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ACTIN, ACTIN-BINDING PROTEINS, AND ACTIN-RELATED PROTEINS IN THE NUCLEUS

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ABSTRACT

Extensive research in the past decade has significantly broadened our view about the role actin plays in the life of the cell and added novel aspects to actin research. One of these new aspects is the discovery of the existence of nuclear actin which became evident only recently. Nuclear activities including transcriptional activation in the case of all three RNA polymerases, editing and nuclear export of mRNAs, and chromatin remodeling all depend on actin. It also became clear that there is a fine-tuned equilibrium between cytoplasmic and nuclear actin pools and that this balance is ensured by an export-import system dedicated to actin. After over half a century of research on conventional actin and its organizing partners in the cytoplasm, it was also an unexpected finding that the nucleus contains more than 30 actin-binding proteins and new classes of actin-related proteins which are not able to form filaments but had evolved nuclear-specific functions. The actin-binding and actin-related proteins in the nucleus have been linked to RNA transcription and processing, nuclear transport and chromatin remodeling. In this paper, we attempt to provide an overview of the wide range of information that is now available about actin, actin-binding, and actin-related proteins in the nucleus.

KEYWORDS

nucleus, nuclear actin, actin-related protein, ARP, actin-binding protein, ABP

INTRODUCTION

The nucleus was first observed by Antonie van Leeuwenhoek in 1719, but the function of the nucleus remained unclear in the following three hundred years (Sutton 1903; Boveri 1904; Morgan et al. 1915), and the first direct evidence for its function came only in 1962 (Gurdon 1962). The generally accepted view still holds that the nucleus is fundamentally different from the rest of the cell in respect of molecular composition, structure, and physical properties (Pederson and Marko 2014). Although the analysis of the cell nucleus still faces many technical difficulties and its compact organization is yet to be understood, current developments in understanding epigenetic regulation (Alexander and Lomvardas 2014; Meagher et al. 2009) and the discovery of nuclear bodies (Dundr 2012) or chromosome territories (Cremer and Cremer 2001) place the nucleus in the focus of broad scientific interest today. One of the most recent and significant findings in this field is the identification of surprisingly numerous cytoskeletal elements in the nucleus (Simon and Wilson 2011; Castano et al. 2010; Kumeta et al. 2012; Rajakyla and Vartiainen 2014). In this paper, we aim to discuss the most important members of this new world: nuclear actin, actin-binding proteins (ABPs), and actin-related proteins (ARPs) by summarizing their discovery and function in the nucleus with emphasis on the most recent advances on the field.

NUCLEAR ACTIN

Actin is one of the most abundant proteins found in all eukaryotic cells. It is a highly conserved globular, multi-functional protein that forms microfilaments in the cytoplasm. Research performed in the past decade has provided convincing evidence for the existence of actin in the cell nucleus and for the involvement of actin in fundamental nuclear functions (Fig. 1). In resting cells, actin localizes mainly to euchromatic regions at the border of heterochromatin blocks and in the fibrillar centers of nucleoli, the sites of rDNA transcription (Dingova et al. 2009). It has also become clear that the cytoplasmic and nuclear pools of actin are functionally linked; the nuclear and cytoplasmic actin pools are constantly being exchanged (Gieni and Hendzel 2009; Skarp and Vartiainen 2013). The actin protein lacks any nuclear localization (NLS) sequence, but it can translocate into the nucleus in monomeric form in complex with cofilin, an actin filament-disassembling protein, and importin 9 (Imp9); however, some data argue that cofilin plays a role in actin import only if high amounts of actin is needed in the nucleus (Miyamoto and Gurdon 2013). Actin contains two nuclear export sequences (NES) (Wada et al. 1998) and is exported from the nucleus in complex with the actin polymerization promoting protein profilin by the transport factor exportin 6 (Exp6) (Stuven et al. 2003; Bohnsack et al. 2006; Dopie et al. 2012). The nuclei of A375 human melanoma cells contain both β- and γ-actin forms, but β-actin exhibits a significantly higher nucleus-to-cytoplasm ratio than γ-actin in these cells which suggests differences in the regulation of the nuclear transport of different actin monomers (Migocka-Patrzalek et al. 2015).

Actin is transported in and out of the nucleus in globular (G-actin) form, but most of the traditional roles of actin in the cytoplasm rely on either actin filaments or their polymerization process; therefore, the form actin takes within the nucleus is an intriguing question. The first observations about actin forms in the nucleus supported the view that the majority of endogenous nuclear actin is in monomeric or in unique oligomeric forms (Schoenenberger et al. 2005). The facts that phalloidin, which specifically recognizes at least seven subunit long filaments, did not stain the nucleus and that nuclear actin filaments were not confirmed by electron microscopy also supported the conclusion that nuclear actin is monomeric (de Lanerolle and Serebryannyy 2011), and the most primitive functions of actin are nuclear and involve mono- and oligomeric forms. In fact, actin is functional

in many nuclear protein complexes in its unpolymerized form (reviewed in Grosse and Vartiainen 2013) which suggests a model that through its ATPase activity actin can promote conformational changes in these nuclear complexes, and this function is directly relevant in the nucleus (Wesolowska and Lenart 2015).

Evidences for nuclear filamentous actin (F-actin) came from studies in which actin-depolymerizing drugs or myosin inhibitors were found to disrupt nuclear processes. In addition, fluorescence correlation spectroscopy (FCS) and fluorescence recovery after photobleaching (FRAP) techniques revealed two actin pools in the nucleus: a mobile pool most likely formed by G-actin and a bound, immobile pool which contains not only nuclear complex-associated actin but also a significant amount (20%) of F-actin (McDonald et al. 2006; Dopie et al. 2012). Nuclear actin filaments are most likely formed by mechanisms similar to those in the cytoplasm (Kokai et al. 2014), but the regulation of polymerization is supposedly different in the two cellular compartments because the factors required for microfilament network formation are not constantly present in the nucleus; they shuttle continuously between the cytoplasm and the nucleus (Kumeta et al. 2012). Moreover, new regulators of actin polymerization have been identified recently in a genome-wide screen in Drosophila S2R+ cell nuclei among which the depletion of Nucleoporin 98, Capt or Lam proteins inhibited the formation of actin rods in the nucleus (Dopie et al. 2015). To date, F-actin structures have only been detected in the nucleus with antibodies that recognize unique actin conformations (Schoenenberger et al. 2005) and under specific conditions such as DMSO treatment (Fukui and Katsumaru 1980), heat shock (Nishida et al. 1987), ATP depletion (Pendleton et al. 2003), nucleus transplantation (Miyamoto et al. 2011), serum induction (Grosse and Vartiainen 2013), activation of the formin mDia in the nucleus (Baarlink et al. 2013), forced overexpression of nuclear actin (Kalendova et al. 2014; Kokai et al. 2014), cell spreading (Plessner et al. 2015), viral infection (Feierbach et al. 2006; Goley et al. 2006), or certain diseases (Bamburg et al. 2010; Munsie et al. 2011). Interestingly, the dynamics of actin network formation as well as the shape of the filaments are remarkably different in the case of different environmental conditions (Plessner et al. 2015; Belin et al. 2015) suggesting that complex and multiple mechanisms regulate actin polymerization in the nucleus. These observations together with the finding that many actin filament assembly proteins have nuclear functions (Weston et al. 2012) argue for the existence and essential roles of F-actin in the nucleus of resting cells as well.

In the nucleus, actin has been linked to a variety of processes including transcription and transcription regulation, RNA processing and export, chromatin organization and remodeling, DNA repair, or even nuclear envelope assembly (reviewed in: Castano et al. 2010; Miyamoto and Gurdon 2013; Percipalle 2013; Falahzadeh et al. 2015; Wesolowska and Lenart 2015). Research over the past decade has accumulated a large body of evidence to indicate that actin as well as its polymerization are essential for RNA transcription (Sjolinder et al. 2005; Vieu and Hernandez 2006; Yoo et al. 2007; Dundr et al. 2007; Miyamoto et al. 2011; Obrdlik and Percipalle 2011). Actin is required for the assembly of the RNA transcription complex, transcription initiation, and it interacts with both the unphosphorylated and the hypo- (PS5) and hyperphosphorylated (PS2) forms of RNA polymerase II (Pol2) (Hofmann et al. 2004; Kukalev et al. 2005; Obrdlik et al. 2008). Moreover, the expression of a mutant form of nuclear myosin 1 (NMI) that cannot bind actin results in the dissociation of Pol2, actin, and NMI from the promoter regions (Almuzzaini et al. 2015) indicating that during transcription actin performs its activity in cooperation with myosins.

Besides its direct involvement in transcription, actin has also been implicated in transcription regulatory processes. A recent genome-wide microarray analysis suggests a positive role for actin in gene expression

regulation (Yamazaki et al. 2015). The transcription regulatory activity of actin is often coupled to changes in cytoskeletal organization that alter the ratio between G- and F-actin forms which, in turn, leads to the activation or repression of factors capable of sensing monomeric or polymeric actin concentrations. One of the best studied example for this phenomenon is the regulation of the activity of serum response factor (SRF), which activates many cytoskeletal genes. In this signaling pathway, nuclear actin - in concert with cytoplasmic actin - can sequester or activate MAL, the G-actin-binding cofactor of SRF (Vartiainen et al. 2007; Baarlink et al. 2013; Esnault et al. 2014). A recent report shows that formins mDia1 and mDia2, which are involved in the polymerization of actin, also play a role in this process in the nucleus (Plessner et al. 2015). Other examples of G-actin level-sensing transcription regulation include the JMY protein which, together with p300, plays a central role in facilitating p53 response and the Hippo pathway, which includes the system of YAP and TAZ transcriptional activators (reviewed in Rajakyla and Vartiainen 2014; Wesolowska and Lenart 2015). The other way of transcription regulation by actin is the direct binding of nuclear F-actin to transcription regulatory complexes. The pathways that have been linked to the polymerization of nuclear actin include the retinoic acid (RA)-induced expression of the HoxB gene and the Nuclear co-repressor (NCoR) complex. The retinoic acid receptor (RAR) activates its target gene together with Prep-1, which binds β-actin (Diaz et al. 2007) and with N-WASP known to activate F-actin polymerization (Ferrai et al. 2009), while in the case of the Nuclear Co-Repressor (NCoR) complex the binding of F-actin to Coronin 2A induces the dissociation of the complex from silenced genes (Huang et al. 2011).

In eukaryotes, after transcription, the primary transcripts associate with proteins to form RNPs and undergo a series of modifications and subsequent nuclear export. Although actin is not able to bind RNA, its association with nuclear hnRNPs has been reported in various species (Brunel and Lelay 1979; Maundrell and Scherrer 1979; Gounon and Karsenti 1981; Percipalle et al. 2001; Percipalle et al. 2002; Obrdlik et al. 2008) suggesting a role for actin in RNA editing and transport. Actin was also found to participate in the nuclear export of viral proteins and RNAs through binding the eukaryotic initiation factor 5A (eIF-5A) (Hofmann et al. 2001) and of the small ribosomal subunit (SSU) protein S6 together with the NMI motor protein (Cisterna et al. 2006). However, actin co-localizes with only 10% of the SSUs in the nucleoplasm, indicating that actin-based movement and export of S6-containing subunits is only a part of the ribosomal export mechanisms. Actin associates with the nucleoplasmic filaments of nuclear pore complexes (Hofmann et al. 2001) and the nuclear pore-linked filament network (Kiseleva et al. 2004) further supporting the idea that actin plays a role in nuclear transport.

Actin is most likely involved in gene expression also as a component of chromatin-remodeling complexes. Not all chromatin remodeling complexes contain actin, but the ATP-dependent chromatin modifying complexes INO80, SWR1, BAF and the NuA4 histone acetyltransferase (HAT) multisubunit complex all contain actin from yeast to human (reviewed in Farrants 2008; Visa and Percipalle 2010). The INO80 complex contains actin and actin-related proteins which associate with the complex through the helicase-SANT–associated (HSA) domain in the core catalytic ATPase subunit (Szerlong et al. 2008). The association of phosphatidylinositol 4,5-bisphosphate (PIP2) with the SWI/SNF-like BAF nucleosome remodeling complex enables the complex to bind and stabilize actin filaments (Rando et al. 2002), which is required for maximal ATPase activity and chromatin binding of the machinery (Zhao et al. 1998). The interaction between actin and actin-related protein 4 (ARP4) within the BAF complex is essential for the integrity of the complex (Nishimoto et al. 2012). In Xenopus

oocytes, the binding of actin and the BAF complex to the regulatory region of the pluripotency gene *OCT4* is essential for the transcriptional reactivation of *OCT4* (Miyamoto et al. 2011). Moreover, this binding is enhanced by the Transducer of Cdc42-dependent actin assembly (Toca-1) protein, which promotes F-actin nucleation. The process of *OCT4* activation is not specific to Xenopus oocytes; it is conserved in vertebrates and among cell types (Yamazaki et al. 2015).

Recently, DNA repair has also been directly associated with nuclear actin. DNA damage induced with various types of genotoxic agents triggers the formation of actin filaments in the nucleus, and cells with lower levels of nuclear actin exhibit a reduction in DNA repair ability. The actin polymerizing factors Formin-2, Spire-1, and Spire-2 were found to be required for F-actin formation during DNA damage response (Belin et al. 2015).

ACTIN-BINDING PROTEINS IN THE NUCLEUS

It is becoming increasingly evident that not only actin and ARPs but also proteins involved in actin filament formation and function are found in the nucleus. To date, more than 30 ABPs have been identified in the nucleus that promote actin filament nucleation, organize actin filaments or sequester actin monomers (Castano et al. 2010; Weston et al. 2012). These nuclear ABPs are Titin, Emerin, Protein 4.1, Spectrins, Tropomyosin, ERM proteins, Myosins, Lamins, and Rho GTPase-regulated ABPs (Fig. 1), however, in most cases it is only assumed that they actually regulate actin in the nucleus. ABPs often co-localize with nuclear actin and are mostly found at the nuclear envelope and within the intranuclear space (Dingova et al. 2009). Their primary function is most likely the regulation of actin dynamics through controlling the amount of nuclear actin and fine-tuning the balance between monomeric and polymeric actin forms in the nucleus. These activities of ABPs control the engagement of actin in transcriptional regulation and reprogramming, which are achieved by direct involvement in polymerase-mediated transcription as well as through indirect mechanisms that rely on G- or F-actin (Miyamoto and Gurdon 2013; Hsiao et al. 2014). On the other hand, it is also possible that nuclear ABPs, together with actin, provide a platform for the assembly of molecular complexes and for their interactions in the nucleus (Visa and Percipalle 2010).

The largest known protein, *Titin* (also known as "connectin") (~3.8 MDa), composed primarily of a linear array of 240 fibronectin and immunoglobulin domains, localizes to the nucleus (Machado et al. 1998). It links Z and M lines in the sarcomere of striated muscle cells, but most eukaryotic cells also have a nuclear isoform of titin, which localizes to the chromatin and is essential for mitotic chromosome condensation and segregation (Machado and Andrew 2000). Titin binds actin (Trombitas and Granzier 1997; Linke et al. 2002), A- and B-type lamins (Zastrow et al. 2006) and interacts with histones H2A, H3 and H4 (King and Jhou 2010) in the nucleus. The N-terminal end of the titin protein contains a functional NLS motif and activates the WNT–β-catenin signaling pathway (Qi et al. 2008), while the proline-rich PEVK domain is responsible for actin binding in a Ca^{2+}-dependent manner; however, this interaction was found to be weaker and Ca^{2+}-independent in the case of skeletal PEVK (Linke et al. 2002).

Emerin is a serine-rich, single-pass inner nuclear membrane protein and a member of the nuclear lamina-associated protein family. It is known to interact with many nuclear proteins such as lamins (Clements et al. 2000), barrier-to-autointegration factor (BAF) (Lee et al. 2001), nesprins (Mislow et al. 2002), NMI (Holaska and Wilson 2007), HDAC3, and transcription factors β-catenin and Lmo7 (Berk et al. 2013); therefore emerin is supposed to be involved in chromatin organization and tethering chromosomes to the nuclear envelope. The F-

actin binding ability of emerin has been confirmed by multiple methods, and the putative actin-binding domain (between amino acid positions 46-222 in human emerin) overlaps with both the lamin- and the repressor-binding (GCL) domains (Lattanzi et al. 2003; Holaska et al. 2004; Holaska and Wilson 2007). Emerin promotes the formation of nuclear actin filaments: it stabilizes the growing actin filament *in vitro* by capping the pointed end (Holaska et al. 2004). In the nucleus, emerin - together with LaminA/C - regulates the activity of the SRF transcription factor by modulating the polymerization of actin (Ho et al. 2013).

Cytoplasmic *Protein 4.1* is essential for maintaining cell shape and membrane mechanical properties through stabilizing the interaction between spectrin and actin in skeletal structures (Diakowski et al. 2006). Protein 4.1 has a functional NLS, and it accumulates at the nuclear membrane in the nucleus, binds emerin, lamin A (Meyer et al. 2011), spectrins, and actin (Correas et al. 1986). A short motif of 8 amino acids (LKKNFMES) within the 10 kDa spectrin-actin-binding domain of 4.1R is responsible for the binding of protein 4.1 to actin (Gimm et al. 2002). The protein 4.1-actin interaction is necessary for nuclear assembly after mitosis (Krauss et al. 2003), and protein 4.1 is clearly important for nuclear structures and functions such as the centrosome - nuclear envelope interaction and the regulation of β-catenin activity (Meyer et al. 2011), however, the underlying mechanisms are unknown today.

Spectrin proteins are long cytoskeletal proteins that line the intracellular side of the plasma membrane. They crosslink F-actin filaments decorated with tropomyosin and protein 4.1, thereby forming an elastic meshwork in the cytoplasm which is essential for plasma membrane integrity and maintenance of the cell shape (Salomao et al. 2008). Three types of spectrins have been found in the nucleus: βIVΣ5, βII, and αII (Tse et al. 2001; Tang et al. 2003; Young and Kothary 2005, respectively). αII Spectrin plays a role in chromosome stability and telomere maintenance by being involved in the repair of DNA interstrand cross-links and is deficient in cells from patients with Fanconi anemia, which are defective in the ability to repair crosslinks (McMahon et al. 2009; Zhang et al. 2015). The F-actin binding of α and β spectrin heterodimers is carried out by the N-terminal calponin-homology domain of β-spectrins (Djinovic Carugo et al. 1997), and this interaction is greatly enhanced by PIP2 (An et al. 2005). The presence of tropomyosin (Dingova et al. 2009), spectrins, actin, and protein 4.1 in the nucleus indicates that, similarly to their cytoplasmic function, they might form an elastic network within the nucleus. Numerous other nuclear proteins, including nesprins, NuMA protein, and α-actinin, also have spectrin-repeat domains raising the possibility of an ancient nuclear function for the spectrin domain-containing proteins in the nucleus (Young and Kothary 2005).

The evolutionarily conserved *ERM protein* family consists of three closely related proteins, Ezrin, Radixin, and Moesin. The three paralogs are present in vertebrates, whereas other species have only one ERM gene. ERMs are major regulators of actin dynamics in the cell by crosslinking membrane proteins to the cortical actin network. They share a conserved N-terminal FERM domain responsible for protein binding and a C-terminal F-actin binding domain (Clucas and Valderrama 2014). Similarly to many other nuclear ABPs, their activity is regulated by PIP2 (Ben-Aissa et al. 2012). Genome-wide proteome analysis identified ERMs in the nuclear extract of human peripheral blood lymphocytes (Bergquist et al. 2001), and an immuno-cytochemical study revealed that all three human ERMs localize to the nucleus (Batchelor et al. 2004). Conserved nuclear localization sequences have also been determined (Krawetz and Kelly 2008; Batchelor et al. 2004).

Myosins are ATP-dependent conserved motor proteins responsible for actin-based motility (Kull and Endow 2013). Although seven different myosin proteins have been described in the nucleus (Simon and Wilson

2011; de Lanerolle and Serebryannyy 2011), only NMI, an isoform of cytoplasmic myosin 1C, has been studied in greater details so far. NMI was the first myosin to be detected in the nucleus (Pestic-Dragovich et al. 2000). The protein contains an NLS within the calmodulin-binding motif, which is also present in myosin 1C, raising the possibility that both protein isoforms are present in the nucleus (Dzijak et al. 2012). NMI associates with RNA polymerase I (Pol1) at active transcription sites (Philimonenko et al. 2004) and with the chromatin remodeling complex WSTF-SNF2h (Percipalle et al. 2006). In the nucleus, NMI cooperates with actin to assemble Pol1 at the promoter region (Grummt 2006), and it is part of the B-WICH multiprotein complex, which is involved in the post-initiation phase of Pol1 transcription (Percipalle et al. 2006; Sarshad et al. 2013). These results suggest that, together with actin, NMI drives the transcriptional machinery and, at the same time, maintains a permissive chromatin structure (Sarshad and Percipalle 2014). Other results indicate that nuclear actin and myosin play a role in maintaining nuclear structure by mediating chromatin arrangement and by interacting with the lamina (Sarshad and Percipalle 2014). MyosinII and myosinVI are involved in Pol2-, while myosinVb in Pol1-mediated gene transcription (Li and Sarna 2009; Vreugde et al. 2006; Lindsay and McCaffrey 2009), respectively). Myosin Va localizes to the nuclear speckles in cells, indicating a role in mRNA splicing (Pranchevicius et al. 2008).

The *nuclear lamina* is the best studied skeletal structure in the nucleus (Gruenbaum et al. 2005; Gerace and Huber 2012). Besides providing mechanical support, it holds the NPCs in place, participates in chromatin organization, and regulates important cellular events such as DNA replication, transcription, and cell division (Dechat et al. 2010; Ho and Lammerding 2012; Burke and Stewart 2013). In the nucleus, lamins have numerous interacting partners (54 was reported in the case of human lamin A and 30 for human lamin B proteins) and undergo many posttranslational modifications (reviewed in Simon and Wilson 2013). Both A- and B-type lamins were shown to directly bind and bundle F-actin *in vitro* (Simon et al. 2010). A conserved actin-binding site was mapped between residues 461-536 in lamin-A with 54% identity with the corresponding domain in lamin B, and a second actin-binding site was also identified in the tail region of lamin A (residues 564-608). Interestingly, the prelamin A tail binds F-actin less efficiently than the mature prelamin A tail, indicating that the residues 647–664, unique to prelamin A, might auto-inhibit the binding to actin (Simon et al. 2010).

Rho GTPases regulate many nuclear ABPs such as cofilin, profilin, formins, filamin-A (Fln), adenomatous polyposis coli (APC) protein, wiscott-aldrich syndrome family proteins (WASp, N-WASp, WAVE), α-actinin, and Thymosin-β4. Since Rho GTPase regulated nuclear ABPs have been summarized recently in excellent reviews (Rajakyla and Vartiainen 2014; Baarlink and Grosse 2014; Verboon et al. 2015), here we will only focus on the most important findings in this field. The role cofilin and profilin play in the nuclear transport of actin has been discussed above (Fig. 1). In the nucleus, cofilin has been linked to transcription elongation both directly (Obrdlik and Percipalle 2011) and in complex with actin (Dopie et al. 2012). Profilin is involved in the regulation of gene expression (Lederer et al. 2005), transcription (Soderberg et al. 2012), and mRNA splicing (Skare et al. 2003). Formin proteins, similarly to actin, are transported through the nuclear pores in a regulated fashion: in the case of mouse diaphanous homolog 2 (mDia2), with the help of Importinα and Crm1, and most likely in an autoinhibited conformation (Baarlink and Grosse 2014). In the nucleus, formins play a role in actin polymerization (Baarlink et al. 2013), Pol1-mediated transcription (Menard et al. 2006), and DNA damage repair (Belin et al. 2015). The dimer of filamin-A crosslinks actin filaments into networks, and, in the nucleus - together with actin - it is linked to the activity of the Pol1 transcription complex

(Deng et al. 2012) and to the repair mechanism of double-strand breaks (Yue et al. 2009). The Wiskott–Aldrich syndrome (WAS) family of proteins associate with actin, the small GTPase CDC42 or Rac1, known to regulate the formation of actin filaments, and the new actin filament-nucleating complex, Arp2/3. In WAS proteins, the VCA module located at the C-terminal end of the proteins is responsible for actin-related interactions. It contains three motifs: the verprolin homology motif (V/WH2), which binds actin monomers and delivers them to Arp2/3, the cofilin homology motif (C), which binds cofilin, and the acidic motif (A), which binds Arp2/3 (Lane et al. 2014). In the nucleus, WASp, N-WASp, and SCAR/WAVE are present and have been implicated as transcriptional regulators (Suetsugu and Takenawa 2003; Wu et al. 2006). In addition to transcriptional effects, *Drosophila* Wash is involved in the organization of the global nuclear architecture (Verboon et al. 2015).

ACTIN-RELATED PROTEINS IN THE NUCLEUS

ARPs belong to the ancient and divergent actin superfamily (Frankel and Mooseker 1996) together with conventional actins, heat shock proteins (e.g. hsp70), hexokinases, and numerous prokaryotic ATP binding proteins. All proteins in this superfamily form an actin fold (Kabsch and Holmes 1995), a well-defined tertiary structure consisting of two alpha-beta domains connected by a hinge region, which enables the proteins to undergo conformational shift in response to the hydrolysis state of ATP/ADP. The surprising feature of the actin fold is that this tertiary structure tolerates enormous sequence diversity, thus, proteins of the actin superfamily often form an almost superimposable X-ray structure without easily discernible sequence similarity (Flaherty et al. 1991). These specific structural alpha and beta subdomains of the actin fold and the capability of conformational change are thought to be crucial for the functions of actin superfamily members. All four conserved actin-like subdomains contain a five-stranded beta sheet of identical topology, suggesting that the molecules may have evolved by gene duplication (Kabsch and Holmes 1995).

Although all ARPs possess actin like features, they often share only modest sequence homology (15-70%) with conventional actins (Dion et al. 2010). ARPs do not show obvious homology with other protein families and unlike conventional actins, they are clearly divergent from each other. Based on their relative similarity to each other and their relationship to conventional actins, distinct classes of ARPs have been defined. It was proposed that the numbering and definition of different subfamilies of ARPs should be based on the degree of similarity to actin (Schroer et al. 1994), where ARP1s represent the most and ARP3s represent the least conserved proteins. Consequently, ARP1s typically show 47-69% amino acid identity to conventional actin and are characterized by small peptide insertions or deletions near to threonine 229 of actin. ARP2s share usually less than 47% identity to actin and contain one peptide insertion near alanine 321 of actin. Finally, ARP3s exhibit around 35% identity to actin and have four peptide insertions (Schroer et al. 1994). When the whole yeast genome sequence became available, six additional, even less conserved subfamilies of ARPs were defined (ARP4-ARP10) based primarily on sequences from *Saccharomyces* (Poch and Winsor 1997). Since then, only one new class of ARP (ARP11) was described (Eckley et al. 1999), but this group turned out to be fungal specific. This so called “orphan” ARP does not group into any of the known well-conserved subfamilies (Goodson and Hawse 2002). The nomenclature was later adopted in other organisms (Harata et al. 2001; Kato et al. 2001; Goodson and Hawse 2002).

The predicted molecular surfaces of the different classes of ARPs are surprisingly divergent, suggesting that they are likely to be involved in unique functions. Available crystal structures of ARPs support the simple

assumption that their basic 3D structure still holds recognizable actin-like features, while the inserted regions form distinct loops opening up the possibility for new interactions. Eight subfamilies of ARPs (ARP1-ARP8) are conserved enough to be recognizable among all eukaryotes (Muller et al. 2005). The discriminative characteristics of different ARPs enabled the development of a web server dedicated to the annotation of ARP sequences: ARPAnno (http://bips.u-strasbg.fr/ARPAnno) (Muller et al. 2005).

In the past decade, it has become apparent that certain ARPs localize not only to the cytoplasm but also to the nucleus (Kandasamy et al. 2005). A growing body of evidence supported nuclear location and functions for ARP4-9 first in yeast (Kandasamy et al. 2003; Deal et al. 2005), later in *Drosophila*, *Arabidopsis,* and mammals (Oma and Harata 2011). However, the nuclear localization in many cases turned out to be cell cycle-dependent (Kandasamy et al. 2003).

Nuclear ARP-coding genes contain single or multiple insertions, as compared to the actin genes (Muller et al. 2005; Kabsch and Holmes 1995). The inserted protein domains disable the polymerization ability of nuclear ARPs but, at the same time, allow them to interact with various protein partners (Ohfuchi et al. 2006) or to form hetero-duplexes with each other as in the case of ARP7 and ARP9 (Lobsiger et al. 2014). In ARP8, the insertions wrap over the active site cleft, rigidifying the domain architecture, which suggests allosterically controlled ATPase activity in this case. Plant nuclear ARP4, ARP5, ARP6, and ARP9 (found in *Arabidopsis* and rice) show strong homology to the corresponding yeast and mammalian ARP proteins (Kandasamy et al. 2004; McKinney et al. 2002), therefore, these four clades of ARPs certainly predate the divergence of the three kingdoms. However, in the case of Arabidopsis ARP7 and ARP8, the phylogenetic relationships to the corresponding ARPs in other eukaryotic kingdoms are not clear; therefore, these two nuclear ARPs of *Arabidopsis* have an orphaned status (Blessing et al. 2004). The uncertainty arises from the finding that protein sequence differences within ARP8 sequences from different kingdoms generally share less than 30% identity (Muller et al. 2005). These data indicate that for some reason ARP8 genes have evolved much more rapidly than other ARP sequences.

In the nucleus, ARPs have been linked to nucleosome remodeling (NR) (Cairns et al. 1998), histone acetylation (HAT), histone variant exchange (HVE) (Kumar and Wigge 2010), transcription regulation, and DNA repair (Weber et al. 1995; Grava et al. 2000; Blessing et al. 2004; Kandasamy et al. 2003; Deal et al. 2005). Surprisingly, the majority of the well-characterized chromatin-modifying complexes with ARP subunits (Fig. 2) also contain monomeric actin (Olave et al. 2002). Many hypotheses were put forward regarding the biochemical functions of ARPs and actin in nuclear NR, HVE, and HAT complexes, but no single function stands out as generally conserved (Blessing et al. 2004). Two major roles have been proposed for nuclear ARPs in chromatin remodeling. First, in some cases, they are responsible for recruiting chromatin remodeling and HAT complexes to the chromatin. This activity of ARPs depends on their specific binding capabilities. Arp4 and ARP8 homologues have been shown to bind core histones directly (Harata et al. 1999; Shen et al. 2003; Nishimoto et al. 2012; Gerhold et al. 2012; Saravanan et al. 2012), while yeast and human Arp8 homologues bind single-stranded DNA with low affinity (Osakabe et al. 2014). Secondly, it was proposed that the ATPase activity of ARPs is utilized in chromatin remodeling complexes (Table1). It is also likely that this activity of ARPs is performed most often only indirectly by activating the DNA-dependent ATPase subunit of the NR and HVE complexes, since available mutations in the predicted ATPase domains of yeast ARP7 and ARP9 did not alter the ATPase activity of the RSC or SWI/SNF-type complexes (Cairns et al. 1998; Szerlong et al. 2003).

Although, nuclear ARPs are detected primarily in chromatin remodeling complexes (Table 1), they often exhibit complex-independent functions as well. ARP6 was found to function independently of the SWR1 complex to regulate the expression of ribosomal genes through mediating their nuclear pore association (Yoshida et al. 2010). In Arabidopsis, ARP8 shows strong nucleolar localization as opposed to the prominent general nucleoplasmic localization of other ARPs (Kandasamy et al. 2008). Moreover, human ARP8 accumulates on the mitotic chromosomes and its depletion leads to chromosome misalignment during mitosis (Aoyama et al. 2008). But the existence of INO80 complex-independent functions of ARP8 is most likely not a general phenomenon, since yeast ARP8 mutants have milder but similar phenotypes than *Ino80* mutants (Shimada et al. 2008) without any apparent nucleolar or mitotic chromosomal localization. Finally, there are examples where ARP4 assisted by ARP8 is not only able to interact with nuclear actin but can depolymerize actin filaments (Fenn et al. 2011), providing additional evidence for the chromatin remodeling complex-independent function of nuclear ARPs.

It is still questionable that the interplay between cytoplasmic actin and myosin with cytoplasmic ARPs could model the nuclear function of these proteins. It is possible that, in the nucleus, they play a role in the long range organization of chromatin, large scale chromatin movements, and in the formation of chromosome territories (Dundr et al. 2007; Chuang et al. 2006; Mehta et al. 2010). The current extensive research on the field promises rapid progress in understanding the exact role of nuclear ARPs, actin, and myosin in long range chromatin organization.

CONCLUDING REMARKS

The research on the nuclear functions of actin, ABPs, and ARPs faces multiple challenges. Most of these proteins, including actin itself, have fundamental functions in the cytoplasm; therefore, elimination or any kind of modification of the proteins affect their activity in the cytoplasm as well. The faithful separation of cytoplasmic and nuclear functions does not seem possible at the moment. One way of solving this problem might be the manipulation of the nuclear transport of cytoskeletal elements, especially import, but in most cases these mechanisms have not been explored and, in addition, the transportins and transport mechanisms uncovered so far are not exclusively specific to them. Another great challenge in the field is the existence of many actin, ABP, and ARP protein isoforms arising from paralogous genes and/or alternative splicing. In vertebrates for instance, six actin isoforms are known, the primary structures of which are highly conserved, and cytoplasmic β- and γ-actin differ from each other in only four amino acids (Vandekerckhove and Weber 1978). But some ABPs (e.g. ERMs, myosins) and most ARPs are also encoded by very closely related genes and thus have highly overlapping functions.

The lack of molecular tools for the visualization of actin without disturbing its manifold functions and binding partners poses another difficulty. Many methods have been developed to detect actin in the cell (reviewed in Spracklen et al. 2014; Belin et al. 2014), but the low amount of actin in the nucleus, the majority of which is in G-actin form, and, more importantly, the observation that the actin-binding proteins used to detect actin and even the smallest modification of the actin protein perturb the kinetics and functionality of actin. Fluorescent derivatives of the heptapeptide phalloidin are used most commonly to visualize actin. But phalloidin needs at least seven actin subunits for binding, it does not penetrate the cell membrane, and is highly toxic making it less effective in experiments with living cells. The G-or F-actin binding domains of ABPs equipped with a fluorescent tag and often with an NLS are widely used (Edwards et al. 1997; Riedl et al. 2008; Burkel et

al. 2007; Belin and Mullins 2013; Johnson and Schell 2009), and recently actin-specific alpaca antibody coupled with GFP and NLS (nuclear actin-Chromobody) has been also developed (Plessner et al. 2015). Actin itself can also be labeled with various epitope tags, chemical fluorophores, or an additional NLS tag to target it to the nucleus. While numerous studies have shown the utility of these tools in analyzing actin structure and dynamics, they seem to interfere seriously with actin function (Aizawa et al. 1997; Roper et al. 2005; Chen et al. 2012; Spracklen et al. 2014).

All these difficulties explain the lack of direct experimental evidence for the nuclear functions of actin, ABPs, and ARPs, which in turn result in controversies in the field. New methods and a lot of effort are needed in the future to answer exciting questions such as for example: 1) What are the exact mechanisms that maintain the differences between the cytoplasmic and nuclear distribution and especially the function of actin, ABPs, and ARPs? 2) If actin and myosins form molecular motors in the nucleus, what role such an acto-myosin complex can play in gene expression and intranuclear transport?

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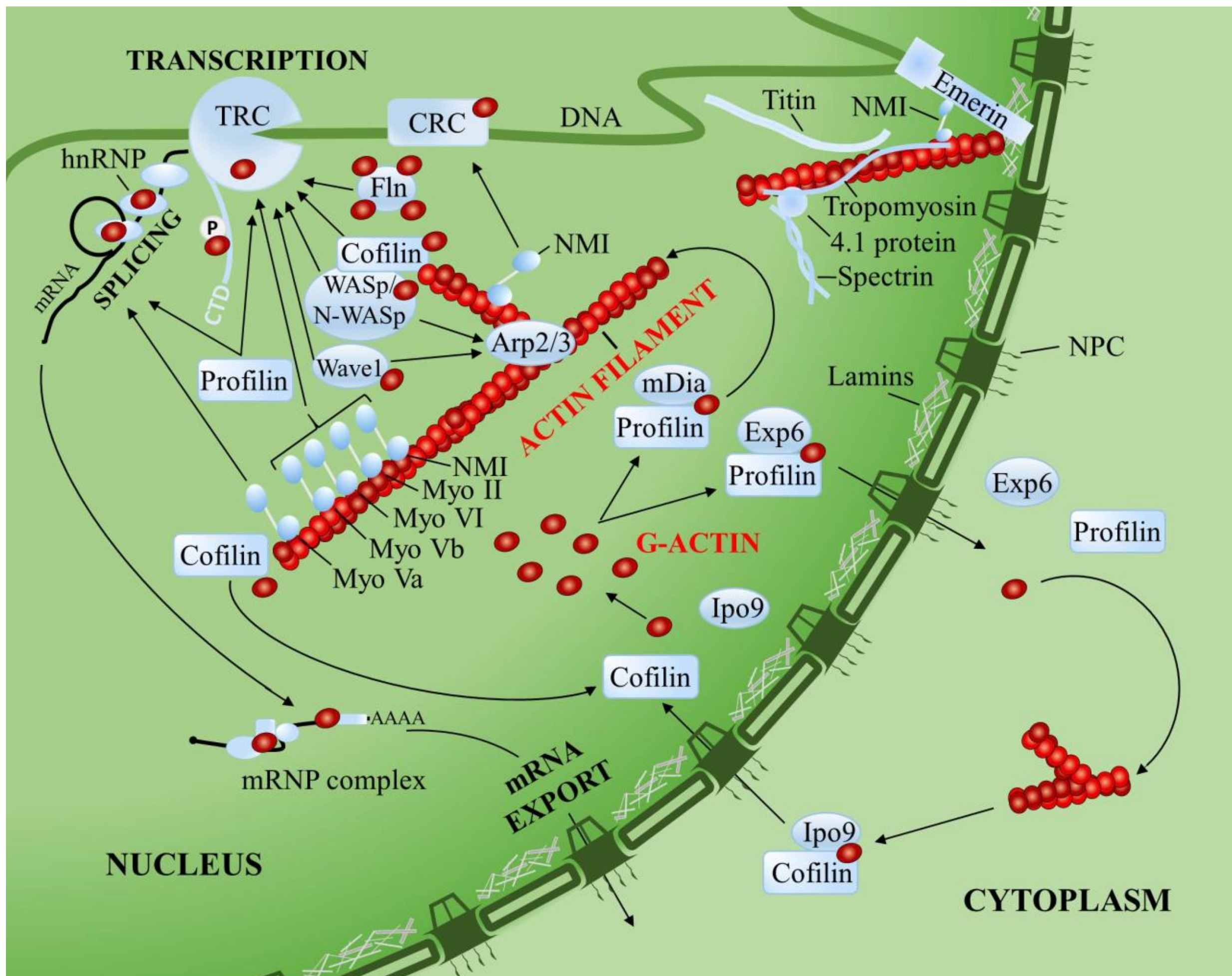

Fig. 1 Summary of the functions of actin and actin-binding proteins in the nucleus. For details see text. NPC-Nuclear Pore Complex, TRC – Transcription Complex, CRC – Chromatin Remodeling Complex, Fln – Filamin.

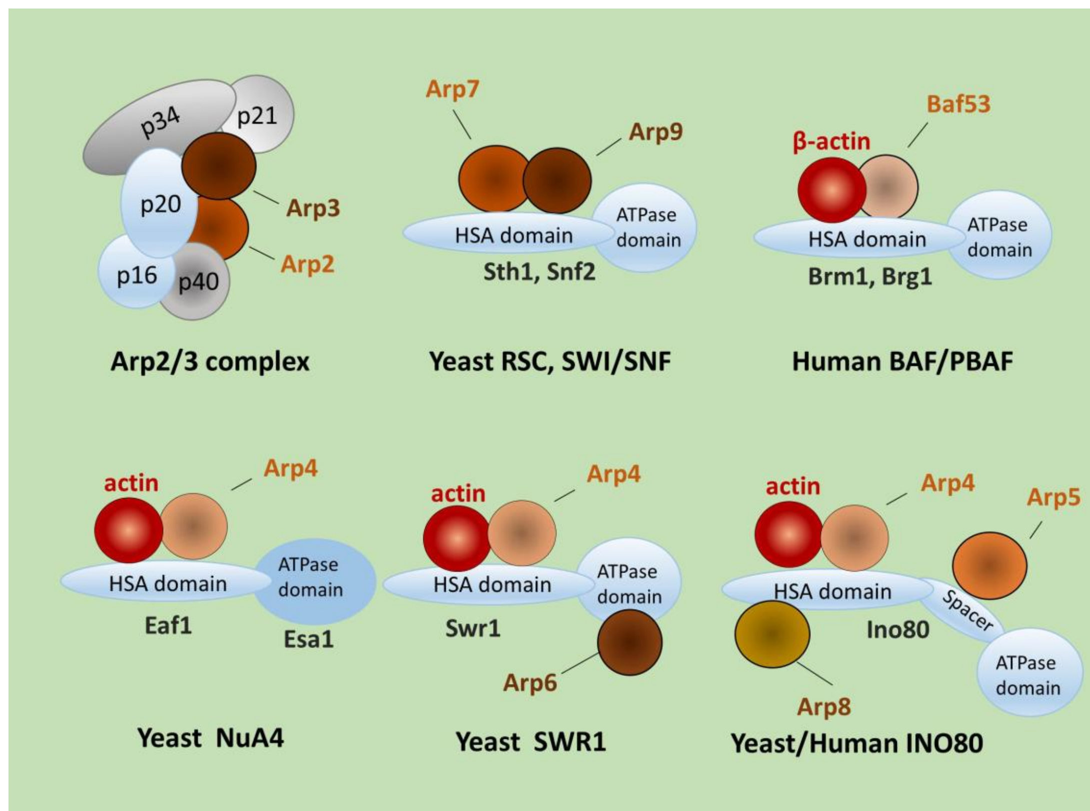

Fig. 2 Schematic representation of ARP-containing complexes in the nucleus. The ARP2/3 complex nucleates a new filament from the side of an already existing actin filament at 70˚ angle. In addition to ARP2 and ARP3, it contains five more proteins (Robinson et al. 2001; Doolittle et al. 2013) and requires additional nucleation promoting factors for its activity. The structure of the Arp2/3 complex is described in (Nolen et al. 2004). The assembly and composition of the complex is conserved among yeast, metazoans, and plants. The Arp2/3 complex was described first in the cytoplasm (Goley and Welch 2006), but it was also found in the nucleus of Arabidopsis pavement cells in a perinucleolar rod like pattern (Zhang et al. 2013), and it has been proposed that in the nucleus it can influence gene expression (Weston et al. 2012).

Composition and structure of other nuclear ARP-containing complexes vary substantially in different model organisms and even in different cell types of the same species (Kadoch and Crabtree 2015). Although, the structures of the INO80 and SWR complexes have been determined recently in yeast by electron microscopy coupled two dimensional class analysis (Watanabe et al. 2015; Tosi et al. 2013), the exact subunit topology of the different chromatin remodeling complexes is still obscure, due to the lack of crystallographic information about the holocomplexes. The main scaffold component in all of the complexes contains ATPase and HSA domains with the exception of the NuA4 complex, where the HSA domain lies in an associated Eaf1 subunit, not in the central ATPase Esa1 (Auger et al. 2008). ARPs are proposed to facilitate nucleosomal and DNA interactions of the complexes. The association of ARPs to the chromatin remodeling complexes is relatively well conserved, they generally form heterodimers with each other or with actin, and bind to the HSA domain of the central ATPase subunit of the given complex (Szerlong et al. 2008). However, the associations of ARP5 and ARP6 to the complexes are unusual because ARP5, together with the Rvb1-Rvb2 subunits (Jonsson et al. 2004), interacts with the conserved spacer region of INO80 (Yao et al. 2015), and ARP6 maps to the ATPase domain region of Swr1 (Wu et al. 2009).