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REVIEW

Actin complexes in the cell nucleus: new stones in an old field

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Abstract Actin is a well-known protein that has shown a myriad of activities in the cytoplasm. However, recent findings of actin involvement in nuclear processes are overwhelming. Actin complexes in the nucleus range from very dynamic chromatin-remodeling complexes to structural elements of the matrix with single partners known as actin-binding proteins (ABPs). This review summarizes the recent findings of actin-containing complexes in the nucleus. Particular attention is given to key processes like chromatin remodeling, transcription, DNA replication, nucleocytoplasmic transport and to actin roles in nuclear architecture. Understanding the mechanisms involving ABPs will definitely lead us to the principles of the regulation of gene expression performed via concerting nuclear and cytoplasmic processes.

Keywords Actin · Actin-binding proteins · Cell nucleus · Chromatin · Transcription · Replication · Nucleocytoplasmic transport · Nucleoskeleton · Regulation

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Introduction: the history of actin and actin-binding proteins in the nucleus

The relevance of actin in the nucleus has been demonstrated during the last few decades, changing the status from a controversial finding to an understanding that actin is a key protein required in several nuclear processes (Chen and Shen 2007; Schleicher and Jockusch 2008). However, the precise structure and mechanism of action of nuclear actin is still enigmatic. In the cytoplasm, actin forms a highly versatile and dynamic filamentous network, which is involved in shaping the cell, distributing the cellular organelles, cellular motility and adhesion just to name some key functions. In the nucleus, however, the situation is different: the notoriously known forms of polymeric actin existing in the cytoplasm have not been found (with some exceptions mentioned below) and actin forms, at most, short stretches of fibers which may represent atypical structures since they do not bind to phalloidin—a hallmark of filamentous actin (Cooper 1987). In addition to actin, there are several well-known actin-binding proteins (ABPs), which are of relevance in a myriad of processes in the cytoplasm (for reviews, see e.g. Insall and Machesky 2009; Pollard and Cooper 2009). Thus, ABPs anchor the actin network to the plasma membrane and other cellular structures, move cargo along the filaments, promote growth of actin fibers by capping the growing ends and shielding them from disassembly, promote the network arboring by branching the filaments, increase the strength of the filaments by bundling them or prune the network by severing and depolymerizing the filaments. Since most of these processes involve polymeric actin, it is quite interesting to note that many of these ABPs are also found in the nucleus. In recent years, the nuclear form of actin and its binding partners have been shown to take part in several key

cellular mechanisms. Table 1 shows a comprehensive list of ABPs that have been found in the nucleus. The large number of proteins fulfilling diverse functions in the cell is indicative of the complex function of nuclear actin. In this review, we will focus on the involvement of ABPs in some of the key nuclear processes: chromatin remodeling, transcription, DNA repair, DNA replication and formation and maintenance of nuclear structure. The facts about nuclear ABPs will be summarized and discussed in separate chapters according to these principal nuclear functions, and the activities of ABPs in the nucleus are schematically depicted in Figs. 1, 2.

ABPs in chromatin remodeling

Modification of chromatin is a key process during cell differentiation, DNA duplication and repair, as well as gene expression. These chromatin modifications are achieved by multi-subunit complexes that exhibit two kinds of activity. They are able to either move and/or replace nucleosomes on DNA strands (remodel chromatin) or mark histones or DNA with covalent modifications. Interestingly, actin and ABPs are part of both types of these complexes and this association is conserved from yeast to humans. In addition to actin, actin-related proteins (Arps) are very prominent components of chromatin-modifying complexes. Arps are actin-derived proteins, which share the same three-dimensional structure of ATP-binding pockets known as the "actin fold". They are classified into 11 subfamilies where Arp 1 is the most similar in sequence to conventional actin, and Arp 11 the least similar (Muller et al. 2005). Arps 4–9 are located in the nucleus and they have all been found to physically associate with chromatin-remodeling complexes. Out of four classes of chromatin remodelers SWI/SNF, ISWI, INO80 and Mi-2/CHD (Bao and Shen 2007), actin together with Arps are prominent parts of two of them: SWI/SNF and INO80. Originally, the association of actin and Arps with SWI/SNF-related remodelers was reported. Later actin and ARPs were found also in INO80 and related SWR1-associated complexes as well as in some histone acetyltransferases (reviewed by Chen and Shen 2007).

Arp4 (in humans one of the Brg1-associated factors, Baf53) is the most widely distributed Arp in chromatin-modifying complexes (for a review, see Meagher et al., 2009). It is present, depending on species, in SWI/SNF and INO80 complexes as well as in various histone acetyltransferases. Arp4 was found as a heterodimer with actin in SWI/SNF of Drosophila and humans, while in yeast SWI/SNF Arp 4/actin is replaced by Arp7/Arp9 dimer. The depletion of Arp4 by siRNA led to the expansion of chromosome territories and decompaction of the chromatin, reduction of H3-K9 dimethylation and an increase of H3-K79 methylation followed by cell cycle arrest. This suggests that Arps are essential for maintenance of global chromatin structure contributing to chromatin fiber folding and/or interactions with non-histone architectural components (Lee et al. 2007a). Arp4 accumulates in the nucleus prior to the onset of mitosis and associates with mitotic chromosomes suggesting that it might be involved in chromatin architecture transition during chromosome decompaction (Lee et al. 2007b). Furthermore, one of the histone acetyltransferases that contribute to chromatin remodeling and subsequent transcription—NuA4 (Doyon and Cote 2004)—is also found in complex with actin and Arp4 (Harata et al. 2002). In fission yeast, a point mutation in a conserved region of Arp4 homolog Alp5 lead to mitotic arrest caused by chromosome missegregation. This phenotype could be rescued by the addition of trichostatin A—an inhibitor of histone deacetylases of classes I and II. Fission yeast Arp4 forms a complex with the histone acetyltransferase Mst1. It was suggested that Arp4 is required for proper function of the kinetochore through its contribution to histone acetylation (Minoda et al. 2005).

In *Saccharomyces cerevisiae*, a second, more abundant SWI/SNF-like complex exists, which is known as RSC complex. Although RSC complexes contain SWI/SNF-like ATPase activity derived from the Sth1 subunit, biochemical studies suggest that SWI/SNF and RSC complexes regulate expression of distinct sets of genes (Szerlong et al. 2003). Arp7 and Arp9 are components of the RSC complex in yeast but homologs can also be found in plants. Arp7 is an essential gene in Arabidopsis required for normal embryo development and survival. Arp7 knockdown by siRNA affected plant architecture and considerably delayed abscission of floral organs (Kandasamy et al. 2005). Immunocytochemical studies showed nuclear localization of Arp7, while aberrant plant embryos did not have detectable levels of Arp7 protein in the nucleus. This data suggested the involvement of Arp7 in plant chromosomal rearrangement during cell development.

Arp6 is a component of INO80 class remodelers that seem to be involved in heterochromatin maintenance and transcription inhibition. In yeast, Arp6 binds to telomere DNA as shown by CHIP analysis (Ueno et al. 2004). Drosophila Arp4/Arp6 co-localizes with heterochromatin protein 1 (HP1) at the pericentric heterochromatin (Kato et al. 2001), and direct interaction of chicken and human Arp6 with HP1 was shown by pull-down experiments and yeast two-hybrid assays (Ohfuchi et al. 2006). On the other hand, Arp6 was also implicated in activation of transcription. For example, in plants, Arp6 has been shown to be required for high expression of FLOWERING LOCUS C in both FRIGIDA-containing lines and in autonomous

Table 1 Overview of actin-binding proteins in the nucleus

Name(s)	MW (kDa)	Organism	Structural domains	Relation to actin	Function in cytoplasm	Nuclear localization	Nuclear (expected) function
c-Abl	125	Animals	Alternative domain, Src-homology domain, SH3, SH2 domains, modular domain, tyrosine kinase, ATP binding, NLS, DNA binding, G- and F-actin binding, NES	Bundling, crosslinker	Signal transduction via non-receptor kinase activity (Van Etten 1999), actin bundling (Van Etten et al. 1994)	Diffuse nucleoplasmic (Nihira et al. 2008)	DNA damage response (regulation of cell cycle, apoptosis) (Wang 2000) proposed possible effect on transcription (Baskaran et al. 1993)
CABP14	260	*Caenorhabditis elegans*	Not determined		Participate in remodeling of cytoskeleton in early development of oocyte, cytokinesis (Aroian et al. 1997)	Along the cleavage furrow of dividing cells (Aroian et al. 1997)	Possible role in cell division (Aroian et al. 1997)
MAL cofactor	92	Eucaryotes	Cytoplasmic localizing domain, actin binding, NLS	Actin inhibits interaction of MAL with SRF	Signaling molecule (Miralles et al. 2003)	Diffuse nucleoplasmic (Posern et al. 2004)	Coactivator of SRF transcription factor (Vartiainen et al. 2007)
Thymosin $\beta 4$	4.9	Mammals	N-terminal helix, G-actin-binding domain, capping helix	Sequestering	Actin-sequestering, regulation of actin polymerization (Zoubek and Hannappel 2007)	Diffuse nucleoplasmic (Huff et al. 2004)	Actin-sequestering (Hannappel 2007)
Arp2	44	Eucaryota	Actin fold	Nucleation	De novo actin filament formation	Diffuse/punctuate nucleoplasmic and cytoplasmic (Yoo et al. 2007)	Possible bridge with N_WASP and PSF-NonO with RNA pol II (Yoo et al. 2007)
Arp3	49	Eucaryota	Actin fold	Nucleation	De novo actin filament formation	Diffuse/punctuate nucleoplasmic and cytoplasmic (Yoo et al. 2007)	Possible bridge with N_WASP and PSF-NonO with RNA pol II (Wu et al. 2006; Yoo et al. 2007)
Arp4	53	Eucaryota	Actin fold	Dimerizes with actin	Not described	Diffuse/punctate nucleoplasmic	Forms part of SWI2/snf2, INO80. INO80, SWR1, NuA4, dBAP, dPBAP, hSWI/SNF, hPBAF, hWINAC, hSRCAP,hp400, hTip60 Remodeling chromosome territories and decompactation of chromatin. Arp4 is the only known nuclear Arp that has been shown to have ATP-binding ability dependent on the conserved ATP/ADP-binding pocket (Chen and Shen 2007; Lee et al. 2003, 2007a, b)
Arp5	68	Eucaryota	Actin fold		Not described	Diffuse (Grava et al. 2000)	Forms part of INO80. Involve in replication (Shimada et al. 2008)
Arp6	50	Eucaryota	Actin fold		Not described		Forms part of SWR1, dISWI, hSRCAP (Chen and Shen 2007; Martin-Trillo et al., 2006)
Arp7	53	Fungi and plants	Actin fold		Not described		Forms part of RSC and SWI/SNF (Chen and Shen 2007)
Arp8	100	Eucaryota	Actin fold		Not described	Diffuse/punctuate nucleoplasmic during mitosis stains the chromosomes (Aoyama et al. 2008)	Forms part of INO80, depletion causes defects in chromosome misalignment during mitosis (Aoyama et al. 2008)
Arp9	51	Fungi and plants	Actin fold		Not described		Forms part of RSC and SWI/SNF chromatin-remodeling complexes (Chen and Shen 2007; Kandasamy et al. 2005; Szerlong et al. 2003)

Table 1 continued

Name(s)	MW (kDa)	Organism	Structural domains	Relation to actin	Function in cytoplasm	Nuclear localization	Nuclear (expected) function
N-WASP	54	Vertebrates	Verprolin-homology domain, a cofilin-homology domain, and an acidic region		Induce filopodium formation	Strong diffuse nucleoplasmic stain and cytoplasmic (Wu et al. 2006)	Interaction with RNA pol II ARP2/3, PSF-NonO (Linardopoulou et al. 2007; Rebowski et al. 2008; Wu et al. 2006)
WASP	52	Eucaryota	Verprolin-homology domain, a cofilin-homology domain, and an acidic region		Regulate actin filament organization, actin polymerization	Diffuse/punctuate nucleoplasmic (Moulding et al. 2007)	Chromatin remodeling
WAVE1,2,3	61, 54, 55, 92 in plants	Eucaryota	Verprolin-homology domain, a cofilin-homology domain, and an acidic region		Involved in actin reorganization in neural tissue, controls depolarization-induced trafficking of the mitochondria to dendritic spines WAVE2 regulating actin polymerization in response to T cell activation, particularly in the formation of the immunologic synapse		Chromatin remodeling
Actinin	100	Eucaryota	N-terminal actin-binding domain, two calponin homology (CH) domains, four spectrin repeats, four EF-hand calcium-binding domains, C-terminal calmodulin-like domain	Crosslinker	A-actinin 1,4 mediate membrane attachment at adherens-type junctions; A-actinin-2,3 are major structural components of Z-disk and analogous dense bodies where they cross-links actin filaments form adjacent sarcomeres	Regions of decondensed chromatin in nucleoplasm and in the granular component of nucleoli in HeLa cells; at interchromatin granules and nucleoli in human lymphocytes (Dingova et al. 2009)	Actinin 4 regulates DNaseY activity during apoptosis (Liu et al. 2004). A-actinin-4 co-localizes with p65/RelA subunit of NF-kappa B during cell activation by epidermal growth factor (EGF) (Babakov et al. 2008). Possibly involved in transcriptional regulation
Filamin	240–280	Eucaryota	N-terminus with two calponin homology domains (CH1 and CH2) followed by a rod region comprised of numerous repeat segments. C-terminal domain for dimerization	Crosslinker	Participate in stability of actin filaments at the cell periphery and link them to the plasma membrane, provide anchor of transmembrane receptors to the actin cytoskeleton and serve as a scaffold for many intracellular signaling molecules	Condensed and decondensed chromatin and nucleoli in HeLa cells, perichromatin in human lymphocytes (Dingova et al. 2009)	Interacts with the androgen receptor (AR) and inhibited transcriptional activity of AR (Loy et al. 2003; Ozanne et al. 2000). Plays an important role in Smad-mediated signaling (Sasaki et al. 2001). Associate with tumor suppressor protein BRCA2 (Meng et al. 2004) and FOXC1 (Berry et al. 2005)
Paxillin	68	Eucaryota	The N-terminus contains five aspartate-rich LD motifs and several SH2-binding domains. The C-terminus consists of four LIM domains	Binds actin	Adaptor protein that recruits a number of signal transducers to focal adhesions and transducing signals from integrins and growth factors to downstream regulation of cell migration and gene expression	Around interchromatin granules in HeLa cells; nucleoplasm in human lymphocytes (Dingova et al. 2009)	Assists in the translocation from the nucleus to focal adhesions for proteins such as Abl and STAT3 (Brown and Turner 2004). Expression of nuclear-localized paxillin LIM domains stimulateDNA synthesis and cell proliferation (Dong et al. 2009)
Spectrin II				Crosslinker		Nuclear in HepG2 hepatocytes	Regulation of Smad localization in the TGF-b signaling pathway (Kitisin et al. 2007)

Table 1 continued

Name(s)	MW (kDa)	Organism	Structural domains	Relation to actin	Function in cytoplasm	Nuclear localization	Nuclear (expected) function
Spectrin IIS	246–270	Eucaryota	Spectrin repeats, actin-binding domain (CH-domains), a pleckstrin homology (PH) domain, a Src homology 3 (SH3) domains, and a calmodulin-like domain	Crosslinker	Control membrane organization, stability and shape, participate in the trafficking of organelles along the secretory pathways, and play a role in regulated secretion	DNA-repair foci or diffuse nuclear in lymhoblastoid cells	Involved in DNA repair and act as scaffolding protein for DNA-repair proteins (Sridharan et al. 2003)
Spectrin IVS5				Crosslinker		PML nuclear bodies and the nuclear matrix (Tse et al. 2001)	Scaffolding for PML body proteins (Tse et al. 2001)
Myo16b	210	Vertebrates	N-terminal ankyrin repeat, motor domain, single IQ domain, and long tail with several polyproline stretches	Motor	Unknown	Punctuate nucleoplasmic (Cameron et al. 2007)	Unknown
Myo18b	285	Vertebrates	Motor domain, single IQ motif, and long tail with predicted coiled-coil regions, ERM domain, AAA domain, and NLS (Salamon et al. 2003)	Motor	Unknown	Cytoplasmic in myoblasts, diffuse nuclear in myocytes (Salamon et al. 2003)	Tumor suppressor (Nishioka et al. 2002)
Myo1c/NM1	120	Vertebrates	Motor domain, three IQ domains, PIP2-binding tail domain	Motor	Adjusting of the hearing sensors, exocytosis, axon growth	Diffuse/punctate nucleoplasmic	Transcription (Hofmann et al. 2006; Pestic-Dragovich et al. 2000; Philimonenko et al. 2004; Ye et al. 2008), chromatin remodeling (Percipalle et al. 2006)
Myo5a	200	Eucaryotes	Motor domain, 6 IQ domains, dilute domain	Motor	Vesicle transport and anchoring, spindle pole alignment and RNA translocation	Nuclear speckles (Pranchevicius et al. 2008)	Not known
Myo6	150	Metazoa	Motor domain, single IQ domain	Motor	Hearing, endocytosis, Golgi complex maintenance, cell motility	Punctate, colocalizes with transcription	Transcription (Vreugde et al. 2006)
Myopodin	80–95	Vertebrates	NLS	Bundling	Unknown	Diffuse nuclear excluding nucleoli in myoblasts, Z-discs in myocytes (Faul et al. 2007; Weins et al. 2001)	Tumor suppressor (Lin et al. 2001)
Syne/nesprin (NUANCE, enaptin)	1,014	Vertebrates	Interacts with chromatin structure regulator barrier-to-auto integration factor, presumably via the LEM domain	Bundling	ENAPTIN belongs to a family of recently identified giant proteins that associate with the F-actin cytoskeleton as well as the nuclear membrane		Integrate the cytoskeleton with the nucleoskeleton
Bpag1	630	Vertebrates	Multi-domain proteins that interacts with microtubules, actin filaments and intermediate filaments, as well as proteins found in cellular junctions		The dystonin/Bpag1 cytoskeletal interacting proteins play important roles in maintaining cytoarchitecture integrity in skin and in the neuromuscular system		Structural
Protein 4.1	80	Eukaryota		Binds actin	Stabilizes the spectrin-actin network and anchors it to the plasma membrane		Structural

Table 1 continued

Name(s)	MW (kDa)	Organism	Structural domains	Relation to actin	Function in cytoplasm	Nuclear localization	Nuclear (expected) function
Anillin	124	Eucaryota	ATPase domain	Binds actin	Bind septins and is a component of the cytokinetic ring	Diffuse/punctate nucleoplasmic	Localizes to the nucleus during interphase, the cortex following nuclear envelope breakdown, and the cleavage furrow during cytokinesis
Lamin A	75	Eucaryota		Binds actin		Nuclear envelope	Nuclear architecture
Emerin	34	Eutheria-mammals	LEM domain, transmembrane domain (Cai et al. 2007), NLS	Capping (Holaska et al. 2004)	Not described	Nuclear envelope (Fairley et al. 1999)	Maintenance of nuclear envelope
Enaptin	1,014 (predicted)	Bilateria-vertebrates and insects	N-terminal alpha actinin-type actin-binding domain, coiled coil rod - spectrin repeats, leucine zipper, C-terminal transmembrane domain, several NLSs	Bundling	Bundling of actin filaments, attachment of nucleus to the cytoskeleton	Nuclear envelope (Padmakumar et al. 2004)	Not known
Plastins	About 64	Eucaryota	EF-hands, Calponin homology actin-binding domains, NES (Delanote et al. 2005)	Crosslinking	Bundling of actin filaments	Diffuse nucleoplasmic	Not known
Tropomodulin	40	Vertebrates	Unstructured N-terminal domain, C-terminal domain contains several leucine repeats, NLS (Kong and Kedes 2004; Kong and Kedes 2006)	Capping	Stabilizing the pointed end of actin filament (Fischer and Fowler 2003)	Diffuse nucleoplasmic	Stabilizing pointed ends of actin filament?
CapG	38	Vertebrates	3 gelsolin-like repeat domains, NLS	Capping	Reversibly capping or blocking actin monomer exchange at the fast growing-barbed ends of actin filaments (Southwick and DiNubile 1986)	Diffuse nuclei and nucleoli (Onoda et al. 1993)	Promotes collagen invasion via modulation of transcription (De Corte et al. 2004)
Flightless I	145	Higher eucaryotes	NLS, NES, 6 gelsolin like repeat domains, 16 leucine-rich repeats (LRR)	Severing	Possessing filamentous actin severing activity via its gelsolin like repeat domains (Liu and Yin 1998)	Diffuse nuclear in fibroblasts (Davy et al. 2001)	Chromatin remodeling, nuclear receptor activation (Lee et al. 2004)
Gelsolin	90	Vertebrates	6 gelsolin-like repeat domains (LRR), 16 leucine-rich repeats	Severing, capping, nucleating	Severing actin filaments and capping the barbed ends, nucleating actin polymerization in a calcium dependent manner (Burtnick et al. 1997)	Diffuse nuclear staining in endothelial cells (Salazar et al. 1999)	Chromosome decondensation by severing actin in the nucleus (Ocampo et al. 2005). Androgen receptor co-activator (Nishimura et al. 2003)
Supervillin	205	Vertebrates	6 gelsolin like repeat domains, NLS, Headpiece domain (HD), Protein kinase A phosphorylation sites	Bundling	Inhibition of cell spreading by binding to myosin IIA and IIB, formation of actin filament bundles (Wulfkuhle et al. 1999)	Diffuse/punctuate nuclear (Pestonjamasp et al. 1997)	Nuclear receptor induced transcription, enhancing of vitamin D receptor activation (Ting et al. 2005)

Table 1 continued

Name(s)	MW (kDa)	Organism	Structural domains	Relation to actin	Function in cytoplasm	Nuclear localization	Nuclear (expected) function
Profilins	14–17	Eucaryotes vaccinia virus		Nucleotide exchange factor, increases polymerization	Regulation of actin dynamics at plasma membranes during cell locomotion, cytokinesis, embryonic development, morphogenesis. Intracellular vesicle trafficking. Endocytosis nad exocytoses at synapses (Jockusch et al. 2007)	Fine granular nucleoplasm staining (Rawe et al. 2006); nuclear gems (Sharma et al. 2005), speckles, Cajal bodies (Skare et al. 2003)	Cofactor of actin export from the nucleus mediated by exportin 6 (Stuven et al. 2003). Regulates the activity of Myb-related transcription factor p42POP (Lederer et al. 2005). Possible involvement in splicing (Skare et al. 2003). Tumor suppressor (Wittenmayer et al. 2004)
ADF/cofilin	15–21	Eucaryotes	ADF-homology (ADF-H) domain	Severing and pointed-end depolymerization	Cell motility, cytokinesis, endocytosis, exocytosis, phagocytosis, regulation of myofibril assembly. Involvement in actin-based motility of pathogenic bacteria (Ono 2007)	Localizes in intranuclear actin rods under stress conditions (Ono et al. 1996; Pendleton et al. 2003)	Chaperoning actin into the nucleus (Pendleton et al. 2003). Repressor of the glucocorticoid receptor (Ruegg et al. 2004)
CAP2		Eucaryotes		Sequestering	Mediator of a signal transduction pathway to actin cytoskeleton. Cell migration, endocytosis, embryonic development (Hubberstey and Mottillo 2002)	Diffuse excluding nucleoli (Peche et al. 2007)	Unknown

pathway mutants. In addition to FLOWERING LOCUS C, Arp6 regulates additional flowering repressors (Martin-Trillo et al. 2006). Arabidopsis Arp6 is located at specific regions of the nuclear periphery as demonstrated by confocal microscopy, and its subnuclear localization is different from that of TFL2, a plant homolog of HP1 (Choi et al. 2005). The mechanism of transcriptional regulation by Arp6 in plants seems to be via promoting both histone acetylation and methylation (Martin-Trillo et al. 2006).

To date, the structural organization and function of actin and Arp molecules in the chromatin remodeling and acetyltransferase complexes is unknown. It is possible that actin together with a myosin partner [Nuclear Myosin 1 (NM1), Myo1C or Myo6] may be needed as a motor for chromatin rearrangement or for the relocation of multi-complex transcription machinery. There is some evidence for the involvement of actin-based myosin motors in chromatin remodeling. During active transcription, 10% of cellular NM1 associates with the chromatin-remodeling complex Williams syndrome transcription factor (WSTF)-SNF2h (Cavellan et al. 2006; Percipalle et al. 2006). Together with several other nuclear proteins, WSTF-SNF2h and NM1 form a large 3-MDa complex referred to as B-WICH. SNF2h is a member of the ISWI family of chromatin-remodeling ATPases, and its functions depend largely on the protein complex in which it is contained. For instance, it partners with TIP5 to form nucleolar remodeling complex (NoRC), a chromatin-remodeling complex that sits on the promoters of unused ribosomal genes and inhibits their transcription (Santoro and Grummt 2005). WSTF associates with both ISWI and SWI/SNF chromatin-remodeling complexes. Together with SWI/SNF chromatin-remodeling complex, it is involved in regulation of vitamin D coupled transcription (Kitagawa et al. 2003). WSTF binds acetylated histones, mainly H3 acetylated at lysine 14, through its bromodomain and tethers the chromatin-remodeling/modification complexes to the promoter of vitamin D regulated genes (Fujiki et al. 2005). Because WSTF associates with two different chromatin-remodeling complexes, it was suggested that it acts as a platform tethering the complexes to chromatin (Kitagawa et al. 2003). NM1 was shown to co-purify and co-immunoprecipitate with WSTF-SNF2h. The complex also contained RNAs: Pol I transcript 45S rRNA and Pol III transcripts 5S rRNA and 7SL RNA (part of signal recognition particle SRP). NM1 was also found on rRNA, 5S and 7SL RNA genes by ChIP. Intriguingly, siRNA knockdown of WSTF decreases 5S and 7SL transcription (Cavellan et al. 2006). RNA Pol I transcription is inhibited by WSTF knockdown only on chromatin templates but not on naked DNA (Percipalle et al. 2006). It was possible to immunoprecipitate Pol I with the WSTF-SNF2h-NM1 complex, but only after in vivo crosslinking, which indicates that the association of the

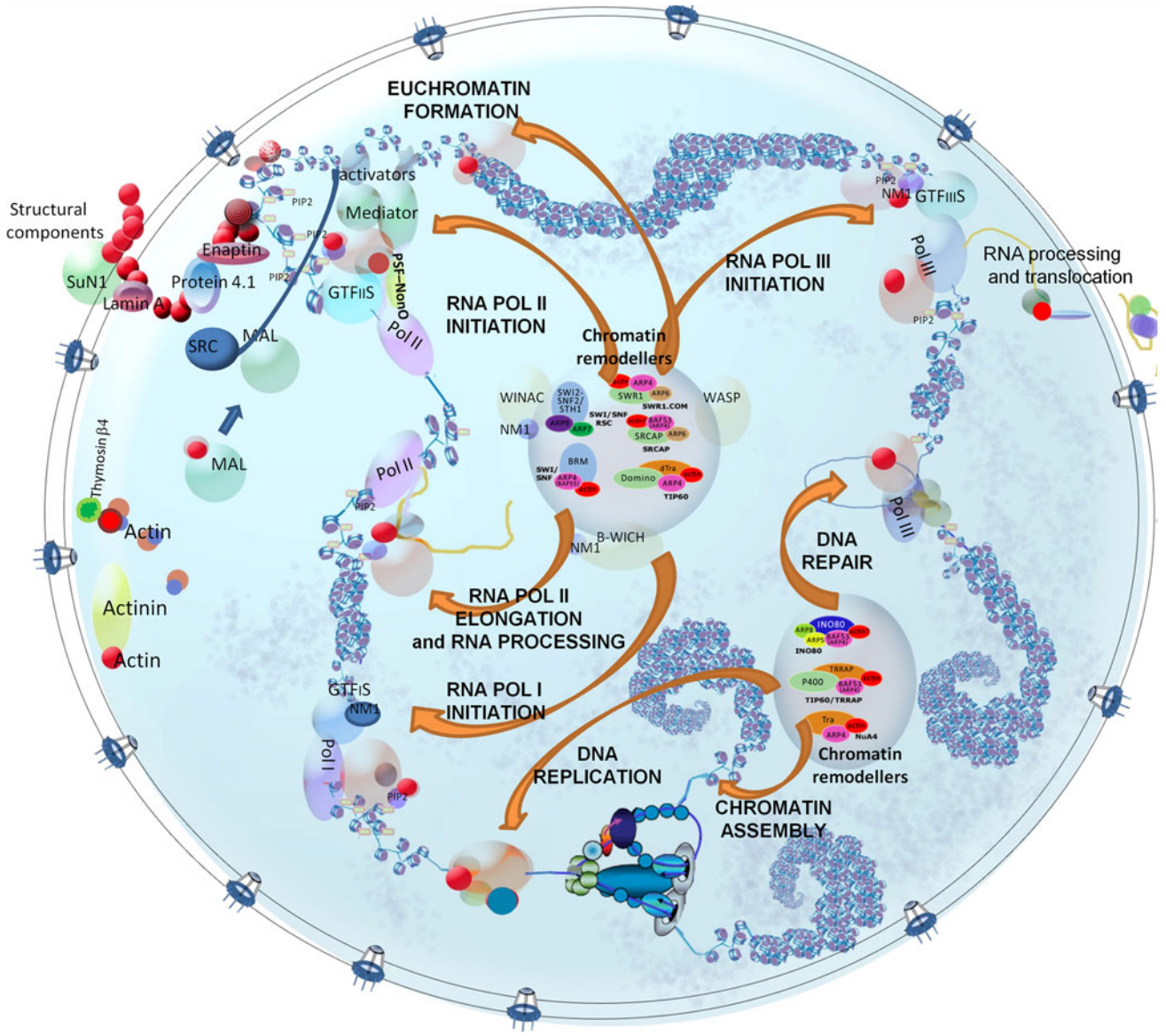

Fig. 1 The model depicts the nuclear processes involving actin and actin-binding proteins and actin complexes in chromatin remodeling, transcription initiation and elongation, DNA repair and replication. The center of the model shows a pool of complexes for chromatin remodeling that may interchange factors depending on the process. Actin may function as a key protein for interchanging such factors by bringing them together like a network that can be used in several processes in the nucleus

complex with RNA Pol I is relatively weak or very dynamic (Percipalle et al. 2006). Moreover, both activation and repression of ribosomal genes could be achieved by similar mechanisms. Ribosomal genes are repressed by NoRC, where TIP5 binds to transcription termination factor 1 on rDNA and brings SNF2h. SNF2h mobilizes histone deacetylases and DNA methyl transferases that modify the chromatin (Santoro and Grummt 2005). Conversely, WSTF could bring the SNF2h and associated factors to the rDNA to activate transcription, and the recruitment of WSTF itself could occur via NM1 or other ABP and the Pol I-bound actin (Grummt 2006; Percipalle and Farrants 2006).

A question remains how myosins would interact with nuclear actin to fulfill their motor function as they require a stretch of polymeric actin, and conventional F-actin is not readily formed in most nuclei. One possibility is that a "twisted" conformation of actin filament (so-called T-actin) is present in nuclei (Egelman 2003). This conformation is more favorable to binding of ADF/cofilin and does not allow tropomyosin binding with subsequent myosin recruitment. However, a few tropomyosin isoforms have been found to interact with actin filaments in the presence of cofilin (Kuhn and Bamburg 2008). It is yet to be explored whether these complexes also allow myosin

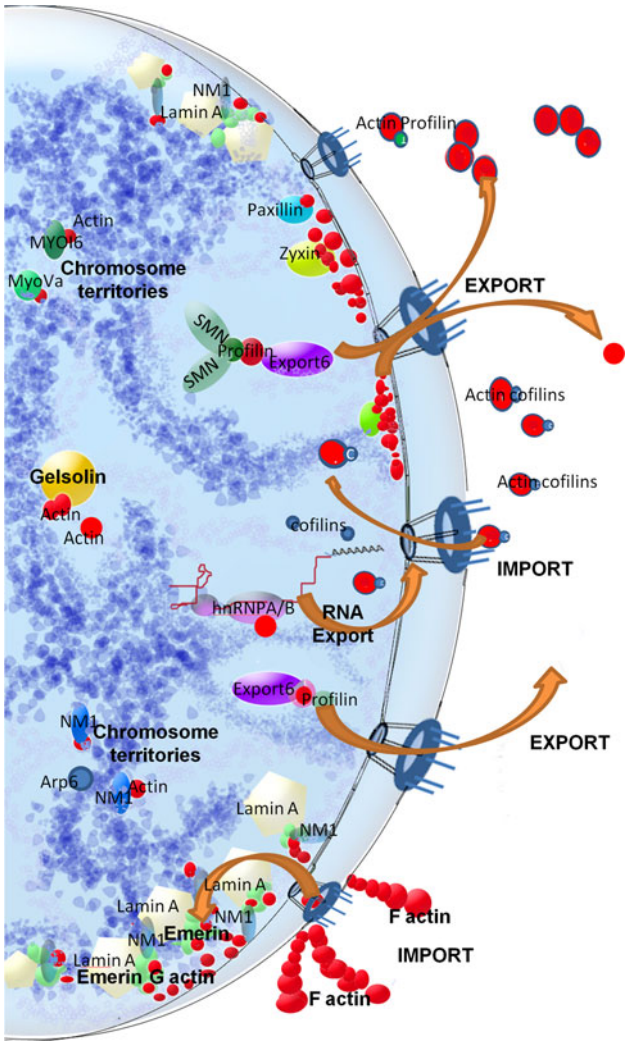

Fig. 2 The model shows actin and actin-binding proteins involved in nuclear structure, nucleocytoplasmic transport as well as chromosomal rearrangements. Actin is well known for its structural roles in the cytoplasm; however, mechanisms for the nuclear structure organization still need to be elucidated. Actin and actin-binding proteins have been shown to participate in such processes, either by a different form of actin polymerization or creating a link with different partners

binding. The fact that 2G2 antibodies, raised against actin–cofilin filaments, stain specifically nuclear actin (Gonsior et al. 1999) speaks in favor of such a model. Alternatively, actin and Arps could be used as bridges between different sets of chromatin remodelers. This would create a link for specific chromatin modifiers with ABPs to a network that can be used in several processes in the nucleus, where different modules can be exchanged depending on the function needed (Hogan and Varga-Weisz 2007). Nevertheless, it remains unclear how myosins could bind to such structures.

Babakov and co-workers (2004) found that α-actinin-4 co-localizes to the nucleus with p65/RelA subunit of NF-kappa B during cell activation by epidermal growth factor (EGF). Cell treatment with EGF leads to translocation of the proteins to membrane ruffles, and eventually to migration into the nucleus. Chakraborty and colleagues (2006) identified α-actinin-1 and -4 as class IIa HDAC-interacting proteins and isolated a novel splice variant of α-actinin-4 that is predominantly localized in the nucleus of HeLa cells.

FliI is a nuclear receptor coactivator, it contains gelsolin-like domain that can bind to actin. The same domain is important for the coactivator function. Co-immunoprecipitation experiments revealed FliI binding to BAF53 via the first of the two gelsolin-like motifs. A point mutation in the actin-binding motif of FliI reduced binding to BAF53 and substantially diminished the co-activator activity of FliI. Yeast two-hybrid screening assays demonstrated FliI binding to histone methyltransferase CARM1, which is a part of p160 coactivator complex (Lee et al. 2004). Based on these findings one can speculate that FliI may ensure the association of SWI/SNF complex to p160 to maintain ATP-dependent chromosome remodeling activity along with histone acetylation by histone acetyltransferase p300 and/or CBP and methylation by histone methyltransferase CARM1 and/or PRMT1.

In vitro studies of the binding properties of SWI/SNF-like BAF chromatin-remodeling complex to actin filaments revealed an interesting role of phosphatidylinositol 4,5-biphosphate (PIP2) (Rando et al. 2002). Isolated BAF complexes were able to associate with actin pointed ends and branch points upon binding to PIP2 micelles. The authors suggested a model where PIP2 binding relieved capping of actin associated with the BAF complex and therefore allowed actin filament binding. They provide some evidence that Brg1, which is also a component of BAF remodeling complex, could be this capping component. However, a role of another actin-capping protein cannot be excluded, and it was hypothesized that this protein could be CapG (Gettemans et al. 2005). CapG is a gelsolin family protein that has both nuclear and cytoplasmic localization (Onoda et al. 1993; Prendergast and Ziff 1991). One recent study shows CapG also in the nucleolus. This study indicates that transport of CapG to the nucleolus is an ATP-dependent process, which requires active RNA polymerase I transcription and translocation of Ran GTPase to the nucleolus along with CapG (Hubert et al. 2008).

All this data shows the relevance of ABPs in chromatin remodeling where they are required for several process as depicted in Fig. 1. However, recent transcriptional experiments using naked DNA templates have shown that actin and ABPs play additional roles in the control of gene expression, as outlined below.

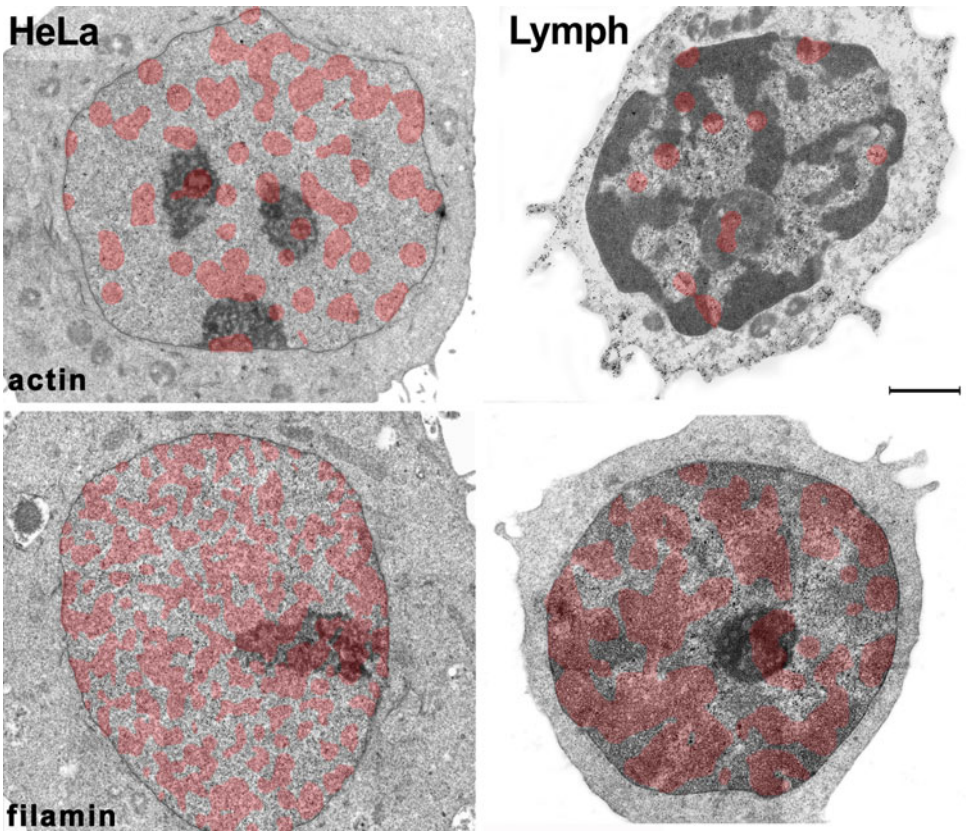

Fig. 3 The distribution of actin and filamin in the nuclei of transcriptionally active HeLa cells and resting human lymphocytes is compartment-specific. Actin labeling in HeLa cells is localized preferentially in decondensed chromatin and in the nucleolus. In resting human lymphocytes, clusters of actin labeling are located mainly in decondensed chromatin at the border of heterochromatin blocks. Filamin labeling in HeLa cells is intense and appears as a dense mesh throughout the whole nucleus, including nucleoli. In human lymphocytes, filamin clusters fuse together to form large labeled areas that occupy a significant proportion of condensed chromatin and perichromatin area but are mainly excluded from interchromatin granules. Ultrathin sections of cells were gold-immunolabeled with antibodies to actin and filamin, and the label density vas evaluated using our self-developed algorithms (Schöfer et al. 2004; http://nucleus.img.cas.cz/gold). The areas of increased labeling density in the nucleus are highlighted with *red* color. Labeling in cytoplasm is not depicted. *Bar* 1 μm. Reproduced from Dingova et al. 2009 with permission

ABPs in DNA transcription

Transcription initiation by all three polymerases was originally investigated at the level of transcriptional machinery recruitment. It became clear as early as in 70s, that polymerases alone were insufficient for this process. Roeder and colleagues were among the first to isolate a set of additional proteins essential for transcription—general transcription factors (GTFs). Their findings showed that GTFs are needed to sustain a low level of in vitro transcription on naked DNA with the addition of RNA polymerases (for a review, see Roeder 2005). Nevertheless, other additional factors are required for activating high-level transcription. Therefore, the hypothesis emerged for transcriptional regulation, in which regulation takes place not only at the promoter level but also at distant control elements, or enhancers. The activators bound to the enhancers were proposed to facilitate promoter initiation recruitment through coactivator mediation of activation signals and DNA looping to allow interaction of proteins bound to distal sites with the GTFs on the promoter. In some cases, it has been suggested that RNA pol II might relocate directly from the enhancer to the promoter during the activation process (Tchurikov et al. 2009). Tracking and looping requires a mechanical force in which actin-interacting molecules together with molecular motors like NM1 might be up to the task. Work by Yoo and colleagues (2007) showed that the Arp2/3 complex physically associates with RNA pol II and is involved in RNA pol II-dependent transcriptional regulation both in vivo and in vitro, as demonstrated by siRNA knockdown of Arp2 and Arp3. A further body of work suggests a bridge for Arp2/3 complex with Neuronal Wiskott–Aldrich syndrome protein (N-WASP) and PSF–NonO complex together with RNA pol II (Wu et al. 2006). It is conceivable that these proteins could properly position RNA pol II on the promoter. Some

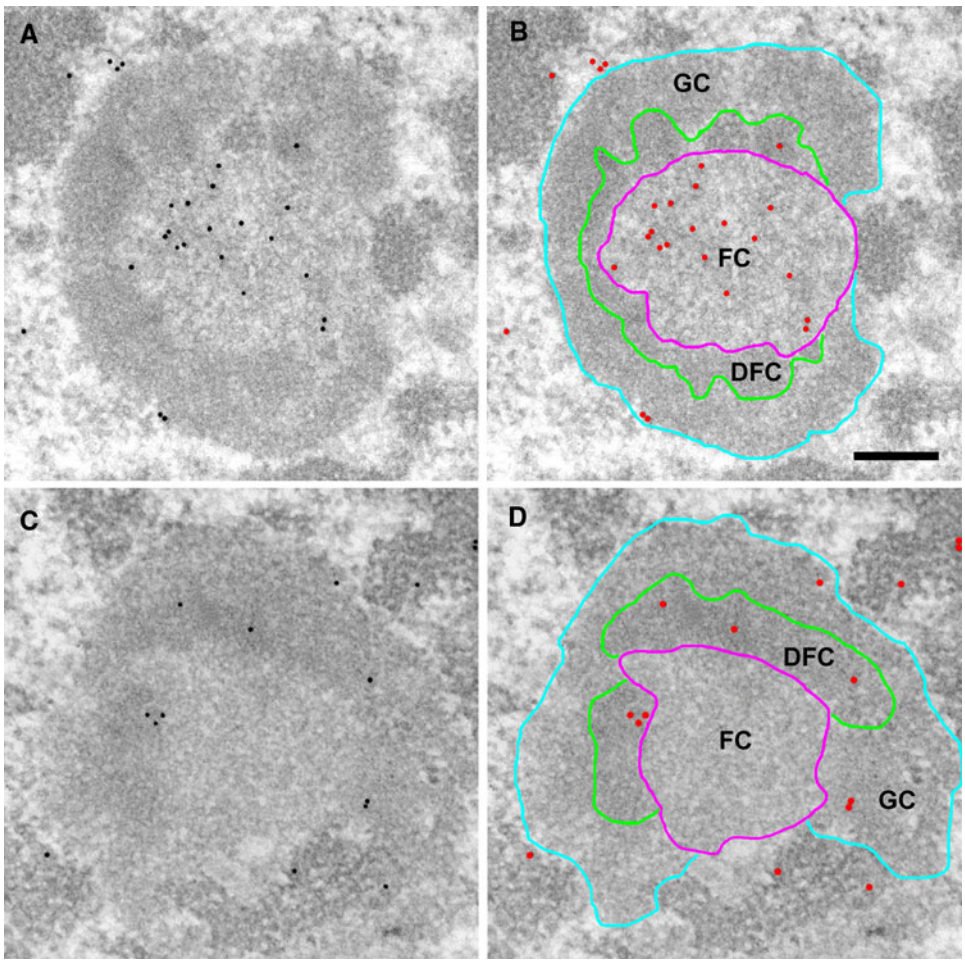

Fig. 4 Actin and NMI are localized in different nucleolar compartment in transcriptionally inactive human lymphocytes. **a** An electron micrograph of resting human lymphocyte nucleolus labeled with anti-actin antibody (12-nm gold particles). **b** The same image as **a**, but the nucleolar compartments are *outlined*. Fibrillar centers (FC), DFC and granular component (GC) are *marked*. Gold particles are highlighted in *red* color. FC is highly positive for actin. **c** An electron micrograph of resting human lymphocyte nucleolus labeled with anti-NMI antibody (12-nm gold particles). **d** The same image as **c**, the nucleolar components are *outlined* and gold particles are highlighted as in **b**. NMI is localized predominantly in DFC. *Bar* 200 nm. Reproduced from Kysela et al. 2005 with permission

experiments have emerged to sustain this hypothesis. It is known that Myo1c/NM1 can bind to actin via its head domain to exert physical tension or movement of their cargo and it was noted early on that NM1 can be found within sites of transcription activity of RNA polymerase I and II. Indeed, Hofmann and co-workers (2006) showed that NM1 colocalizes and copurifies with RNA pol II. Antibodies to NM1 inhibit Pol I in in vivo and in vitro transcription assays, while addition of NM1 activates RNA pol I transcription in vitro in a dose-dependent manner (Philimonenko et al. 2004). Microinjections of anti-NM1 antibodies reduce RNA pol II transcription in vivo. Interestingly, antibodies to NM1 added to reconstituted RNA pol II transcription system do not inhibit formation of the RNA pol II pre-initiation complex but block the formation of the first phosphodiester bond during transcription initiation (Hofmann et al. 2006). On the other hand, the experiments with RNA Pol I transcription in nuclear extracts indicate the involvement of NM1 in the later steps of transcription, such as promoter escape or elongation (Percipalle et al. 2006). Since NM1 can directly interact with actin and N-WASP-PSF-NonO-RNA Pol II, this may help the process of translocation from promoter regions to transcription sites within the nucleus, as well as for further fine positioning. However, the mechanism of how actin and NM1 may function within these processes has not yet been thoroughly tested.

Myo6 is another actin molecular motor recently found in the cell nucleus and it seems to have very similar properties to those of NM1. It colocalizes with RNA pol II and newly transcribed mRNA in a transcription-dependent manner, co-immunoprecipitates with RNA pol II complex, it is present at the promoter and coding region of active genes; knockdown of Myo6 inhibits transcription of these genes, and antibodies to Myo6 reduce RNA pol II transcription in vitro (Vreugde et al. 2006). Myo6 can also interact with RNA pol II, apparently dimerizing upon cargo binding and in this manner gaining processivity, i.e. the ability to "walk" many steps along a single actin filament before dissociating. Myo6 is therefore especially interesting because of its ability to exert force toward the minus end of the actin filament and it can play further roles in which a molecular motor is required (for review see Sweeney and Houdusse 2007).

Other mechanisms in which ABPs affect transcription involve interactions with additional activators or coactivators. In particular, the members of the nuclear hormone receptor family in which ABPs can activate or repress their function are an excellent example. Ozanne and co-workers (2000) identified filamin as an ABP that interacts with the androgen receptor affecting its nuclear translocation. Loy and colleagues (2003) showed that C-terminus of the filamin A (FLNa) inhibits transcription of the androgen receptor by modulating its activity since it competes with its coactivator TIF2. FLNa also interacts with regulatory proteins such as the tumor suppressor protein, BRCA2 (Yuan and Shen 2001) and protein FOXC1, which is a component of a larger complex that regulates the initiation of transcription. Moreover, FLNa is required for nuclear localization of transcription factor PBX1 (Berry et al. 2005). Filamin also plays an important role in the signaling mediated by Smad, protecting Smad proteins from ubiquitin-mediated degradation by masking an ubiquitin ligase-binding site of Smads (Sasaki et al. 2001). Supervillin, another member of villin/gelsolin family, is a nuclear/cytoplasmic actin-bundling protein and it is the primary coactivator of androgen receptor, as it enhances the activity of peroxisome proliferator-activated receptor-γ (PPAR-γ), glucocorticoid receptor and estrogen receptor (Archer et al. 2004; Ting et al. 2002). This stimulation differs from other nuclear receptor coactivator stimulations. While other coactivators increase the activation between N-terminal and C-terminal halves of the receptor, supervillin slightly suppresses it. A supervillin fragment (831–1281) was also found to colocalize with the androgen receptor in the nucleus when 5 alpha-dihydrotestosterone was added (Ting et al. 2002; Yu et al. 1990). The Ca^{2+}-calmodulin-dependent protein kinase type II binds to FliI and influences β-catenin dependent gene expression (Seward et al. 2008). FliI also regulates the development of *Caenorhabditis elegans* affecting anterior-posterior polarity and asymmetric cell division (Deng et al. 2007). FliI was shown to localize in the nucleus in the fibroblasts, where it translocates upon serum stimulation into the periphery of the cell from the nuclear/perinuclear region. FliI not only binds to actin but also binds to ARP4 as well as to p160 coactivators (Lee et al. 2004). Coimmunoprecipitation studies show that FliI associates with nuclear receptors such as thyroid hormone receptor and estrogen receptor, and siRNA silencing of FliI affects hormone-stimulated reporter gene expression (Lee et al. 2004). Furthermore, a G-ABP MAL is a coactivator of serum response factor. This is a transcription factor that regulates many mitogen-responsive and muscle-specific genes (Philippar et al. 2004). MAL binding to nuclear G-actin makes it unable to bind to serum response element and trigger transcription. MAL is then exported from the nucleus to the cytoplasm in complex with G-actin and Crm1 exporter. When actin is polymerized, the pool of free G-actin is reduced and the cofactor is released (Vartiainen et al. 2007). Free MAL can complex with serum response factor, which is able to bind serum response sequence and trigger transcription (Miralles et al. 2003).

The third mechanism in which ABPs affect transcription by RNA pol II is protein phosphorylation. It is known that phosphorylation of RB by cyclin-dependent kinases at the G1/S boundary leads to RB release and therefore activation of the ABP c-Abl tyrosine kinase. Activated nuclear c-Abl was shown to phosphorylate the C-terminal domain of RNA pol II to modulate transcription (Baskaran et al. 1993).

In the case of RNA pol I transcription, NM1 was observed in the dense fibrillar compartment, where transcription of ribosomal genes takes place. Here, it colocalizes with actin (Fomproix and Percipalle 2004; Nowak et al. 1997). Moreover, NM1 is indeed required for RNA Pol I transcription and it is associated with RNA Pol I through the basal transcription factor TIF-IA, a key regulator of Pol I transcription (Philimonenko et al. 2004).

In addition to the chromatin-remodeling process, these mechanisms for RNA pol I and II transcription show how ABPs are involved in several key steps for transcription control. ABPs together with actin and Arps may help to create a very dynamic scaffold in which nuclear processes can take place. As depicted in Fig. 1, ABPs are heavily involved at different stages of gene regulation. The elucidation of how the three-dimensional structures including actin, ABPs, and associated enzymes participate in these processed will be part of future research needed to truly understand gene activation in eucaryotic cells.

ABPs in DNA replication and repair

The most established role for ABPs in DNA replication and repair involves chromatin remodeling. The process of nucleosomes removal and their reincorporation are crucial steps both in DNA replication and repair, for which chromatin remodelers with bound actin and histone-modifying enzymes are needed. INO80 chromatin-remodeling complex plays a role in DSB DNA repair through recognition and eviction of phosphorylated form of histone H2A (in mammals called γH2AX) from DSB site to facilitate ssDNA formation and subsequent repair events. The Arp4, Arp5, Arp8 and actin form part of the INO80 complex and are essential for nucleosome-remodeling activity in vitro. It has been also shown that *arp5* and *arp8* mutants are hypersensitive to DNA damage agents. For Arp4, a role in recruitment of the complex to DSBs through interaction with γH2AX has been proposed. Furthermore, INO80 was shown to promote recovery of stalled replication forks in *S.*

cerevisiae. INO80 complex is associated with stalled replication forks genome-wide in yeast, and strains lacking INO80 show significant defects in the resumption of DNA replication. The mechanism of INO80 function in resumption of replication at stalled forks appears to be different from its activity in DSB repair. The recruitment of Arp5 to sites of initiation of DNA replication was independent of γH2A. Consistently, deletion of nhp10, which is responsible for the recruitment of INO80 complex to DSBs, did not have the same effect as *ino80* or *arp5* mutants on the recovery from replication arrest (Shimada et al. 2008).

Another chromatin remodeler, SNF2h, plays a role in DNA replication. It binds the WICH complex through WSTF to proliferating-cell nuclear antigen (PCNA) on replicated chromatin and prevents premature formation of heterochromatin. This therefore allows the re-binding of factors that transmit the epigenetic state to the newly synthesized DNA (Poot et al. 2005). NM1 was shown to be associated with a fraction of WICH involved in RNA Pol I transcription (Percipalle et al. 2006). It might be therefore interesting to investigate whether NM1 participates also in replication of heterochromatin.

Other functions of ABPs during DNA replication/repair could be recruitment of factors and scaffolding of functional complexes on filamentous actin. McMahon and colleagues (1999, 2001) identified spectrin as a direct binding partner of the Fanconi anemia protein FANCA. Sridharan and co-workers (2003) demonstrated that spectrin relocalizes to the same nuclear foci along with DNA-repair proteins, FANCA and XPF (nucleotide excision repair protein) after damage with a DNA cross-linking agent. This study suggested that nuclear spectrin may have an important function of in the nucleus providing a scaffold and aiding the recruitment of repair proteins to sites of the DNA damage. Myo16b displays overlapping localization with PCNA and cyclin in neuronal nuclei and tends to associate with nuclear compartment containing profilin and polymerized actin. It would be tempting to assume that Myo16b works as a motor to direct the movement of protein complexes in the nucleus during S phase. However, an analysis of the sequence of Myo16b ATP-binding pocket shows an amino acid replacement that significantly reduces actin-dependent ATPase activity. Thus, a scaffolding function of Myo16b is more likely than a motor function. Moreover, overexpression of Myo16b delays the progression through S-phase and decreases BrdU incorporation. In cells that incorporate BrdU, Myo16b does not colocalize with nascent DNA (Cameron et al. 2007). So, Myo16b is obviously involved in regulation of replication and S phase progression, but the precise mechanism should be elucidated. Furthermore, elevated Myo6 expression was induced by p53 during DNA damage. Upon p53 activation, Myo6 translocates from endocytic vesicles, membrane ruffles and cytoplasm to the Golgi complex, perinuclear membranes, and to the nucleus where it may be involved in DNA repair. RNAi knockdown of Myo6 leads to attenuated p53 activation and impaired Golgi integrity (Jung et al. 2006). Another example is thymosin beta$_4$, which is transported to nucleus in complex with mismatch DNA repair enzyme hMLH1, interacts with actin and may help to direct the enzyme to other steps of this process (Brieger et al. 2007).

ABPs involved in nucleocytoplasmic transport

The first evidence of actin involvement in nucleocytoplasmic transport was obtained as early as 1986 from isolated rat liver nuclei (Schindler and Jiang 1986). Antibodies to actin or myosin significantly reduced the flux rate of 64-kDa fluorescent dextran through the nuclear pores as measured by FRAP. Moreover, while addition of ATP greatly enhanced the flux rate in control nuclei, the addition of actin-affecting drugs such as cytochalasin D or phalloidin inhibited this stimulation of transport. Although these results may be criticized for use of isolated nuclei, more recent work confirms the role of actin in nucleocytoplasmic transport in intact cells. Hofmann and colleagues (2001) demonstrated that intranuclear microinjection of 2G2 antibodies raised against actin–profilin complex (Gonsior et al. 1999) blocked the nuclear Rev- and TAP-mediated export of viral RNAs as well as export of protein kinase A inhibitor both in Xenopus oocytes and in somatic cells. This export was also blocked by latrunculin B, which binds to G-actin but not by swinholide A that stabilizes actin dimers. By using 2G2 antibody, it was also possible to visualize actin present in the gelsolin-resistant fibers emanating from the nuclear envelope and associated with nuclear pore complexes (Hofmann et al. 2001). Another independent study also demonstrated a network of pore-linked filaments containing actin and an ABP 4.1 in Xenopus oocyte nuclei (Kiseleva et al. 2004). Interestingly, heterogeneous nuclear ribonucleoproteins (hnRNPs) appear to bind actin (Kukalev et al. 2005; Percipalle et al. 2002, 2003), some of them being able to shuttle between the nucleus and cytoplasm. This opens another interesting possibility that such actin fibers may in general help to dock the protein–RNA complexes at the pores via an ABP present in the complex and thus facilitating their export to cytoplasm. This model, at least for the case of preribosomal subunits protein–RNA complexes, was supported by very recent findings of Obrdlik and colleagues (2010). They showed that NM1 is present in the complex with mature rRNA transcripts and immunolocalized it at the top of nuclear pore basket in Xenopus oocyte nuclei.

Actin itself is exported from the nucleus by a nuclear export receptor Exportin 6 in complex with an ABP profilin (Stuven et al. 2003). Profilins are small proteins of molecular weight 18–14 kDa. They pass through the nuclear pores by simple diffusion and are quickly replenished in the nucleus. The dimer actin–profilin can couple profilin-binding proteins to Exportin 6 and they can be subsequently exported into the cytoplasm. Stuven et al (2003) have also found other proteins that bind profilin and actin to be present in a complex with Exportin 6. The survival motor neuron (SMN) protein has been shown to bind profilins I and II via the polyproline-rich motif (Giesemann et al. 1999). SMN is ubiquitously expressed protein that functions in assembly and transport of diverse ribonucleoprotein complexes (Kolb et al. 2007). Therefore, the Exportin 6-actin–profilin pathway may also participate in the export of SMN protein complex to the cytoplasm. Profilin also appears to play a significant role in nuclear export in Drosophila. The mutants with down-regulated profilin show mislocalization of RanGAP, protein that catalyses the hydrolysis of GTP in Ran, and have defects in nuclear export. Drosophila mutants that have down-regulated NTF2, a protein that imports small GTPase Ran into the nucleus, exhibits few survivals with small or no eyes. This phenotype was successfully rescued by crossing with a stream that has down-regulated profilin (Minakhina et al. 2005).

A CRM1-dependent nuclear export pathway is also involved in the regulation of the nuclear pool of actin, although actin does not bind CRM1 directly (Stuven et al. 2003). An earlier study by Wada et al. (1998) showed that after long exposure of cells to a CRM1 inhibitor leptomycin B, nuclear rod-like structures containing actin could be observed. The Exportin 6 pathway was not able to reduce the levels of nuclear actin so another mechanism to export actin to the cytoplasm must exist and is apparently dependent on CRM1. Thus, the plausible explanation for the nuclear rod effect is that they appear after nuclear sequestering of actin via blocking the nuclear export of another nuclear ABP that mediates binding of actin to CRM1 complex.

Due to its relatively low molecular weight of 43 kDa, monomeric actin may be able to pass the nuclear pore by diffusion. However, an active mechanism must exist that transports actin into the nucleus since actin fused to GFP is also able to localize into the nucleus (McDonald et al. 2006). One candidate for facilitating nuclear import of actin is cofilin. Actin and cofilin are observed together upon nuclear accumulation, and a function for cofilin was suggested to chaperone actin into the nucleus. Anti-cofilin antibody blocked nuclear entry of actin in permeabilized cells upon treatment with latrunculin B and ATP depletion (Pendleton et al. 2003). Nuclear translocation of cofilin is possibly triggered by dephosphorylation, as shown in fibroblasts (Nebl et al. 1996; Ohta et al. 1989) and in T cells (Samstag et al. 1994), while other data do not confirm this (Abe et al. 1993; Saito et al. 1994).

Another candidate for involvement in nucleocytoplasmic transport is paxillin. Paxillin shuttles between focal adhesions and the nucleus, as demonstrated by the experiments showing nuclear accumulation of paxillin after mutation/deletion of its NES domain or after inhibition of CRM1-dependent nuclear export by leptomycin B (Dong et al. 2009; Woods et al. 2002). A function of paxillin was proposed to assist in the translocation from the nucleus to focal adhesions for such proteins as Abl and STAT3 (Lewis and Schwartz 1998; Silver et al. 2004).

Taken together, these observations have shown that ABPs together with actin are significantly involved in the nuclear transport, as depicted in Fig. 2. However, the mechanisms in which they work during this process still remain mostly unresolved.

ABPs involved in nuclear architecture, dynamics and sensing outside

Structural integrity and spatial compartmentalization of the cell nucleus is important for its proper functioning. The best characterized structural component of the cell nucleus is nuclear lamina, composed of lamins belonging to the family of intermediate filament proteins. Furthermore, A-type lamin proteins are not only located at the nuclear periphery, but also are part of the internal nucleoskeleton/nuclear matrix. They are essential for nuclear structural integrity, DNA replication, transcription, splicing, cell signaling, DNA repair and cellular proliferation (Andres and Gonzalez 2009; Dechat et al. 2009; Gonzalez-Suarez et al. 2009; Vlcek and Foisner 2007). An interaction of the carboxy-terminal domain of lamin A with actin has been demonstrated in vitro, thus rendering lamin A a "non-classical" ABP (Sasseville and Langelier 1998). A-type lamins together with nesprins and SUN domain proteins participate in the formation of the linker of cytoskeleton and nucleoskeleton (LINC) complex. Nesprins are rod-like nuclear membrane proteins, which interact with F-actin and can mediate SUN protein binding. Nesprin 1 and 2 on the outer nuclear membrane connect cytoplasmic actin microfilaments to SuN1 and SuN2 on the inner nuclear membrane; SuN1, in turn, binds to lamin A on the nuclear scaffold (Crisp et al. 2006; Ostlund et al. 2009). Another protein belonging to the nesprin family, enaptin, was immunolocalized to actin stress fibers, the nuclear membrane, and interestingly, the nucleoplasm of COS7 cells thus being a part of the nuclear structural assembly (Padmakumar et al. 2004). LINC complex is important for nuclear

positioning and movement within the cell. It can also play a role in the transmission of mechanical signals from the cytoplasm to the nucleus. Pulling on integrins in cultured cells induces realignment of individual actin stress fibers and nucleoli, and alters their positions and orientation along the newly applied tension lines (Hu et al. 2005). It is not clear what is transferring the tension inside the nuclei; however, actin-based structures could well play this role.

Another protein that significantly contributes to the nuclear structure is emerin. Emerin is an inner nuclear membrane protein that is expressed in all differentiated cell types. It interacts with chromatin structure regulator barrier-to-auto integration factor, presumably via the LEM domain (Bengtsson and Wilson 2004). The lamin–emerin interaction has been implicated in maintaining the structural integrity of the nucleus and in efficient progression of the cell through the cell cycle. Emerin interacts with transcription factors (GCL, Btf, Lmo), splicing regulators (YT521-B), nuclear membrane protein nesprin-1α, actin and NM1 (Holaska 2008). The first evidence that emerin could bind α and β actin was provided by (Fairley et al. 1999). Holaska and collaborators (2007) showed later that emerin binds F-actin at the pointed end and identified NM1 as a direct ATP-independent binding partner of emerin, also by affinity purification of emerin-containing complexes from HeLa nuclear extracts. They found that NM1 is present along with actin, αII-spectrin and lamins in one protein complex that could participate in structural maintenance of the nuclear membrane.

There are two recent works that directly demonstrate the role of actin and ABPs in structural properties of nuclei. Bohnsack and co-workers (2006) found out that exportin 6, which is responsible for the nuclear export of actin, is not expressed in Xenopus oocytes before the onset of meiotic maturation. Furthermore, after microinjection of exogenous exportin 6 into oocyte nuclei, the intranuclear actin network disappeared, and at the same time the nuclei became extremely fragile. This effect was highly specific for exportin 6 injections and not observed upon control microinjections. These results point to the necessity of intranuclear actin network for the stabilization of giant oocyte nuclei. Indeed, application of actin-depolymerizing drug cytochalasin B also made the nuclei very fragile, while co-injection of F-actin-stabilizing phalloidin together with exportin 6 prevented nuclear fragility. Krauss and co-workers (2002, 2003) used Xenopus cell-free system of nuclear assembly to demonstrate that actin, ABP 4.1 and their functional interaction are required for proper formation of reconstituted nuclei and their replication competence. Protein 4.1 is an actin-scaffolding protein that can also bind spectrin (Correas et al. 2001). Interestingly, functional aminoacid sequences in the 4.1 domains responsible for binding to spectrin and to NuMa were also required for assembly of functional nuclei (Krauss et al. 2002).

This functional data is supported by ultrastructural work of several groups. Intranuclear actin-containing filaments were shown by electron microscopy in amphibian oocytes (Hofmann et al. 2001; Kiseleva et al. 2004). Such filaments emanated from the nuclear envelope and were often associated with nuclear pore complexes. Interestingly, filaments containing actin together with protein 4.1 formed a network that attached to Cajal bodies and other subnuclear organelles in Xenopus oocytes (Kiseleva et al. 2004; Pederson and Aebi 2002). Actin-based intranuclear structures might thus contribute to nuclear compartmentalization. Wang and co-workers (2006) reported that actin polymers participate in the reorganization of interchromatin granules clusters upon inhibition of transcription and form a special compartment, where transcription begins after release from inhibition. Preferential distribution of various ABPs, such as α-actinin, filamin, paxillin, spectrin and tropomyosin in specific nuclear compartments was shown ultrastructurally (Dingova et al. 2009), see an example in Fig. 3. Interestingly, the intranuclear distribution of actin and NMI was different in resting and activated human lymphocytes (Kysela et al. 2005). Figure 4 demonstrates that while actin and NMI are involved in rDNA transcription, in resting human lymphocytes with very low levels of transcription these two proteins localize in different nucleolar compartments. Actin and ABPs can be involved also in higher-order nuclear compartmentalization, such as organization and dynamics of chromosomal territories. Mehta and colleagues (2010) found that chromosome territories relocated rapidly within the cell nucleus when serum was removed from the culture medium. This relocation was energy-dependent and inhibited by drugs affecting polymeric actin or by NMI knock-down by RNA interference.

Other ABPs in the nucleus can contribute to the structural properties by regulating the polymerization state and dynamics of nuclear actin. Cyclase-associated protein 2 (CAP2) enhances actin filaments turnover. It is strongly enriched in the nuclear membrane fraction as well as in the nuclei. CAP2 is tightly bound and is released from the nucleus primarily by adding 2 M NaCl, which indicates that the detergent-resistant CAP2 is immobilized by attachment to non-chromatin structures (Peche et al. 2007). Furthermore, plastins may act in the nucleus as actin cross-linking proteins, which are generally thought to generate force by organizing actin filaments into bundles (Loomis et al. 2003; Vignjevic et al. 2003). Myopodin is also an actin-bundling protein, which is localized in the nuclei of differentiating myobasts (Weins et al. 2001). Formins also nucleate and elicit rapid processive assembly of filaments from profilin–actin, remaining bound to the growing barbed end (Chan and Leder 1996). Furthermore, in C2C12

cells, the Bpag1 localizes predominantly to the nucleus, its actin-binding domain interacts with the actin cytoskeleton and with the plakin domain region as it translocates the proteins to the nucleus. These results indicate that it is necessary for regulating the localization and function of plakin proteins required for structural work (Young et al. 2003).

Conclusions

Taken together, from all these observations, one can see the vast and complex scenario in which actin, ABPs and Arps are involved in a multitude of nuclear functions. Various functions are schematically summarized Figs. 1, 2. Interestingly, their actions extend from the nucleus to the cell surface as they seem to be also a part of the integral signaling pathways about events occurring on the cell surface, and our limited knowledge points now especially to the focal adhesions. Obviously, the still very fragmented data on nuclear functions of these proteins need to be seen not only as nuclear, but they need to be understood in the cellular aspect. The crucial questions about nuclear actin structure and about molecular properties of various sophisticated complexes that include varieties of actin, ABPs and Arps and their dynamics are still ahead. We can therefore foresee that there is a long way to understand the complexity of nuclear actions of actin, ABPs and Arps in the structural and functional networks in the entire cell.

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