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Exploring Secrets of Nuclear Actin Involvement in the Regulation of Gene Transcription and Genome Organization

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1. Introduction

Actin is one of the most abundant proteins in eukaryotic cells. It is a 43-kDa protein that was originally identified and purified from skeletal muscle. Once thought to be simply a component of muscle cells, actin has later been shown to be a highly conserved and ubiquitiously distributed protein in eukaryotic cells. It has been extensively studied as a cytoplasmic cytoskeletal protein that is involved in a wide range of cellular processes, including cell motility, growth and cytokinesis; endocytosis, exocytosis and secretion; signal transduction, synaptic transmission as well as intracellular trafficking (Ascough, 2004;Brakebusch and Fassler, 2003;Suetsugu and Takenawa, 2003). In the cytoplasm, actin exists in equilibrium between monomers (globular- or G-actin) and polymers (filamentous- or F-actin). The dynamics of actin, the coordinated assembly and disassembly of actin filaments in response to cellular and extracellular signaling, is critical for the diverse functions of actin and is tightly regulated by a plethora of actin-binding proteins (ABPs) in the cytoplasm (dos Remedios *et al.*, 2003). To date, over 70 distinct classes of ABPs have being identified and the inventory is still far from been completed (Pollard and Borisy, 2003).

While the cytoplasmic functions of actin are well established, the findings obtained from studies on nuclear actin have encountered consistent skepticism for many years. Presence of actin in the nucleus was considered to be cytoplasmic contamination from extraction or fixation procedures, or antibody cross-reactivity (Pederson and Aebi, 2002;Shumaker *et al.*, 2003). In addition, many known functions of actin in the cytoplasm are associated with the polymerization of actin into filaments, which can be detected by phalloidin staining. However, under normal conditions, nuclei cannot be stained by phalloidin. Nevertheless, in the past decade, there has been convincing data demonstrating that actin, actin-related proteins (Arps) as well as ABPs are not only present in the nucleus but also play important roles in diverse nuclear activities. Actin has been localized to specialized subnuclear compartments such as the nucleoli, splicing speckles and Cajal bodies (Fomproix and Percipalle, 2004;Gedge *et al.*, 2005;Saitoh *et al.*, 2004). In these subnuclear compartments, actin proves to be involved in almost all the processes associated with gene expression, from chromatin remodeling via transcription to ribonucleoprotein (RNP) assembly and maturation, as well as mRNA nuclear export (Blessing *et al.*, 2004;Chen and Shen, 2007;Olave *et al.*, 2002). Other nuclear processes in which actin is implicated, include

assembly of the nuclear structure (Krauss *et al.*, 2003;Krauss *et al.*, 2002;Olave *et al.*, 2002), genome organization, and regulation of transcription factor activity (Olave *et al.*, 2002;Vartiainen *et al.*, 2007).

In this chapter, the several aspects related to the nuclear actin presence and its importance in the regulation of gene expression will be reviewed.

2. Nuclear architecture and distribution of actin

The cell nucleus is a complex and multi-functional organelle, which displays a high degree of spatial organization and structural integrity. The most well characterized structural component of the cell nucleus is the nuclear lamina, mainly composed of A- and B-type laminas as well as lamina–associated proteins (Stewart *et al.*, 2007). The laminas are evolutionarily conserved nuclear-specific intermediate filaments that are essential for many nuclear functions, including the maintenance of nuclear shape, DNA replication, transcription, chromatin organization, cell cycle regulation and apoptosis (Andres and Gonzalez, 2009;Vlcek and Foisner, 2007;Wiesel *et al.*, 2008). Actin has been shown to interact with the c-terminus of A-type laminas (Sasseville and Langelier, 1998). A-type laminas are connected to the cytoskeleton by a linker of nucleoskeleton and cytoskeleton (LINC) complex found in the nuclear envelope. Connecting the A-type laminas to the cytoskeleton is necessary for nuclear migration and positioning within the cell as well as for transmitting mechanical signals from the cytoplasm to the nucleus (Starr, 2009;Tzur *et al.*, 2006;Worman and Gundersen, 2006).

Two important components of the LINC complex are Sun domain proteins and Nesprins. Located on the outer nuclear membrane, Nesprin 1 and 2 can interact with F-actin as well as Sun 1 and Sun 2 located on the inner nuclear membrane. Sun proteins, in turn, bind to lamina A (Crisp *et al.*, 2006;Ostlund *et al.*, 2009). Emerin, a lamina-associated protein, is also important for nuclear structure and has been shown to bind to actin. The interactions between actin, lamina and emerin indicate that an actin-containing structural network exists at the nuclear envelope and is involved in maintaining the nuclear structure and nuclear functions (Fairley *et al.*, 1999;Holaska and Wilson, 2007;Lattanzi *et al.*, 2003). The importance of actin in nuclear assembly was demonstrated using *Xenopus* egg extracts in which nuclear assembly is initiated after fluorescence-labelled actin is added. Moreover, the nuclear assembly gets blocked by Latrunculin A, which binds to G-actin and inhibits F-actin formation, suggesting that F-actin is required for nuclear assembly. In addition, the interaction between actin and protein 4.1 is implicated in this process (Krauss *et al.*, 2003;Krauss *et al.*, 2002).

Actin has also been associated with the nuclear matrix (Capco *et al.*, 1982;Okorokov *et al.*, 2002;Valkov *et al.*, 1989;Verheijen *et al.*, 1986). The nuclear matrix is a network of proteins throughout the inside of nucleus, which provides a structural framework for maintaining spatial order within nucleus and for proper nuclear functions , such as DNA replication and repair, gene transcription, RNA splicing and transport (Berezney, 2002;Berezney *et al.*, 1996;Hancock, 2000). It is tempting to speculate that nuclear actin acts as a component of intranuclear filament network (or nucleoskeleton) that is analogous to cytoskeleton. This was supported by a study showing a colocalization between actin and EAST (enhances adult sensory threshold), a structural protein of the nucleus. In a Drosophila model, EAST has been shown to be a ubiquitious nuclear protein forming a network throughout the

nucleus (Wasser and Chia, 2000). A number of studies have also confirmed that an actin-containing filament network exists in the nucleus. Studies of the *Xenopus* oocyte nuclei using electron microscopy have found that filaments containing actin and protein 4.1 form a network that attach to Cajal bodies and other subnuclear organelles (Kiseleva *et al.*, 2004). In this manner, the meshwork of actin-containing filaments might contribute to the nuclear compartmentalization.

3. Regulation of nuclear actin

3.1 The form of actin in the nucleus

Actin has been shown to be involved in diverse nuclear processes; but how and in what form actin takes part in these events remains to be elucidated. It has been suggested that nuclear actin coexists as a monomer (G-actin), short oligomer and polymer structure (Gieni and Hendzel, 2009;McDonald *et al.*, 2006). These different forms of nuclear actin are believed to be required for a variety of processes in the nucleus. There has been a great body of evidence in support of the presence of G-actin in the nucleus (Pederson and Aebi, 2002;Pederson and Aebi, 2005). Firstly, a number of G-actin binding proteins have been identified in the nucleus, including cofilin, profilin, β-thymosin, gelsolin and gelsolin-like protein (Huff *et al.*, 2004;Pendleton *et al.*, 2003;Percipalle, 2009;Prendergast and Ziff, 1991;Skare *et al.*, 2003). Secondly, using DNase I affinity chromatography, actin can be copurified with RNA polymerase I and II machinery (Fomproix and Percipalle, 2004;Kukalev *et al.*, 2005;Obrdlik *et al.*, 2008). DNase I binds to G-actin with very high affinity and F-actin with low affinity (Zechel, 1980). This suggesting that actin co-precipitated with RNA polymerase I and II is likely to be present in its monomeric or short oligomeric form. Thirdly, monoclonal antibodies directed against epitopes which are unique to monomeric or dimeric actin, display distinctive immunostaining of the nucleus (Jockusch *et al.*, 2006). Fourthly, the nuclear lamina proteins, such as lamina A (Sasseville and Langelier, 1998), emerin (Lattanzi *et al.*, 2003), and nesprin (Zhang *et al.*, 2002a) form complexes with actin. Biochemical evidence reveals that G-actin is present in these complexes.

It has been very challenging to document polymerization status of actin in the nucleus. Phalloidin staining is the most common method used for detecting actin filaments in the cytoplasm. Under physiological conditions, nuclear actin present in most of the cells cannot be detected by phalloidin staining, which specifically recognizes actin filaments of at least seven subunits in length. However, under certain cellular stress conditions, distinctive actin rods (also called bundles or paracrystals) can be induced in the nucleus in a variety of cell types. These conditions include dimethyl sulfoxide (DMSO) treatment (Sanger *et al.*, 1980a;Sanger *et al.*, 1980b), heat shock (Iida *et al.*, 1986;Welch and Suhan, 1985), Latrunculin B treatment and ATP deletion (Pendleton *et al.*, 2003) as well as viral infection (Charlton and Volkman, 1991;Feierbach *et al.*, 2006). Cellular stress-induced formation of actin filaments seems to be caused by an increased nuclear actin level because nuclear translocation and accumulation of actin are also observed at the same time. This is supported by the observation that actin filaments exist in the *Xenopus* oocytes, which have a very high concentration of actin (~2mg/ml) due to the lack of nuclear export receptor, exportin 6 (Bohnsack *et al.*, 2006;Clark and Rosenbaum, 1979;Roeder and Gard, 1994;Stuven *et al.*, 2003). In addition, some nuclear-actin dependent functions, such as nuclear export of RNA and proteins (Hofmann *et al.*, 2001), nuclear envelope assembly (Krauss *et al.*, 2003), transcription (McDonald *et al.*, 2006) and intranuclear movement of Herpes simplex virus-1 capsid

(Forest *et al.*, 2005) as well as movement of chromosome loci (Hu *et al.*, 2008) can be inhibited by Latrunculin B, a drug that binds G-actin with high affinity and prevents polymerization and thus F-actin formation (Spector *et al.*, 1989). These indirect evidence imply that some sort of polymerized actin exist in the nucleus to carry out corresponding nuclear functions. The presence of polymeric actin in the nucleus was also shown (McDonald *et al.*, 2006) in living cells using fluorescence recovery after photobleaching (FRAP) experiments. In that study, FRAP, which allows to analyze the dynamic properties of GFP-actin in the nucleus, shows that both a fast recovery and a slow recovery GFP-actin exist in the nucleus. Moreover, the latter type of actin is sensitive to actin mutants and Latrunculin B. Therefore, the slow species represents a polymeric form of actin with distinctive dynamics which is quite different from the actin dynamics observed in the cytoplasm. Interestingly, recent studies provided evidence that the nuclear polymeric actin is important for RNA polymerase I-mediated transcription and transcriptional activation of HoxB genes by RNA polymerase II (Ferrai *et al.*, 2009;Ye *et al.*, 2008).

3.2 Regulation of nuclear translocation of actin

Extracellular stress can induce nuclear translocation of actin. Sanger and colleagues demonstrated that a disappearance of stress fibers from the cytoplasm and a reversible translocation of cytoplasmic actin into the nucleus occur after treatment of PtK2 and WI-38 cells with 10% DMSO (Sanger *et al.*, 1980a;Sanger *et al.*, 1980b). Courgeon and colleagues showed that heat shock causes actin to accumulate in the nucleus of *Drosophila* cells (Courgeon *et al.*, 1993). In mast cells, entry of actin into the nucleus was induced by either treatment with Latrunculin B, or ATP depletion (Pendleton *et al.*, 2003). Most recently, nuclear translocation of actin was found in HL-60 cells and human peripheral blood monocytes when differentiated to macrophages by phorbol 12 myristate 13-acetate (PMA) (Xu *et al.*, 2010). These results suggest that actin is able to shuttle between the cytoplasm and the nucleus. To date, the molecular mechanism by which actin enters into the nucleus in response to cellular stress has not been established.

The nuclear envelope is a lipid bilayer that forms a barrier between the nuclear and cytoplasmic spaces. The traffic between nucleus and cytoplasm is mediated through nuclear pore complexes (NPCs) embedded in the nuclear envelope. NPCs allow passive diffusion of small molecules (such as ion and protein smaller than 40 kDa) but restrict the movement of larger molecules across the nuclear envelope. Macromolecules usually carry specific signals allowing them to access the nucleocytoplasmic transport machinery. Monomeric actin has a molecular weight of ~43 kDa, therefore it is unlikely to enter into nucleus by diffusion. Actin lacks a classical nuclear localization signal (NLS) and to date, no specific import receptor for actin has been identified. Therefore it most likely relies on an active carrier which guides it into the nucleus. Cofilin, an actin-binding protein, is suggested to be involved in the regulation of nuclear import of actin. Cofilin contains a NLS and it has been recognized as a component of intranuclear actin rods in response heat shock and DMSO treatment (Nishida *et al.*, 1987). A study by Pendleton *et al.* showed that stress-induced nuclear accumulation of actin was blocked by an anti-cofilin antibody, demonstrating that cofilin is required for actin import into the nucleus (Pendleton *et al.*, 2003).

For nuclear export, actin seems to use an active transport mechanism. The actin polypeptide has two well conserved nuclear export signals (NESs). In yeast, these two sequences were specifically recognized by chromosome region maintenance 1 (CRM1, also known as exportin 1), a general export receptor for cargos bearing leucine-rich export signals, and

actin can then be rapidly removed from nucleus. Transfection of cells with mutant actin lacking NESs or inhibition of CRM1 by leptomycin B results in nuclear accumulation of actin (Wada *et al.*, 1998). Exportin 6, a member of the importin β superfamily of transport receptor, is responsible for nuclear actin export in mammalian cells (Stuven *et al.*, 2003). Knockdown of exportin 6 by RNA interference also leads to nuclear accumulation of actin and the formation of actin rods. Interestingly, exportin 6 recognizes the actin:profilin complex rather than actin or profilin individually, suggesting a difference in the form of actin being presented to CRM1 and to exportin 6.

So far, the exact roles of nuclear accumulation of actin in response to external signals remain to be understood. Nuclear actin controls transcription of its target genes through several different ways: (1) Actin specifically binds to a 27-nt repeat element in the intron 4 of the endothelial nitric oxide synthase gene to regulate its expression (Ou *et al.*, 2005;Wang *et al.*, 2002); (2) Actin participates in chromatin remodeling for gene activation as a component of the chromatin remodeling complex (Rando *et al.*, 2002;Song *et al.*, 2007;Zhao *et al.*, 1998); (3) Actin plays a direct role in RNA transcription by being part of the pre-initiation complex with RNA polymerase II (Hofmann *et al.*, 2004). (4) Actin participates in transcriptional elongation as a component of RNP particles. Therefore, it is tempting to speculate that under stress, actin translocates into nuclei to function as a transcriptional modulator, playing an important role in the regulation of gene transcription along with stress-activated transcription factor. This hypothesis is supported by recent studies showing that nuclear accumulation of actin is involved in transcriptional activation of SLC11A1 gene during macrophage-like differentiation of HL-60 cells induced by PMA (Xu *et al.*, 2011;Xu *et al.*, 2010).

3.3 Regulation of actin polymerization

It is believed that the concentration of nuclear actin is sufficient for spontaneous polymerization. Therefore, in order to have dynamic equilibrium of the different forms of actin, an active process preventing polymerization is required.

Many of the regulators known to control cytoplasmic actin dynamics have also been shown to be present in the nucleus (Table 1). These regulators include Arps such as Arp 2/3; and ABPs such as cofilin, profilin and CapG; and signalling molecules (see section 3.4). In humans, Arp2/3 represents a stable complex of two Arps (Arp2 and Arp3) and five other subunits including p16, p20, p21, p34, p41 (Deeks and Hussey, 2005;Welch *et al.*, 1997). The Arp2/3 complex is capable of initiating *de novo* polymerization of actin and stimulating the formation of branched actin filaments when activated by members of Wiskott-Aldrich syndrome protein (WASP) family (Higgs and Pollard, 2001;Machesky and Insall, 1998;Pollard and Borisy, 2003;Volkmann *et al.*, 2001). The WASP family members share a common C-terminal verprolin-cofilin-acidic (VCA) region. Polymerization of actin is initiated by the interaction of the VCA region with both Arp2/3 complex and an actin monomer, forming the first subunit of *de novo* actin polymer (Dayel and Mullins, 2004;Kim *et al.*, 2000;Prehoda *et al.*, 2000;Rohatgi *et al.*, 1999). The potential role of Arp2/3 in the regulation of actin dynamics in the nucleus was suggested based on the viral infection studies, for example infection with baculovirus, results in accumulation of Arp2/3 complex in the nucleus, where it becomes activated by WASP-like virus protein p78/83. This event in turn results in Arp2/3-mediated actin polymerization that is essential for virus replication (Goley *et al.*, 2006). Furthermore, it has been demonstrated that N-WASP and Arp2/3 complex associate with RNA polymerase II and regulate the efficiency of gene transcription.

Induction of actin polymerization through the N-WASP-Arp2/3 complex pathway has been shown to be required for efficient transcription by RNA polymerase II (Wu *et al.*, 2006;Yoo *et al.*, 2007). Importance of the Arp2/3 complex –mediated actin polymerization in other nuclear actin-dependent processes remains to be fully elucidated.

Protein	Roles in the nucleus	References
Arp 2/3	De novo actin polymerization	Higgs and Pollard, 2001
	Formation of Branched actin filaments	Pollard et al., 2003
	Associated with transcription by pol II	Wu et al., 2006; Yoo et al., 2007
N-WASP	Activating ARP2/3-mediated actin polymerization	Higgs and Pollard, 2001; Volkmann et al. 2001
	Regulating transcription by pol II	Wu et al., 2006; Yoo et al., 2007
Gelsolin	Serving actin polymers	Ocampo et al., 2005
	Androgen receptor co-activator	Nishimura et al., 2003
Flightless I	Chromosome remodelling	Archer et al., 2005
Supervillin	Nuclear receptor-induced transcription	Ting et al., 2002
Filamin	Androgen receptor action	Ozanne et al., 2000
CapG	Unknown	De Corte et al., 2004
Profilin	Nuclear export of actin mediated by exportin 6	Stuven et al., 2003
	Possible involvement in pre-mRNA splicing	Skare et al., 2003
Thymosin β4	Sequestering actin and blocking actin polymerization	Hannappel et al., 2007; Huff et al., 2004
Cofilin	Nuclear import of actin	Pendleton et al., 2003
	Repressor of the glucocorticoid receptor	Ruegg et al., 2004
	A component of nuclear actin-rods	Nishida et al., 1987
Emerin	Nuclear architecture	Holaska et al., 2004
Myo1c/NM1	Transcription	Hofmann et al., 2006 ; Ye et al., 2008
	Chromatin remodeling	Percipalle et al., 2006
Tropomodulin	Unknown	Kong and Kedes, 2004
Protein 4.1	Nuclear assembly	Krauss et al., 2003
Actinin	Nuclear receptor activator (actinin alpha 4)	Khurana et al., 2011
	Regulation of DNase Y activity (actinin alpha 4)	Liu et al., 2004
Spectrin II α	Involved in DNA repair	Sridharan et al., 2003
Paxillin	Stimulating DNA synthesis and Promoting cell proliferation	Dong et al., 2009
CAP2	Unkown	Peche et al., 2007
CABP14	Possible role in cell division	Aroian et al., 1997

Table 1. Proteins known to modulate cytoplasmic actin dynamics exist in nucleus

Actin filaments capping proteins bind the barbed (or fast growing end) of an actin filament and therefore block filament assembly or promote disassembly at that end. In the cytoplasm, members of the gelsolin family are characterized by the ability to cap, sever and bundle actin filaments in a Ca^{2+}-dependent manner in the cytoplasm (Archer *et al.*, 2005). Several members of gelsolin family has been detected in nucleus, including gelsolin (Nishimura *et al.*, 2003;Salazar *et al.*, 1999), CapG (De, V *et al.*, 2004;Onoda *et al.*, 1993), flightless (Lee *et al.*, 2004) and supervillin (Wulfkuhle *et al.*, 1999). In the nucleus, gelsolin has been found to be involved in chromosome decondensation by severing actin (Ocampo *et al.*, 2005). Flightless I has been found to bind to actin and Arp BAF53, a subunit of mammalian chromatin remodelling complex, and negatively regulates actin polymerization (Archer *et al.*, 2005). It is currently unclear whether other members regulate actin dynamics in the nucleus. Interestingly, many of them appear to function as transcriptional coactivators for nuclear hormone receptors (Gettemans *et al.*, 2005).

Many G-actin binding proteins are also present in the nucleus. Thymosin β4 is the most abundant polypeptide of the β-thymosin family in the cytoplasm and regulates F-actin polymerization by sequestering polymers (Huff *et al.*, 2004). In the nucleoplasm, thymosin β4 is present at a high level and suggested to sequester nuclear actin and block actin polymerization (Hannappel, 2007;Huff *et al.*, 2004). In addition, it has been shown to interact with ATP-dependent DNA helicase II to regulate specific gene expression (Bednarek *et al.*, 2008). Despite its small size (~4.9 kDa), Huff et al. showed that passive diffusion of thymosin β4 through the NPC can be ruled out (Huff *et al.*, 2004), and its nuclear localization has been reported to be regulated by the DNA mismatch repair enzyme human mutL homolog 1 (hMLH1) (Brieger *et al.*, 2007). Profilin is a small protein that binds specifically with G-actin. It enhances the nucleotide exchange on actin to convert ADP actin into ATP actin, which can readily be incorporated in to a growing filament. In the nucleus, formation of profilin-actin complex is required for nuclear export of actin through exportin 6 (Stuven *et al.*, 2003), to avoid excess actin polymerization in the nucleus. This was supported by Bohnsack and colleagues' work (Bohnsack *et al.*, 2006).

ADP/cofilins represent a family of small actin-regulatory proteins that bind to both actin monomers and filaments, and remove actin filaments by severing and depolymerising (Maciver and Hussey, 2002). Using fluorescence resonance energy transfer assay, they have been shown to bind to actin directly in the nucleus and at levels much higher than in the cytoplasm (Chhabra and dos Remedios, 2005). As mentioned in section 3.2, actin accumulates in the nucleus and forms intranuclear actin rods under a variety of cellular stress conditions. Cofilin has been recognized as a component of the actin rods (Gettemans *et al.*, 2005). The high level of cofilin present in the nucleoplasm and in the actin rods might explain the reason why actin filaments appear to be restricted in the nucleus since the cofilin/actin structures cannot be stained with phalloidin (Nishida *et al.*, 1987). The formation of nuclear actin rods is highly dynamic and is reversible when the cellular stress conditions are removed (Gieni and Hendzel, 2009), suggesting that cofilin might play a role in restricting the excess accumulation of polymeric actin, which otherwise could affect the polymeric actin-mediated nuclear process.

3.4 Signalling molecules regulating actin dynamics

The activities of ABPs are tightly controlled through various signalling pathways to ensure proper spatial and temporal regulation of actin dynamics in the cells. Several signalling molecules, including small GTPases, Ca^{2+} and phosphoinositides which display well-characterized effects on actin dynamics in the cytoplasm, are also found in the nucleus.

Small GTPases of the Rho family, such as Cdc42 and Rac1, have been found in the nucleus, (Williams, 2003). As discussed above, Arp2/3 is an important candidate for regulating nuclear actin polymerization and N-WASP, the most potent inducer of Arp2/3 –mediated actin nucleation remains to be the only member of the WASP family found in the nucleus (Suetsugu *et al.*, 2001;Zalevsky *et al.*, 2001). In the cytoplasm, N-WASP is activated by Cdc42, linking Rho family GTPase signalling with Arp2/3 –mediated actin polymerization (Rohatgi *et al.*, 1999). N-WASP is also activated by Rac1, and both Cdc42- and Rac1-mediated stimulation of N-WASP activity is further enhanced by the presence of phosphatidylinositol 4,5-bisphosphate (PIP2). The functional significance of the presence of Rho GTPases in the nucleus is not fully known. Some downstream effectors of Rho family GTPase, such as LIM

kinases (LIMK), has been shown to localize to the nucleus. LIMK can phosphorylate and inactivate cofilin, suggesting that Rho GTPase signalling pathway may play an important role in regulation of nuclear actin cytoskeleton. Rac1 was shown to shuttle in and out of the nucleus during the cell cycle and to accumulate in the nucleus in late G2 phase. In addition, GTP-bound Rac1 and a Rac1/Cdc42 GTPase activating- protein, MgcRacGAP, bind directly to phosphorylated transcription factors, STAT3 and STAT5, to mediate their translocation into the nucleus. Therefore, nuclear accumulation of Rac1 may also regulate actin polymerization influencing RNA polymerase II-mediated transcription.

Phosphoinositides (PIs) are major regulators of actin dynamics in the cytoplasm (Mao and Yin, 2007). PIs control actin polymerization by modulating the activity of regulatory proteins promoting actin assembly and inhibiting disassembly of actin filaments. For example, PIP2 activates nucleation of actin filaments induced by N-WASP-Arp2/3 complex and inhibits the actin-binding activity of cofilin (Hilpela *et al.*, 2004). PIP2 also binds and inhibits capping proteins, and seems to remove capping proteins from capped ends of actin filaments, which may help to stimulate actin assembly (Kim *et al.*, 2007). Based on the observations, one can speculate that PIs also modulate actin-binding activity of capping proteins in the nucleus. So far, the downstream targets of PI signalling remains poorly identified. Several studies have linked chromatin remodelling complexes with PIs. For example, PIP2 participates in the recruitment of mammalian chromatin remodelling complex, BRG1/BRM associated factor (BAF), to nuclear matrix-associated chromatin, upon activation of antigen receptor in T-lymphocytes (Zhao *et al.*, 1998). Further analysis has revealed that PIP2 can bind directly to BRG1, an ATPase subunit of the BAF complex, modulate the actin-binding activity of BRG1 (Rando *et al.*, 2002). Within the BAF complex, BRG1 is associated with β-actin and Arp BAF53 through two actin-binding domains. Interestingly, one of the acting-binding domains of BRG1 is required for PIP2 binding. Based on these findings, a model is designed in which interaction between PIP2 and BRG1 would essentially uncap β-actin or BAF53, thereby allowing them to interact with actin filaments in the nuclear matrix (Rando *et al.*, 2002).

In the cytoplasm, actin dynamics is also controlled by Ca^{2+} level. The activity of several ABPs, including members of gelsolin family, are regulated by Ca^{2+} influx (Archer *et al.*, 2005). For example, Ca^{2+} activates gelsolin to allow capping and severing of actin filaments. The importance of Ca^{2+}-regulated actin severing has been well-documented in platelet activation (Witke *et al.*, 1995). Gelsolin has six Ca^{2+} binding sites within domain S1-S6. When domains S5 and S6 are occupied by Ca^{2+} at submicromolar concentration gelsolin is activated to bind actin. However, for full activation of severing activity, higher Ca^{2+} concentrations are required most likely filling the sites on domains S1, S2 and S4 (Burtnick *et al.*, 2004;Choe *et al.*, 2002). It is clear that nuclear Ca^{2+} level is regulated which in turn regulates the activity of transcription factors, such as DREAM (Carrion *et al.*, 1999) and CREB (Chawla *et al.*, 1998). Likewise, it is possible that nuclear Ca^{2+} level could modulate the activity of actin-containing chromatin remodelling complex by controlling activity of certain nuclear ABPs.

4. Involvement of actin in chromatin remodelling

Eukaryotic DNA is tightly packaged into nucleosome repeats. Each nucleosome unit consist of a histone octamer core surrounded by a segment of 146 base pairs of double stranded

DNA. Histone octamer core is composed of two-molecule each of H2A, H2B, H3 and H4 proteins. This kind of packaging of genomic DNA in chromatin represents barriers that restrict access to a variety of DNA regulatory proteins involved in the processes of transcription, replication, DNA repair and recombination machinery. To overcome these barriers, eukaryotic cells possess a number of multiprotein complexes which can alter the chromatin structure and make DNA accessible. These complexes can be divided into two groups, histone-modifying enzymes and ATP-dependent chromatin remodelling complexes. The histone-modifying enzymes post-translationally modify the N-terminal tails of histone proteins through acetylation, phosphorylation, ubiquitination, ADP-ribosylation and methylation (Sterner and Berger, 2000;Wang *et al*., 2007). On the other hand, ATP-dependent chromatin remodelling complexes use the energy of ATP hydrolysis to disrupt the DNA-histone contact, move nucleosomes along DNA, and remove or exchange nucleosomes (Gangaraju and Bartholomew, 2007). Actin and Arps were first identified as integral components of the BAF complex, a mammalian SWI/SNF-like chromatin remodelling complex, that is involved in T-lymphocyte activation (Zhao *et al*., 1998). Since then, actin and Arps have been found to be present in a wide variety of chromatin remodelling and histone-modifying complexes (Figure 1C) in yeast, *Drosophila* and mammalian cells.

4.1 Actin–containing chromatin remodelling complex

The ATP-dependent chromatin remodelling complexes can be classified into at least four different families based on their central ATPases: SWI/SNF complex (or BAF complexes) with a SWI2/SNF2 ATPase; ISWI complex with an ISWI ATPase; Mi-2 (or CHD) complex containing a chromodomain-helicase-DNA binding protein ATPase; and INO80 complex with an INO80 ATPase (Farrants, 2008). Only the complexes of SWI/SNF and INO80 families have actin and Arps as subunits that are bound directly. Most members of SWI/SNF family contain actin and Arp4 homologues. In *Drosophilia*, the orthologous complexes BAP (Brahma associated proteins) and PBAP (polybromo-associated BAP) each contains actin and the Arp BAF55. In mammals, the orthologous complexes BAF, PBAF and p400 all contain actin and the Arp BAF53. The yeast SWI/SNF complex was the first to be discovered in *S. cerevisiae*. Many components of the SWI/SNF complex were initially identified in independent screens for genes that regulate mating-type switching (SWI genes) and sucrose non-fermenting (SNF genes) phenotype in yeasts (Abrams *et al*., 1986;Carlson *et al*., 1981;Nasmyth and Shore, 1987;Neigeborn and Carlson, 1984;Neigeborn and Carlson, 1987;Stern *et al*., 1984;Vignali *et al*., 2000). The yeast SWI/SNF complex contains 11 known subunits, of which the SWI2/SNF2 subunit possesses both chromatin remodelling and DNA-dependent ATPase activities. In yeast, the SWI/SNF complex and another orthologous complex RSC lack actin but were shown to contain two yeast specific Arps - Arp7 and Arp9 (Table 2). Interestingly, the yeast genome encodes both actin and Arp4 but they are replaced with novel Arps.

The INO80 family includes the yeast INO80 complex and its orthologues Pho-dINO80 (*Drosophila*) and INO80 (human); the yeast SWR1 complex and its orthologue SRCAP (human); and the yeast NuA4 complex and its orthologues TIP60 (*Drosophila*) and TRAAP/TIP60 (human) (Table 3). The yeast INO80 complex contains actin and Arp 4, Arp5 and Arp8, of which Arp5 and Arp8 and actin are conserved in *Drosophila* and mammals. Arp4 and actin are also components of yeast SWR1 and Nu4 complex. BAF53, a mammalian orthologue of Arp4, is present in the mammalian orthologous complex INO80, SRCAP, and TIP60 (Hargreaves and Crabtree, 2011).

Complex	SWI/SNF	RSC	BAP	PBAP	BAF	PBAF	nBAF	npBAF
Species	Yeast	Yeast	Drosophila	Drosophila	Human	Human	Mouse	Mouse
ATPase	Swi2/Snf2	Sth1	BRM	BRM	BRG1/hBRM	BRG1	BRG1	BRG1
Actin	No	No	β-actin	β-actin	β-actin	β-actin	β-actin	β-actin
ARP	ARP7, ARP9	ARP7, ARP9	BAP55 or BAP47	BAP55 or BAP47	BAF53a or BAF53b	BAF53a	BAF53b	BAF53a
Main subunits			OSA	BAP170	BAF250a or	BAF200	BAF250a or	BAF250a
or					BAF250b		BAF250b or	BAF250b
or							BAF200	BAF200
		Rsc1, Rsc2, Rsc4		Polybromo		BAF180		
	Swi3	Rsc8	BAP155	BAP155	BAF155 and/or	BAF155 and/or	BAF155 and/or	BAF155
and/or					BAF170	BAF170	BAF170	BAF170
	Swp73	Rsc6	BAP60	BAP60	BAF60a or BAF60b or BAF60c	BAF60a	BAF60a	BAF60a
	Snf5	Sfh1	BAP45/SNR1	BAP45/SNR1	BAF47/hSNF5	BAF47/hSNF5	BAF47/SNF5	
BAF47/SNF5			BAP111	BAP111	BAF57	BAF57	BAF57	BAF57
Unique Subunits	Swi1, Swp82 Taf14, Snf6 Snf11	Rsc3, 5, 7, 9, 10, 30 Htl1, Lbd7, Rtt102						

Table 2. Complexes of the SWI/SNF family

Complex	INO80	Pho-dINO80	INO80	SWR1	SRCAP	NuA4	TIP60	TRAAP/TIP60
Species	Yeast	Drosophila	Human	Yeast	Human	Yeast	Drosophila	Human
ATPase	Ino80	dIno80	hINO80	Swr1	SRCAP		Domino	p400
Actin	Act1	dActin	β-actin	Act1	β-actin	Act1	Act87E	β-actin
ARP	ARP4, ARP5 ARP8	dARP5, dARP8	BAF53a, ARP5 ARP8	ARP4, ARP6	BAF53a, ARP6	ARP4	BAP53	BAF53a
Main subunits	Rvb1, Rvb2	Reptin, Pontin	Tip49a, Tip49b	Rvb1, Rvb2	Tip49a, Tip49b		Reptin, Pontin	Tip49a, Tip49b
	Taf14			Yaf9	GAS41	Yaf9	dGAS41	GAS41
	Ies 2		hIes 2					
	Ies 6		hIes 6					
				Swc2	YL-1		dYL-1	YL-1
				Swc4	DMAP1	Swc4	dMAP1	DMAP1
				Bdf1			dBrd8	BRD8/TRCp120
				Swc6	Znf-HIT1			
						Tra1	dTra1	TRAAP
						Eaf3	dMRG15	MRG15
						Eaf6	dEaf6	FLJ11730
						Eaf7	dMRGBP	MRGBP
						Esa1	dTip60	Tip60
						Epl1	E(pc)	EPC1
						Yng2	dING3	ING3
Unique Subunits	Ies 1, Ies3, 4, 5 Nhp10	Pleiohomeotic	Amida, MCRS1, FLJ20309, UCH37 NFRKB, CCDC95	Swc3, 5, 7		Eaf1, 5		

Table 3. Complexes of the INO80 family

Actin was first identified in the mammalian BAF complex. Biochemical analysis indicated that actin is not only tightly bound to BRG1, the ATPase subunit of BAF, but also needed for the ATPase activity required for BAF association with chromatin (Zhao *et al*., 1998). To date, the molecular mechanisms that underlie the functions of actin and Arps in the chromatin remodelling remain largely unknown. Recently, a helicase-SANT-associated (HSA) domain was identified in the ATPase of several chromatin remodelling complexes. This domain is required for the binding of actin and Arps. Altering the HSA domain causes a loss of actin and Arps in these complexes and reduces ATPase activity, confirming the important role of actin and Arps in chromatin remodelling (Szerlong *et al*., 2008).

4.2 Actin recruits histone modifying enzymes

Actin has been identified as a component of pre-mRNA particles (pre-mRNPs) via binding to heterogeneous nuclear ribonucleoprotein particles (hnRNPs) in insects and mammals (Kukalev *et al*., 2005;Percipalle *et al*., 2003;Percipalle *et al*., 2002;Percipalle *et al*., 2001;Zhang *et al*., 2002b). In the dipteran insect *Chironomus tentans*, actin was found to bind directly to the nuclear protein HRP65-2 (HRP65 isoform 2). Disruption of this interaction by a competing peptide, which mimics the actin-binding motif of HRP65, inhibited RNA polymerase II-mediated transcription at the level of transcript elongation (Percipalle *et al*., 2003). The inhibitory effect of this peptide can be counteracted by a general inhibitor of histone deacetylases (trichostatin A), suggesting that actin-HRP65-2 interaction is involved in acetylation/deacetylation of histones. Indeed, HRP65-2 and actin were shown to form a complex with p2D10 *in vivo*. p2D10 is a histone H3 –specific acetyltransferase, a *C. tentans* ortholog of the largest subunit of the transcription factor TFIIIC (Sjolinder *et al*., 2005). Disruption of the interaction between HRP65-2 and actin releases p2D10 from RNA polymerase II-transcribing gene, coinciding with reduced H3 histone acetylation and inhibition of transcription, indicating that HRP65-actin interaction provides a molecular platform to recruit chromatin modifying factors to the transcribing genes allowing to maintain genes in an active state (Figure 1B) (Sjolinder *et al*., 2005).

Similarly, in human cells, the interaction between actin and hnRNP U, another component of pre-mRNPs, was also shown to be essential for RNA polymerase II-mediated transcription elongation. hnRNP U has been shown to bind to actin via a conserved actin-binding motif located at the C-terminus. Both actin and hnRNP U were shown to be associated with the phosphorylated C-terminal domain (CTD) of polymerase II and antibodies against either of these components are able to block transcription of class II genes (Kukalev *et al*., 2005). Furthermore, the actin - hnRNP U complex was shown to be required for the recruitment of histone acetyltransferase (HAT), PCAF, to actively transcribed genes, and they are all present at promoter and coding regions of constitutively expressed class II genes (Figure 1 B) (Obrdlik *et al*., 2008). It was previously shown that binding of hnRNP U to RNA polymerase II inhibited the phosphorylation of the CTD mediated by TFIIH, suggesting that actin-hnRNP U interaction might modify the inhibitory effect of hnRNP U on CTD phosphorylation, and that this modification is required for transcription elongation (Kim and Nikodem, 1999;Kukalev *et al*., 2005).

5. Involvement of actin in transcription machinery

Transcription is a process of synthesizing an RNA molecule from a sequence of DNA. The major steps of transcription include pre-initiation, initiation, elongation and termination.

Transcription is performed by an enzyme called RNA polymerase. Eukaryotic cells have three distinct classes of RNA polymerases characterized by the type of RNA they synthesize. RNA polymerase I is located in the nucleolus, a functionally highly specialized subnuclear compartment, and it is responsible for transcribing ribosomal RNA (rRNA). RNA polymerase II is located in nucleoplasm and responsible for synthesizing the precursors of messenger RNA (mRNA) and most small nuclear RNAs (snRNA) and microRNA (miRNA). RNA polymerase III is also located in nucleoplasm, and transcribes 5S rRNA, transfer RNA (tRNA), U6 snRNA and other small RNAs.

The first finding that demonstrated a role of nuclear actin in transcriptional process was documented by Smith et al. (Smith *et al.*, 1979). The authors found that actin co-purified with RNA polymerase II from the slime mold *Physarum polycephalum*. Following this original finding, the subsequent studies demonstrated that actin was present in transcriptionally active nuclear extracts from HeLa cells and calf thymus, and was able to initiate the transcription by RNA polymerase II *in vitro* (Egly *et al.*, 1984). Another study, published about the same time, showed that transcription of lampbrush chromosomes was inhibited when antibodies directed against actin or ABPs were microinjected into the nuclei of living oocytes of *Pleurodeles waltl*. This study provided first solid evidence for an association between actin and transcription (Scheer *et al.*, 1984). However, these two important findings were largely ignored and postulated as being artifacts of contamination. Although a number of key advances in the nuclear actin field occurred after 1984, skepticism of new data remained until two decades later when several studies finally provided convincing and non-contestable evidence for the involvement of actin in gene transcription (Grummt, 2006;Pederson and Aebi, 2002; Percipalle and Visa, 2006). However, many questions remain to be answered to fully understand the exact molecular mechanism of regulation of transcription by various forms of actin.

5.1 Role of actin and nuclear myosin 1 in gene transcription by RNA polymerase I

Actin has been shown to be present not only in mammalian nucleoplasm but also in nucleoli (Andersen *et al.*, 2005), suggesting a role for actin in transcription by RNA polymerase I. Indeed, co-immunoprecipitation and chromatin immunoprecipitation (ChIP) assays showed that actin is associated physically with RNA polymerase I and present on actively transcribing ribosomal genes at both the promoter and transcribed regions (Fomproix and Percipalle, 2004; Philimonenko *et al.*, 2004). Microinjection of anti-actin antibodies into the nuclei inhibited rRNA synthesis in living cells (Philimonenko *et al.*, 2004). Furthermore, *in vitro* transcription assays revealed that antibody against actin also inhibited rRNA synthesis in cell-free systems containing either naked rDNA or pre-assembled chromatin templates (Philimonenko *et al.*, 2004). Interestingly, anti-actin antibody did not affect the synthesis of initial trinucleotide (initiation phase) but inhibited the synthesis of run-off transcripts (elongation phase), indicating that actin is required for RNA polymerase I transcription in post-initiation steps.

Nuclear myosin 1 (NM1), a short-tailed myosin acting as an actin-dependent ATPase, has also been found in nucleoli (Fomproix and Percipalle, 2004), suggesting that actin and myosin might work together as actomyosin in transcription. NM1 and actin are present in a complex with RNA polymerase I (Fomproix and Percipalle, 2004; Philimonenko *et al.*, 2004). The same as actin, NM1 is present on the rDNA promoter and antibodies directly against

NM1 also inhibited RNA polymerase I transcription both in *in vivo* and *in vitro* transcription assays (Percipalle *et al.*, 2006;Philimonenko *et al.*, 2004). Previously, two contradictory findings were reported on this subject. One study showed that NM1 is not associated with the coding region (Philimonenko *et al.*, 2004); however another similar study using different anti-NM1 antibodies demonstrated that a fraction of nucleolar NM1 is associated with the coding region (Percipalle *et al.*, 2006). A possible reason for these discrepant findings could be that NM1 has different conformations during different steps of transcription, which could be recognized by different antibodies. Philimonenko and co-workers have shown that actin can directly interact with RNA polymerase I independent of whether or not it is engaged in transcription; however, NM1 binds to the transcription machinery via interaction with TIF-IA (Philimonenko *et al.*, 2004). TIF-IA is a RNA polymerase I-specific transcription initiation factor that mediates growth-dependent regulation of RNA polymerase I activity and rRNA transcription (Grummt, 2003). Based on these findings, one could speculate that actin and NM1 get close in proximity that they can interact with each other during the formation of transcription initiation complex and presumably activate RNA polymerase activity and rRNA synthesis. Ye and co-workers' studies provided further support to this hypothesis (Ye et al., 2008). In addition, NM1 was also found to be present on the coding region of 18S and 28S genes as a component of the chromatin remodelling complex B-WICH, which comprises the William syndrome transcription factor (WSTF) and SNF2h besides NM1, and is required for RNA polymerase I transcription activation and maintenance (Percipalle *et al.*, 2006). This suggests that MN1 is also implicated in the post-initiation phases of transcription. Recently, a study showed that knockdown of WSTF resulted in reduced recruitment of HATs at the rDNA which coincided with a lower level of histone acetylation.

5.2 Role of actin in transcription by RNA polymerase II

A number of studies have supported the role of actin in RNA polymerase II transcription machinery. Firstly, actin is co-purified with RNA polymerase II (Egly *et al.*, 1984;Hofmann *et al.*, 2004;Smith *et al.*, 1979), which maybe a general feature, as actin is also co-purified with RNA polymerase I (see 5.1) and III (see 5.3). Secondly, microinjection of anti-actin antibodies into the nuclei of *Xenopus* oocytes blocks chromosome condensation (Rungger *et al.*, 1979), and microinjecting antibodies directed against actin or Arps inhibit RNA polymerase II-mediated transcription (Hofmann *et al.*, 2004;Scheer *et al.*, 1984;Xu *et al.*, 2010). Thirdly, actin is a component of preinitiation complexes (Figure 1A), and the formations of preinitiation complexes are blocked by depletion of actin from nuclear extracts (Hofmann *et al.*, 2004). Fourthly, ChIP assays showed that actin can be recruited to the promoters of actively transcribed genes (Hofmann *et al.*, 2004;Xu *et al.*, 2010). For example, actin is absent from the promoters of the interferon-γ-inducible gene MHC2TA and interferon-α-inducible gene G1P3 before induction but it is associated with their promoters after gene induction. Recently, using ChIP-on chip assays, we have demonstrated that actin is recruited to a wide range of gene promoters during the PMA-induced macrophage-like differentiation of HL-60 cells. These data disprove the notion that actin might non-specifically interacts with the promoter regions. If this was the case, β-actin would have been found at the promoter of all genes even in the absence of induction. Even though significant progress has been made, the mechanisms of how actin is getting selectively recruited to the target genes still remains unknown.

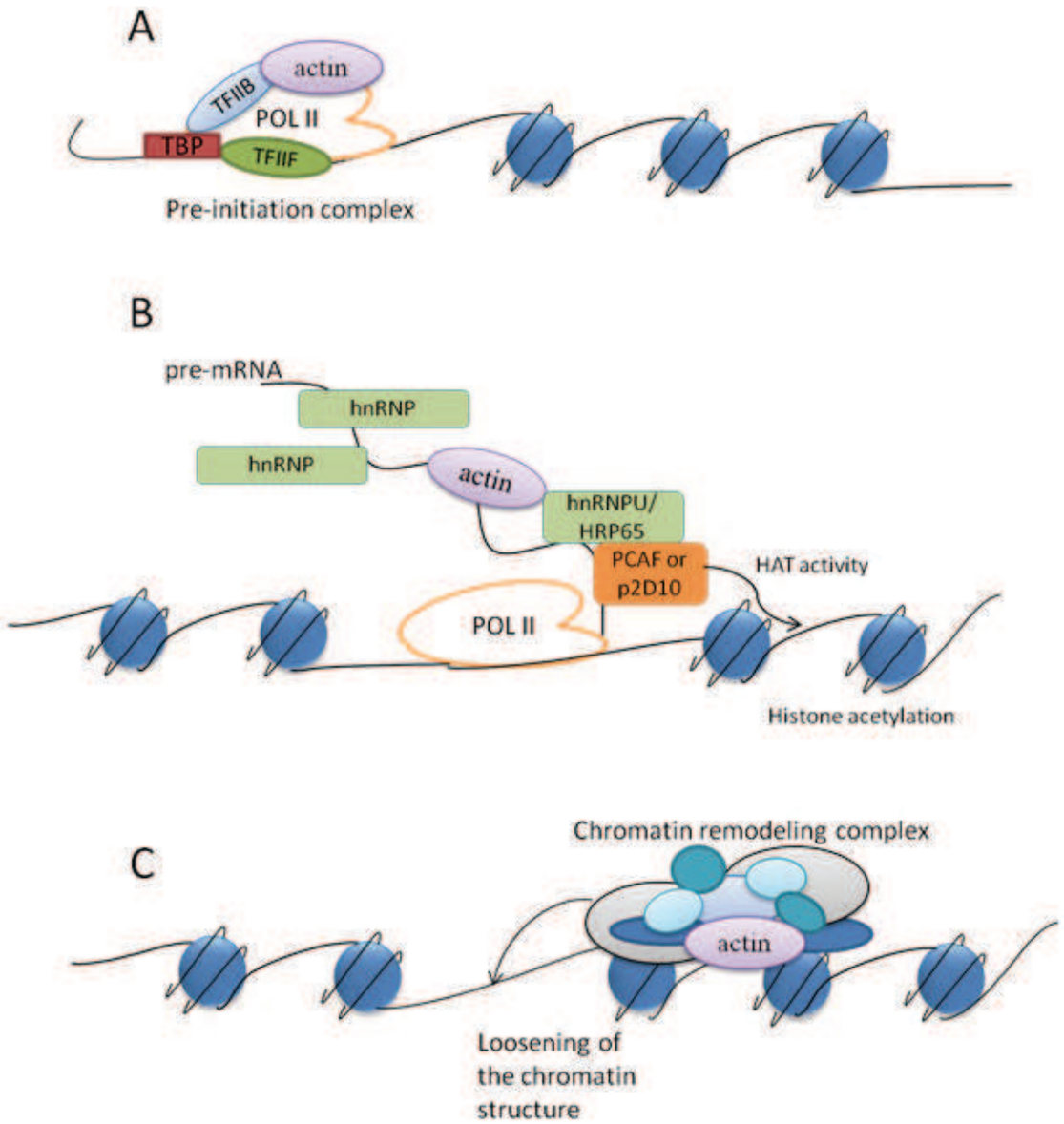

Fig. 1. Model for the function of actin in RNA polymerase II mediated transcription.

(A) Actin can interact with RNA polymerase II and is involved in the formation of preinitiation complex, and affect transcription directly. (B) Actin participates in the recruitment of histone modifying enzymes to protein-coding genes. Actin binds to hnRNP proteins and becomes incorporated into pre-mRNPs. Actin forms a complex with adaptor proteins, such as hnRNP U in mammals and HRP65 in *C. tentans*, and facilitates the recruitment of HATs, such as PCAF and p2D10 to the transcribing gene. HATs acetylate histones that maintain genes in active state. (C) Actin is implicated in chromatin remodelling as a component of ATP-dependent chromatin remodelling complexes. TBP, TATA binding protein; TFII B and TFII F, transcription factor II B and transcription factor IIF; Pol II, RNA polymerase II; hnRNP U, heterogeneous nuclear protein U; HAT, histone acetyltransferase.

5.3 Role of actin in RNA transcription by RNA polymerase III

Actin also plays an important role in RNA polymerase III transcription. Hu and colleagues have shown that actin can be co-purified with either tagged or endogenous RNA polymerase III, like with polymerase I and II (Hu *et al.*, 2003;Hu *et al.*, 2004). Moreover, β-actin was found to be associated with RNA polymerase III via direct protein-protein interactions with at least one of three RNA polymerase III subunits RPC3, RPABC2 and RPABC3. ChIP assays showed that β-actin is located at the promoter region of actively transcribed U6 gene, and can be dissociated from RNA polymerase III complex after inhibition of transcription by methane methylsulfonate (MMS), which resulted in the appearance of an inactivate RNA polymerase III. Notably, in an *in vitro* U6 transcription system, this inactive RNA polymerase III was not able to perform transcription, while adding exogenous β-actin reconstituted the transcriptional activity. These data indicate a crucial role for actin in RNA polymerase III-mediated transcription.

5.4 Regulation of subcellular localization and activity of transcription factor

It has been shown that nuclear actin is associated with the transcription activity of the serum response factor (SRF), a member of highly conserved MADX box family of transcription factors. SRF regulates the expression of immediate-early genes such as c-fos and actin, as well as muscle-specific genes, and these target genes are involved in cell growth, proliferation, differentiation and cytoskeletal organization (Miano, 2003). Myocardin and myocardin-related transcription factors (MRTFs) act as powerful cofactor of SRF in mammalian cells (Cen *et al.*, 2004;Parmacek, 2007). MRTF-A (also known as MAL and MKL1) is a G-actin binding protein and its subcellular localization and activity are regulated by the concentration of monomeric actin (Miralles *et al.*, 2003;Vartiainen *et al.*, 2007). In serum-starved NIH 3T3 cells, MRTF-A predominantly resides in the cytoplasm, where it interact with G-actin via its N-terminal RPEL domain (Guettler *et al.*, 2008;Miralles *et al.*, 2003). Activation of RhoA signalling, by stimulation with serum for example, results in increased actin polymerization and decreased G-actin level, respectively. Sensing depletion of the G-actin pool, MRTF-A dissociates from G-actin and rapidly accumulates in nucleus. In the nucleus, MRTF-As physically associate with SRF, facilitating the binding of SRF to CArG box to activate the transcription of target genes (Du *et al.*, 2004;Vartiainen *et al.*, 2007;Zhou and Herring, 2005). MRTF-A contains an unusually long bipartite NLS located within the RPEL domain. Pawlowski and colleagues demonstrated that importin α/β heterodimer competitively binds to the RPEL domain with G-actin via interaction with NLS. Importantly, this binding was shown to mediate the nuclear import of MATF-A (Pawlowski *et al.*, 2010). MRTF-A also binds G-actin in the nucleus and this association is required for export of MRTF-A from the nucleus (Guettler *et al.*, 2008;Vartiainen *et al.*, 2007). Furthermore, actin binding to MRTF-A in the nucleus inhibits the activity of the latter, and subsequently SRF-mediated transcription. Therefore, actin regulates SRF activity through modulating the sublocalization of MRTF-A and its activity within the nucleus (Vartiainen *et al.*, 2007). (Figure 2).

Striated muscle activator of Rho signalling (STARS), a muscle-specific ABP, is capable of stimulating the transcription activity of SRF through a mechanism involving RhoA activation and actin polymerization. MRTFs, including MRTF-A and MRTF-B, were shown to serve as a linker between STARS stimulation and SRF activity (Arai *et al.*, 2002). Studies have demonstrated that STARS can substitute for serum signalling and promote the nuclear traslocation of MRTF-A and MRTF-B, and subsequently activate the SRF-dependent transcription (Kuwahara *et al.*, 2005). The STARS protein contains a conserved actin-binding

domain within the 142 residues of C-terminus (Arai *et al.*, 2002). The C-terminal mutant of STARS, N233, which cannot bind actin, was unable to induce the nuclear translocation of MATF-A and MATF-B and to enhance the MRTF-mediated activation of SRF- dependent transcription. In contrast, the C-terminal 142 amino acids of STARS, which can bind actin , was shown to induce the nuclear accumulation of MRTFs and to synergistically enhance the MRTF-mediated transcription activation as efficiently as full-length STARS (Kuwahara *et al.*, 2005). In addition, stimulation of nuclear translocation of MRTFs by STARS can be inhibited by Latrunculin B. Similarly, inhibition of Rho A activity by treatment with C3 transferase or by the expression of dominant-negative Rho A prevents nuclear accumulation of MRTFs and subsequently MRTF-mediated SRF activation (Kuwahara *et al.*, 2005). Although Rho A activity is required in this process, it seems not to act as a downstream effector of STARS, since Rho A activity in STARS-transfected cells does not appear to be different from that observed in untransfected cells. However, it has been well documented that STARS requires Rho-actin signalling to evoke its stimulatory effects. As STARS binds to actin and induces actin polymerization (Arai *et al.*, 2002;Kuwahara *et al.*, 2005), it has been suggested that STARS stimulates the MRTF activity by inducing the dissociation of MRTF from actin and subsequently promoting its nuclear accumulation (Figure 2).

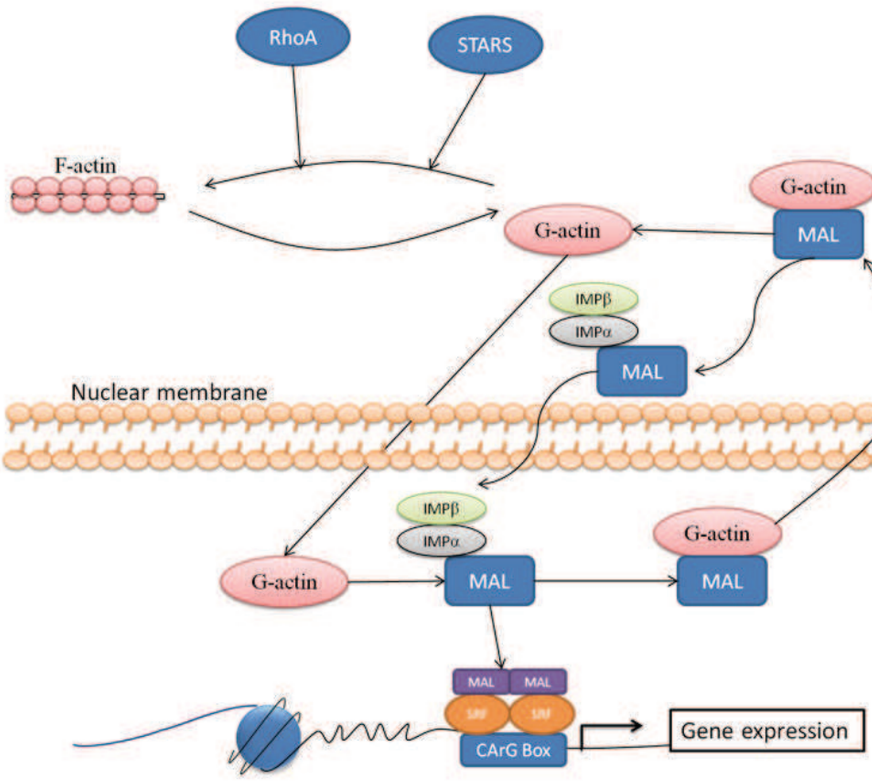

Fig. 2. Model for actin dynamics regulating SRF activity. Rho signalling (non-muscle cells) or STARS signalling (muscle cells) promote the assembly of F-actin from monomeric G-actin. Sensing depletion of G-actin, MAL dissociates from G-actin and is imported into nucleus through binding to heterodimer importin α/β. In the nucleus, MAL binds and activates SRF activity. G- actin also binds MAL in the nucleus and mediates the nuclear export of MAL. STARS, striated muscle activator of Rho signalling; MAL, also known as MRTF-A, myocardin-related transcription factor A; IMPα/β, importin α/β; SRF, serum response factor.

Interestingly, SRF activity is regulated by actin/MRTF interaction and in turn, SRF controls the transcription of many genes encoding actin isoforms and ABPs (Posern and Treisman, 2006;Sun *et al.*, 2006). SRF-regulated genes can encode structural components of actin microfilament (for example, actin), effectors of actin turnover (for example, cofilin 1) as well as regulator of actin dynamics (for example, filamin A)(Olson and Nordheim, 2010).

6. Roles of actin in genome organization

It is well known that the eukaryotic nucleus is highly organized into morphologically and functionally distinct subnuclear compartments, which spatially separate different physiological processes. These compartments include chromatin territories, proteinaceous nuclear bodies (e.g. nucleolus, Cajal body, speckle and PML body), compartmentalized multiprotein complexes such as transcription factories, and nuclear pore complexes that regulate nucleocytoplasmic transport of certain molecules. Within the interphase nuclei, chromosomes are non-randomly organized, but occupy discrete regions, known as chromosome territories (CTs). This was first suggested by Rabel in 1885, but until almost one hundred years later, Cremer and his group carried out experiments to indirectly demonstrate the existence of CTs (Cremer *et al.*, 1982). By using non-radioactive *in situ* hybridization, several groups unequivocally confirmed that the chromosomes are not distributed throughout the nucleus during the interphase, but confined to subnuclear domains (Borden and Manuelidis, 1988;Lichter *et al.*, 1988;Schardin *et al.*, 1985). Initial reports, based mainly on fluorescence *in situ* hybridization (FISH) demonstrated that these CTs are non-overlapping. However, Branco and co-workers (Branco and Pombo, 2006), using a high resolution cryo-FISH technique, revealed a significant intermingling of CTs in interphase, suggesting CTs interact more than previous thought. Interestingly, gene-rich CTs tend to occupy the interior of the nucleus, whereas many of the gene-poor chromosomes are associated with the nuclear periphery (Cremer *et al.*, 2001;Croft *et al.*, 1999). The gene-density-correlated radial organization of CTs was confirmed by analyses comprising all human chromosomes (Boyle *et al.*, 2001). This non-random radial distribution of CTs was also observed in rodents (Neusser *et al.*, 2007), cattle (Koehler *et al.*, 2009) and birds (Habermann *et al.*, 2001), suggesting that it has been evolutionary conserved. In addition, chromosome size-correlated radial arrangements have also been described (Sun *et al.*, 2000) and such organization seems to occur in flat nuclei (Bolzer *et al.*, 2005). However, the genome organization of eukaryotic cells is dynamic and chromosome arrangement can change in response to cellular signals.

An association of actin with various chromatin states has been shown by a number of studies (Milankov and De, 1993;Sauman and Berry, 1994). Bacterial actin was shown to be involved in plasmid and chromosome segregation (Becker *et al.*, 2006;Moller-Jensen *et al.*, 2007). In eukaryotic cell, chromosome segregation is generally driven by microtubules, however, in the oocyte of starfish, chromosome congression requires actin polymerization (Lenart *et al.*, 2005). Mehta and colleagues have recently demonstrated that CTs relocate in quiescent human fibroblasts (Mehta *et al.*, 2010). In the absence of serum stimulation, a number of chromosomes were observed to change position in the interphase nuclei; however, this kind of chromosome movement can be prevented by the inhibition of actin and myosin polymerization or knockdown of nuclear myosin 1β by RNA interference experiments. Inhibition of ATPase and/or GTPase also blocked the chromosome movement

upon serum withdrawal, suggesting that this kind of chromosome movement is an energy-dependent active process. In an earlier study, using a novel tool to visualize chromatin movement in living cells, Chuang and co-workers (Chuang *et al.*, 2006) reported long-range vectorial movements of chromatin exceeding 1μm. Furthermore, the authors found that repositioning of a chromatin locus was completely abolished in cells transfected with a nonpolymerizable actin mutant, whereas a mutant stabilizing filamentous actin accelerated locus redistribution. Transfection with a myosin mutant significantly delayed locus reposition. Dundr and colleagues (Dundr *et al.*, 2007) analyzed the dynamic association between Cajal bodies and U2 snRNA gene. Upon transcriptional activation, the chromosome region containing U2 snRNA genes moved toward the Cajal bodies which are relatively stably positioned. Inactivated U2 snRNA genes do not associate with the Cajal bodies. Similarly, this process was also found to be actin-dependent.

Actin and NM1 are also required for estrogen-induced interchromosomal interactions. Two estrogen-regulated loci, TFF1 and GREB1, located in different chromosomes colocalize after stimulation with 17β-estradiol (Hu *et al.*, 2008). This interaction was blocked by treatment of the cells with Latrunculin or jasplakinolide, which inhibit actin polymerization and depolymerisation, respectively. Depletion of actin or NM1 by siRNAs or nuclear microinjection of specific antibodies against NM1 also blocked the interaction. Furthermore, the inhibitory effect of anti-NM1 antibodies could be rescued by the expression of wild-type NM1, but not by the expression of NM1 mutant deficient in ATPase or actin-binding activity. The results demonstrate that the dynamics of nuclear actin affect the chromatin movement and gene positioning. How actin and NM1 cooperate to organize genome and facilitate the regulation of gene expression still needs to be studied in more detail.

7. Conclusion

The past decade has seen great advances in discovering the versatile functions of actin in the nucleus. Actin participates not only in the basal transcription mediated by all three RNA polymerases, as a component of RNA polymerase complex or pre-mRNP particles, but also in the transcriptional regulation as a component of chromosome remodelling complex. Actin also plays a role in movement, organization, and regulation of chromatin and activated genes in the nucleus. In addition, actin acts as a multifunctional brick in the nuclear architecture to help maintain nuclear shape, spatial order and nuclear functions. The challenge now is to understand the molecular mechanisms that underlie the many functions of actin in these nuclear processes.

In recent years, studies have shown that nuclear actin can exist as a polymeric form and that actin polymerization is implicated in transcription (Wu *et al.*, 2006;Ye *et al.*, 2008;Yoo *et al.*, 2007). However, the form of actin in various complexes associated with transcription seem to be monomeric and its functions in theses complexes do not appear to require polymerization/depolymerisation dynamics. There are two possible explanations for why this is so. First, actin polymerization may maintain a proper G-actin pool for transcription. Second, the polymeric state affects the movement of gene loci (Hu *et al.*, 2008), therefore, may affect the transcription. From this view point, it is important to address the dynamic behaviour of nuclear actin in order to understand how actin regulates transcription, for example, how actin polymerization is regulated inside the nucleus. What are the roles of

ABPs in the nucleus? It seems that many APBs have specific nuclear functions that are not related to the regulation of actin dynamics. Therefore, identifying novel ABPs is expected to be an important way to understand the regulation of actin polymerization. In addition, there is evidence to show the existence of a communication between cytoplasmic actin and nuclear actin pool (Vartiainen *et al.*, 2007). But what are the signalling pathways that link cytoplasmic actin dynamics and nuclear actin behaviour? What are the mechanisms that controlling the nucleocytoplasmic shuttling of the actin? Although actin has functional NESs, it is always found to be exported in a complex with other cargo, for example with profilin and with MRTF-A.

Recently, studies have well documented that both nuclear actin and NM1 are implicated in the movement of CTs and chromosomal loci. The interactions of chromosomal loci with functional subnuclear domains, such as Cajal bodies, as well as interactions between distinct chromosomal loci are important for transcriptional regulation and genome-based nuclear processes. It is most likely that actin cooperates with NM1 as a motor to drive and direct the movement of chromosomal loci. Nevertheless, actin may also acts as a component of chromatin remodelling complex to relax the chromatin structure. New technologies need to be developed to investigate exact mechanisms of involvement of actin and NM1 in movement of chromosomal loci. In summary, there is still a long way to fully understanding the complexity of actin in the structural and functional networks of the nucleus.

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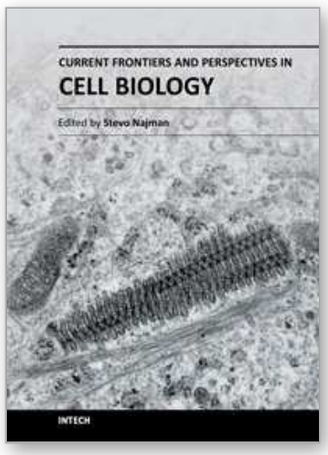

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