This review summarizes the recent advances in understanding the function of nuclear actin and Arps, with a focus on their roles in chromatin modifications.

Nuclear actin

While actin’s roles in the cytoskeleton and cytoplasm are well established, the existence of nuclear actin has been controversial for many decades, owing to the lack of definitive evidence. With the recent emerging evidence indicating association of actin with multiple nuclear complexes, the existence of nuclear actin is slowly being accepted. So far, actin has been implicated in many nuclear functions, such as transcription, mRNA processing, chromatin remodeling and nuclear matrix association ([8]; for review, see [9–11]). It is required for transcription by all three RNA polymerases (Pol I, II and III) [12–14]. Specifically, β -actin was demonstrated to be a component of RNA Pol II pre-initiation complexes (PIC). The interaction of actin-like MreB with RNA

Table 1

Summary of actin and actin-related proteins

Subfamily	Localization	Function	Organisms	Complexes
Actin	Cytoplasm	Cell skeleton, cell motility	Human to yeast	Microfilament, dynactin, Arp2/3 INO80, SWR1, NuA4, PIC, dBAP, BAF, dPBAP, hSWI/SNF, hPBAF, hp400, hTip60
	Nucleus	Transcription, mRNA processing, chromatin remodeling, nucleoskeleton	Human to yeast	
Arp1	Cytoplasm	Dynein motor function	Human to yeast	Dynactin
Arp2	Cytoplasm	Actin polymerization, actin filament branching	Human to yeast	Arp2/3
Arp3	Cytoplasm	Actin polymerization, actin filament branching	Human to yeast	Arp2/3
Arp4	Nucleus	Chromatin remodeling, histone binding	Human to yeast	INO80, SWR1, NuA4, dBAP, dPBAP, hSWI/SNF, hPBAF, hWINAC, hSRCAP, hp400, hTip60
Arp5	Nucleus	Chromatin remodeling	Human to yeast	INO80
Arp6	Nucleus	Chromatin remodeling, heterochromatin binding	Human to yeast	SWR1, dISWI, hSRCAP
Arp7	Nucleus	Chromatin remodeling	Yeast	SWI/SNF, RSC
Arp8	Nucleus	Chromatin remodeling, histone binding	Human to yeast	INO80
Arp9	Nucleus	Chromatin remodeling	Yeast	SWI/SNF, RSC
Arp10	Cytoplasm	Dynein motor function	Human to yeast	Dynactin
Arp11	Cytoplasm	Dynein motor function	Human to yeast	Dynactin

polymerase in *E. coli* [15] indicates that the association of actin with RNA polymerases might be conserved from prokaryotic to eukaryotic organisms. However, it remains unclear how actin physically interacts with the transcription machinery, how actin contributes to transcription mechanistically, and whether actin functions as monomers or polymers in the context of transcription. In the process of chromatin modifications, the actin-containing chromatin-modifying complexes appear to contain monomeric actin as a subunit. Although actin has been suggested to contribute to chromatin remodeling complex activities, for example in the BAF complex and INO80 complex [16,17], a definitive demonstration of actin contributing to chromatin remodeling is lacking, particularly *in vivo*.

Despite the many connections between actin and nuclear processes, the function, form and mechanisms of nuclear actin remain to be investigated. The actin pool in the nucleus contains monomeric, oligomeric and polymeric populations, as recently reported by McDonald and colleagues using FRAP [18]. It is possible that actin is involved in distinct nuclear functions in distinct forms. Whether its state is monomeric or polymeric, and whether it is ATP- or ADP-bound, may be determinant factors for its nuclear functions. Therefore, a universal model for nuclear actin function may not exist and novel mechanisms distinct from the known cytoplasmic actin mechanisms may be uncovered. In practice, monoclonal antibodies specific to particular actin conformations have been produced and extensively used in the nuclear actin research [19,20], and turn out to be a useful approach to address the links between actin forms and nuclear

functions. For example, the C4 actin antibody recognizes monomeric actin, and has been used to show actin in the nucleus by immuno-staining techniques. Although actin appears to be monomeric within chromatin modifying complexes, it has been reported that the actin-containing BAF complex can bind to F-actin *in vitro* [21]. It remains to be determined whether the actin in chromatin modifying complexes functions as a monomer or can form polymers, particularly *in vivo*. Nonetheless, in chromatin modifications, nuclear actin functions are clearly linked to the nuclear Arps, which are discussed below.

Arp4

Arp4 was the first Arp protein shown to be localized in the nucleus and its nuclear localization is evolutionarily conserved from human (ArpN α , ArpN β /BAF53) to yeast [22–24]. Arp4, together with conventional actin, exists as shared stoichiometric subunits in all known actin/Arp-containing chromatin remodeling and histone acetyltransferase complexes from human and *Drosophila* to yeast, except in members of the yeast SWI/SNF subfamily, which contain Arp7 and Arp9 (Table 1). *ARP4* is an essential gene in human and yeast cells [25], and Arp4 is structurally and functionally required for the integrity and functions of NuA4 and INO80 complexes [17,26].

Many studies support the idea that Arp4 functions both in activation and repression of gene transcription. For instance, certain *arp4* mutants identified using SPT phenotypes affect the activity of *his-912 δ* and some native promoters by decreasing their binding to the promoter regions [27]. In some *arp4* mutant strains, the transcription level of stress-response genes is up-regulated [28,29]

as a result of the defect in the transcriptional repression function of the NuA4 complex [30]. Although Arp4 is involved both positively and negatively in transcription, it probably mediates its effects only through the chromatin modifying complexes, since it is not found outside these complexes and, unlike actin, is not associated with basal transcription machinery. Similarly, since Arp4-containing chromatin modifying complexes has been implicated in DNA replication and DNA damage repair, Arp4 is implicated in these nuclear functions as well. For example, certain mutants of Arp4 are hypersensitive to hydroxyurea and ultraviolet irradiation [28].

In terms of the mechanisms underlying Arp4 functions, several lines of evidence suggest that Arp4 physically interacts with chromatin. Although no DNA binding activity was found for Arp4, it has ability to bind histones, histone modifications and nucleosomes. Arp4 was shown to interact with all core histones with different preferences. *In vitro*, GST–Arp4 insertion II fusion protein binds preferentially with chicken histones H3 and H2B, and yeast H3. Two-hybrid analysis of Arp4 insertion II showed its preferential interaction with H2A [7]. Furthermore, Arp4 has been shown to bind to histone H3, H4 and H2A N-terminal tails and to form a stable ternary complex with nucleosome [26]. Moreover, it was recently demonstrated that Arp4 plays a significant role in DNA double-strand break repair. Arp4 specifically interacts with H2A phosphoserine-129 (P-Ser-129) at the sites of DNA damage, promoting the binding of Arp4-containing complexes (NuA4, SWR1 and INO80) to chromatin to facilitate stepwise DNA repair [31].

In addition to its histone-binding ability, Arp4 is the only known nuclear Arp that has been shown to have ATP-binding ability dependent on the conserved ATP/ADP-binding pocket. The switch between ATP-unbound and -bound states appears to regulate Arp4 association to and dissociation from the NuA4 complex and possibly other nuclear complexes [32*]. This suggests the shift between these distinct states of Arp4 is correlated with the dynamics of chromatin modifying complexes [32*], and may serve as a mechanism to regulate these complexes. In conclusion, as a multifunctional nuclear protein, Arp4 is involved in many nuclear activities as a subunit of chromatin-modifying complexes, functioning to maintain the integrity and regulate the dynamics of these complexes and to target them to chromatin via its interaction with core histones. It is notable that actin and Arp4 are always present together in actin/Arp-containing chromatin modifying complexes, suggesting either that actin and Arp4 physically form a dimer, or that they might be functionally connected within these complexes.

Arp6

Unlike other nuclear Arps, which are mostly associated with transcriptional activation, Arp6 is required to

maintain gene silencing in heterochromatin. Consistent with the colocalization of *Drosophila* Arp6 and heterochromatin protein 1 (HP1) in pericentric heterochromatin, it was shown that human and chicken Arp6 interact with HP1 directly *in vitro*. Both studies also demonstrated that *Drosophila* and chicken Arp6 are expressed abundantly during early embryogenesis [33,34]. However, fission yeast $\Delta arp6$ mutant shows impaired transcriptional silencing at telomere but not centromere. Furthermore, Arp6 and the fission yeast HP1 ortholog, Swi6, function independently [35].

Recent findings show that Arp6 is a subunit of the SWR1 chromatin remodeling complex in budding yeast. The SWR1 chromatin remodeling complex specifically exchanges major histone H2A for histone variant H2AZ by hydrolysis of ATP [36]. Arp6 and Swc6, as subunits of SWR1 complex, are proposed to form a module that regulates the interaction with H2AZ [37*]. H2AZ is enriched in euchromatin regions near yeast telomere and at the HMR locus, and functions both in silencing antagonization, by preventing the spread of heterochromatin, and in silencing promotion, by contributing to the assembly of specialized chromatin structure [38,39].

Drosophila H2Av (H2AZ) is required for euchromatin silencing, HP1 recruitment and heterochromatin formation [37]. More interestingly, Rangasamy *et al.* reported that H2AZ is enriched in and functions to assemble pericentric heterochromatin during early mouse and human development [40,41]. Taken together, the localization and functions of Arp6 and H2AZ implicate Arp6-containing chromatin remodeling complexes — for example, SWR1 — in the formation of pericentric heterochromatin and/or telomere during early embryogenesis (in case of *Drosophila* and mammals). Currently, unlike actin and Arp4, Arp6 has not been found in other classes of chromatin remodeling complexes. Therefore, Arp6 may confer distinct activities for the SWR1 subfamily of complexes. In the SWR1 complex, Arp6 appears to be monomeric, and it may function by interacting with other proteins, rather than forming filaments. Although Arp6 does not appear to directly interact with H2AZ [37], it remains possible that Arp6 could interact with other features of chromatin.

Arp5 and Arp8

Arp5 and Arp8 are specific subunits of the conserved INO80 complexes. Both of them are mainly found within the INO80 complex in yeast (M Chen and X Shen, unpublished). $\Delta arp5$ and $\Delta arp8$ deletion mutants show $\Delta ino80$ mutant phenotypes, which is consistent with results showing that Arp5 and Arp8 are essential subunits for INO80 chromatin remodeling activities (DNA binding, nucleosome mobilization and ATPase activity) [17]. But mutations of the predicted ATP-binding sites in the actin fold of Arp5 and Arp8 have little or no effect on

INO80 function *in vivo* [17]. Like Arp4, Arp8 is able to bind to all four core histones *in vitro*. Arp8 showed preference for binding to H3 and H4 over H2A and H2B. It is possible that the prominent insertion regions of Arp8 might be responsible for the histone binding activity, as a similar mechanism has been revealed for Arp4 histone binding. Taken together, emerging evidence suggests that the nuclear Arps have histone chaperone functions, and may contribute to chromatin modifications by interacting with different histones or histone modifications [7,17,26,31].

Arp5 and Arp8 are not only important for the enzymatic function of INO80. Arp8 also plays a structural role in assembling other subunits into the INO80 complex. For instance, Arp8 is required for the association of Arp4, actin and Anc1 (Taf14) to the N-terminal region Ino80 protein [17]. This modular organization is also found in the SWRI complex. It has been proposed that the N-terminal region of Swr1 protein is also responsible for the association of Arp4, actin and three other subunits to the complex [37]. Conversely, INO80 ($\Delta arp5$) complex does not exhibit loss of actin and Arp4 [17]. Incorporation of Arp5 into INO80 complex requires both Rvb1/Rvb2 in an ATP-dependent manner [42]. Therefore, increasing evidence suggests that nuclear actin and Arps may form distinct modules in different chromatin-modifying complexes. These actin/Arp modules may be the fundamental structural units underlying nuclear actin/Arp functions.

There is no evidence that Arp5 and Arp8 are present in other complexes outside the INO80 complex, suggesting that these two conserved subfamilies of nuclear Arps have highly important and dedicated functions within the INO80 complex. Both Arp5 and Arp8 appear to be monomeric in the INO80 complex and may function in two distinct modules within the INO80 complex, as discussed above. One mechanism of Arp5 and Arp8 functions within these modules is to interact with histones and chromatin, as proposed for Arp4. In addition, Arp5 has the largest insertion (223 out of 755 amino acids) and Arp8 has the greatest number of insertions (881 amino acids) among all the Arps [1^{••},43]. These insertions may carry out their unique nuclear functions, distinct from those of the other nuclear Arps, by interacting with other non-histone proteins. These interactions in turn may target or regulate the INO80 complex in diverse nuclear functions, such as transcription and DNA repair [44,45].

Conclusions

During the past ten years, evidence for the existence of nuclear actin and Arps is steadily accumulating. Nuclear actin probably exists in multiple forms and is likely to perform distinct functions in the nucleus. In the context of chromatin-modifying complexes, we propose that nuclear actin functions as a part of actin/Arp modules within these complexes, and that these actin/Arp modules

interact with chromatin and other proteins. In this model, actin is likely to act as a monomer. However, it is possible that the mechanisms of actin participation in various other nuclear processes are highly distinct from the situation with chromatin modification, and may involve actin polymerization. Although chromatin modification was not the first nuclear process in which actin was implicated, recent studies in different organisms clearly show that nuclear actin and Arps are functional subunits of chromatin-modifying complexes, and these studies have established chromatin modification as a highly defined system for studying nuclear actin and Arps. Important goals for the future will be the further characterization of the structural and regulatory roles of nuclear actin and Arps in the context of chromatin-modifying complexes. By studying these distinct actin/Arp modules, we will understand the mechanisms of nuclear actin and Arps, and reveal fundamental similarities and differences between actin functions in and outside the cell nucleus. These studies will ultimately uncover the under-appreciated yet highly conserved nuclear functions of actin and Arps.

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