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Essay

Nuclear Actin Extends, with No Contraction in Sight

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Within the past two years, actin has been implicated in eukaryotic gene transcription by all three classes of RNA polymerase. Moreover, within just the past year, actin has been identified as a constituent of filaments attached to the nuclear pore complexes and extending into the nucleus. This review summarizes these and other very recent advances in the nuclear actin field and emphasizes the key present issues. On the one hand, we are confronted with a body of evidence for a role of actin in gene transcription but with no known structural basis; on the other hand, there is now evidence for polymeric actin—not likely in the classical F-actin conformation—in the nuclear periphery with no known function. In addition, numerous proteins that interact with either G- or F-actin are increasingly being detected in the nucleus, suggesting that both monomeric and oligomeric or polymeric forms of actin are at play and raising the possibility that the equilibrium between them, perhaps differentially regulated at various intranuclear sites, may be a major determinant of nuclear function.

INTRODUCTION

Actin and myosin were first discovered as actomyosin by Kuhne in 1861, but it was not until 1939–1942 that actin itself was isolated by Straub, Bonga and Szent-Gyorgyi, and myosin was discovered to be an ATPase by Engelhardt and Lyobimova (Szent-Gyorgyi, 2004). By the 1970s, the presence of actin and myosin in nonmuscle cells had been firmly established (Hatano and Oosawa, 1966; Adelman and Taylor, 1969a,b; Ishikawa *et al*., 1969; Pollard *et al*., 1970; Weihing and Korn, 1971; Pollard and Korn, 1973; Lazarides and Weber, 1974; Garrels and Gibson, 1976), and although their localization was mainly cytoplasmic, numerous subsequent observations suggested the existence of nuclear actin and myosin as well. Recently, we and others have reviewed the nuclear actin field (Pederson and Aebi, 2002; Olave *et al*., 2002; Shumaker *et al*., 2003; Bettinger *et al*., 2004; Blessing *et al*., 2004). The two key questions have been "in what form" and "what for"? Particularly significant progress has been made in just the past year or so, and thus it is already time to assess these new developments and ask whether a coherent picture is now coming into view.

ACTIN AND mRNA TRANSCRIPTION

The first solid evidence for a link between actin and gene transcription came from experiments in which actin antibodies or actin-binding proteins were injected into the germinal vesicle of salamander oocytes, resulting in a retraction of nascent RNA on the lateral loops of the meiotic ("lampbrush") chromosomes (Scheer *et al*., 1984). These investigators also reported the formation of a perichromosomal meshwork of filaments when transcription was inhibited by actinomycin and suggested that these filaments were actin, based on their observed fragmentation by the F-actin-severing protein fragmin. Although the Scheer *et al*. article had a degree of impact, it did not generate a following in the eukaryotic transcription field. Ironically, at just the same time there was a beacon from a major transcription laboratory hinting at actin as an important factor (Egly *et al*., 1984), but this finding, too, was also largely ignored. It is sobering to note that virtually all of the experimental systems and biochemical knowledge of transcription that have very recently been used to definitively implicate actin were available in 1984. As often happens, it was a paradigm shift that was needed, not the development of new technology. Although a number of key advances in the nuclear actin field occurred after 1984 (Olave *et al*., 2002; Pederson and Aebi, 2002), it was 17 years before the issue was investigated in further depth. This time, the concept took hold.

In 2001, actin was found to be associated with the Balbiani ring 2 nascent pre-mRNA in *Chironomus* salivary gland polytene chromosomes (Percipalle *et al*., 2001), and soon thereafter the same group reported that actin also forms complexes with the pre-mRNA binding hnRNP A- and B-type proteins (Percipalle *et al*., 2002). Subsequently this group provided evidence that the role of actin in stimulating or sustaining pre-mRNA transcription requires its interaction with heterogeneous nuclear ribonucleoprotein (hnRNP) proteins (Percipalle *et al*., 2003). In short order, another study strongly implicated nuclear actin in RNA polymerase II transcription in growing mammalian cells (Hofmann *et al*., 2004), indicating that a transcriptional role of actin is not limited to the meiosis-arrested amphibian oocyte (Scheer *et al*., 1984) or the insect larval polytene nucleus (Percipalle *et al*., 2001, 2002; Percipalle *et al*., 2003), however implausible that hypothesis might have been.

There have been numerous reports linking nuclear actin to the phenomenon of chromatin remodeling (reviewed in Olave *et al*., 2002), although there has not been uniform

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acceptance of this conclusion. A recent investigation in the aforementioned *Chironomus* system has now added further evidence for a connection among nuclear actin, chromatin remodeling, and RNA polymerase II transcription (Sjölinder *et al*., 2005.) In this study, it was found a peptide that inhibits the actin-nascent pre-mRNP association was counteracted by trichostatin A, which inhibits histone deacetylation. Additional experiments revealed that both actin and the pre-mRNP protein hrp65 are complexed in situ with the histone H3-specific acetyltransferase p2D10 and that disruption of the actin–hrp65 interaction causes release of p2D10 from Pol II-transcribing genes coincident with reduced H3 acetylation and diminished transcription. These new findings (Sjölinder *et al*., 2005) considerably bolster the notion of a link among nuclear actin, chromatin remodeling, and Pol II transcription—the connection between the latter two phenomena already well established.

BEYOND mRNA SYNTHESIS: ACTIN IN RNA POLYMERASE I AND III TRANSCRIPTION

By 2003, most investigators of the nucleus had taken note of the growing evidence for a role of actin as well as a nucleus-specific isoform of myosin I in transcription by RNA polymerase II (Pederson and Aebi, 2002). Then, in rapid succession, two groups published evidence that actin is also involved in transcription by RNA polymerases I and III. Actin was found to be associated with purified Pol III and was also shown to be localized in vivo on a gene known to be transcribed by Pol III (Hu *et al*., 2004). These investigators also reported experiments indicating that when Pol III is inactivated by a specific inhibitor, its associated actin is released and that the polymerase's activity is restored when actin is added back (Hu *et al*., 2004).

At about the same time, evidence was gathered for an involvement of both actin and myosin I in Pol I transcription (Fomproix and Percipalle, 2004; Philimonenko *et al*., 2004). Although Pol II and Pol III transcription takes place on extended chromosomes situated in the nucleoplasm, Pol I transcription occurs deep within the compact nucleolar structure. There is thus no simple large-scale architectural homology between the environment of Pol II- and III-transcribed genes on the one hand, and the setting of Pol I transcription on the other, and this suggests that the role of actin in transcription by all three polymerases is not related to some common element of nuclear organization.

DOES ACTIN BIND A COMMON FACTOR DURING TRANSCRIPTION BY ALL THREE RNA POLYMERASES?

Because actin has now been implicated in transcription by all three RNA polymerases, it is obvious to consider an actin-binding target that is common to the respective transcription machineries. The actin-binding hnRNP A- and B-proteins (Percipalle *et al*., 2002) are unlikely candidates because these only interact with Pol II transcripts. Actin has recently been reported to bind to the C-terminal domain (CTD) of the largest subunit of Pol II (Kukalev *et al*., 2005), but this domain is not present in any of the subunits of Pol I or Pol III. In Pol III transcription, actin was observed to bind directly to three of the enzyme's 17 subunits (when tested individually): RPC3, RPABC2, and RPABC3 (Hu *et al*., 2004). Interestingly, the latter two are common to all three polymerases. In this regard, it is to be borne in mind that the actin-binding properties of the individual subunits of Pol I have not been examined and that in the recent Pol II study the experiments focused on the interaction of actin solely with the hyperphosphorylated CTD of the largest subunit. In addition, it is to be noted that the actin interactions with the polymerases I and II were observed to be influenced by other transcription-related proteins: the Pol I initiation factor TIF-1A (Philimonenko *et al*., 2004), and the hnRNP U protein in the case of Pol II (Kukalev *et al*., 2005). Remaining before us are mechanistic issues such as the specific step or steps of transcription in which actin is involved, presently looking like at least elongation in the case of Pol II (Percipalle *et al*., 2003; Kukalev *et al*., 2005; although see Hofmann *et al*., 2004) and the identity of the actin-interactive proteins such as hnRNP U that collaborate with actin in transcription.

WHAT LIES BENEATH? ACTIN INSIDE THE NUCLEAR ENVELOPE

The studies that implicated actin in gene transcription did not focus on the form of actin that is involved. It had long been known that the nucleus (germinal vesicle) of amphibian oocytes contains unpolymerized actin at a level very close to the critical concentration for polymerization (~0.1 μM; Clark and Merriam, 1977; Gounon and Karsenti, 1981). Whether the nucleus of these oocytes, or any other nuclei, contain some polymerized form of actin—not necessarily in the F-actin conformation—in the living state, amid a vast ocean of monomeric actin, had been long pondered.

In early 2004, field emission scanning electron microscopy (EM) evidence was published for distinct actin and protein 4.1 containing nuclear "pore-linked filaments" (PLFs) that are attached to the nuclear pore complexes of *Xenopus* oocytes and extend into the nucleus (Kiseleva *et al*., 2004). These investigators demonstrated that these PLFs collapsed upon exposure of the oocytes to the actin filament depolymerizing agent latrunculin A. In contrast, jasplakinolide, which stabilizes preexisting actin filaments (Lee *et al*., 1998) and can also induce actin polymerization (Spector *et al*., 1999), produced PLFs with a more open substructure. Immunogold EM of oocyte nuclei revealed that actin and protein 4.1 each localized on PLFs. Whereas the actin-gold epitopes were irregularly spaced along PLFs, the protein 4.1-gold epitopes were spaced at ~120-nm intervals and were often paired (~70 nm apart) at filament junctions. Together, these observations make it rather unlikely that the backbone of PLFs, exhibiting a typical thickness of 40 nm (range, 12–100 nm), is made of F-actin filaments. Thus, it is plausible that PLFs are heterotypic. The p270/Tpr protein has previously been identified as a constitutive component of pore complex-attached intranuclear filaments (Cordes *et al*., 1997), and preliminary immunogold labeling studies (cited in Kiseleva *et al*., 2004) also suggest that PLFs are specifically labeled by antibodies directed against a Tpr-related epitope. Last but not least, the Kiseleva *et al*. images also suggested that some of these PLFs might interact with more internally located nucleoplasmic structures involved in gene transcription (i.e., Cajal bodies and snurposomes; vide infra.) It is also noteworthy that just before the Kiseleva *et al*. study, actin and protein 4.1 had been colocalized in the nucleus of (detergent extracted) human fibroblasts by immuno-EM (Krause *et al*., 2003), although the intranuclear location of these sites relative to the nuclear envelope was not reported.

NUCLEAR ACTIN "RODS"

Nuclear actin "rods," "bundles," and "tubules" have been described by a number of investigators (Fukui and Kat-

sumaru, 1979; Iida *et al*., 1986; Iida and Yahara, 1986; Nishida *et al*., 1987; Wada *et al*., 1998), but their supramolecular organization has remained elusive except for one case (Sameshima *et al*., 2001). These investigators have described a new type of actin rods formed both in the nucleus and the cytoplasm of *Dictyostelium discoideum* that have been implicated in the maintenance of dormancy and viability at the spore stage of the developmental cycle. Examination of their ultrastructure has revealed these actin rods as bundles of hexagonally packed actin tubules consisting of three actin filaments each.

In several instances, cofilin seems to be a major component of intranuclear actin rods (Nishida *et al*., 1987; Wada *et al*., 1998; Aizawa *et al*., 1999). Moreover, because it has been shown that Exp6 mediates export of nuclear actin in a complex with profilin (Stuven *et al*., 2003), it would be important to determine whether profilin is in fact a component of the intranuclear actin bundles. In this context, profilin has been observed in mammalian cell Cajal bodies and interchromatin granule clusters (Skare *et al*., 2003), the latter constituting the mammalian homologues of amphibian oocyte snurposomes. In addition, actin has been reported to partially colocalize with Cajal bodies (Gedge *et al*., 2005), and actin has also been implicated in mRNA export from the nucleus (Hofmann *et al*., 2001; Kimura *et al*., 2000). The discovery of actin-containing filaments attached to the nuclear envelope (Kiseleva *et al*., 2004) together with other recent findings (Dahl *et al*., 2004; Holaska *et al*., 2004; Libotte *et al*., 2005) are beginning to raise the possibility that there is a perinucleoplasmic, infranuclear envelope "cortex" of actin that dynamically interacts with the nuclear lamina and nuclear pore complexes and that plays a critical role in molecular export from the nucleus or nucleocytoplasmic interactions. Here, too, it is (very) early days, particularly when it comes to the question as to the form that this putative nuclear actin cortex assumes in terms of actin conformation, oligomerization, and/or polymer formation.

DISTINCT ANTIGENIC SIGNATURES OF NUCLEAR VERSUS CYTOPLASMIC ACTIN

At the time of our previous review (Pederson and Aebi, 2002), there was some evidence that nuclear actin exhibited epitopes that are "shielded" in cytoplasmic actin and vice versa, such that they differentially react with a monoclonal anti-actin antibody (Gonsior *et al*., 1999). The hypothesis that nuclear actin (or some fraction of the nuclear actin) possesses a distinct immunological signature, and therefore presumably a distinct conformation and/or oligomeric/polymeric state, has been supported in a recent study in which two monoclonal anti-actin antibodies were compared whose reactivities provide evidence that more than one conformation of actin is present in the nucleus of mammalian cells (Schönenberger, Buchmeier, Sutterlin, Aebi, and Jockush, personal communication of unpublished results). Also to be borne in mind is the possibility that the nuclear and cytoplasmic populations of actin in a given cell are distinct isoforms of the protein. Vertebrate genomes contain multiple genes encoding distinct isoforms of nonmuscle (non-α)-actin (Engel *et al*., 1982; Pollard, 2001) and it is certainly possible that the major nuclear and cytoplasmic populations differ in amino acid sequence. The fact that actin dynamically exchanges between the nucleus and cytoplasm in *Xenopus* oocytes (Clark and Merriam, 1977) does not exclude the possibility of a second isoform being more nuclear restricted. We may recall here that at least in vitro, actin can form supramolecular assemblies that are different from the classical F-actin filament (e.g., Millonig *et al*., 1988; Steinmetz *et al*., 1997; Schoenenberger *et al*., 2002). In fact, these assemblies are built from an actin dimer (the so-called "lower dimer" based on its migration in nondenaturing gel electrophoresis) that assumes a conformation distinct from that of F-actin (Bubb *et al*., 2002; Reutzel *et al*., 2004).

ARE THERE OTHER ROLES FOR NUCLEAR ACTIN?

A recent study has revealed that herpesvirus particles are transported within the nucleus of infected cells by a spatially directed process that is dependent on metabolic energy and blocked by the alleged myosin-targeting inhibitor 2,3-butanedione dioxime (BDM) and also by latrunculin-A (Forest *et al*., 2005). The facts that BDM is no longer accepted as a specific myosin inhibitor and that viral transport within the nucleus was insensitive to actin depolymerization mediated by cytochalasin D weaken the authors' conclusion. However, that the transport was spatially directed and dependent on metabolic energy were convincingly demonstrated and certainly suggest a filament-based transport process. These findings take on added interest in view of the fact that several studies have revealed that host cell proteins and RNAs move within the nucleus of mammalian cells by a diffusion-driven process (Politz *et al*., 1999, 2003; Politz and Pederson, 2000; Misteli, 2001; Shav-Tal *et al*., 2004), indicating that the intranuclear transport of herpesvirus capsids may be an exception.

Yet another recent investigation has demonstrated a role for actin polymerization in chromosome capture and metaphase congression during activation of meiosis I in large oocytes in which spatial considerations had raised the possibility of a nonmicrotubule-based mechanism (Lenart *et al*., 2005). Although this is a most intriguing new finding, it is not yet clear (despite the article's title) whether the actin that participates in this phenomenon is intranuclear before nuclear envelope breakdown. The starfish oocytes used in this study are arrested at prophase and have intact nuclear envelopes before activation so it is possible that the participating actin is initially cytoplasmic and moves into the former nuclear zone, in either an unpolymerized or polymerized state, after nuclear envelope breakdown. This caveat in no way reduces the significance of these findings but simply leaves open the question of whether this is a role of nuclear actin sensu stricto. In another recent study a role of actin was uncovered in meiotic telomere clustering in *Saccharomyces cerevisiae* (Trelles-Sticken *et al*., 2005.) This actin-based telomere clustering produces a chromosomal "bouquet" at the at the leptotene-zygotene transition. Because this stage of meiosis precedes nuclear envelope disassembly, this recently described role of actin in telomere clustering constitutes an intranuclear phenomenon.

ACTIN-BINDING PROTEINS IN THE NUCLEUS

A rather large number of actin-binding proteins has now been identified in the nucleus of various cells, summarized in Table 1. These are to be contrasted with nuclear actin-*related* proteins, or arps, which have been reviewed in detail recently (Blessing *et al*., 2004) and are not discussed further here. As can be seen, the reported nuclear actin-binding proteins include ones that classically bind to either G- or F-actin, but in no case has the form of nuclear actin bound by these proteins been unequivocally established. It is also to be noted that some of the entries in Table 1 bind actin rather weakly, e.g., the protein 4.1–actin interaction has a dissociation equilibrium constant in the millimolar range. The func-

Table 1. Actin-binding proteins in the nucleus

Protein	Function	Reference
Profilin I	Unknown	Skare *et al.* (2003)
Thymosin β_4	Unknown	Huff *et al.* (2004)
Myosin I	RNA polymerase I transcription	Fomproix and Percipalle (2004), Philimonenko *et al.* (2004), Pestic-Dragovich *et al.* (2000)
Filamin	Androgen receptor action	Ozanne *et al.* (2000)
Supervillin	Androgen receptor action	Ting *et al.* (2002)
Gelsolin	Androgen receptor action	Nishimura *et al.* (2003)
CapG	Unknown	De Corte *et al.* (2004)
Emerin	Cortical network at the inner nuclear membrane	Holaska *et al.* (2004)
Band 4.1	Nuclear pore-attached filament association	Kiseleva *et al.* (2004)
Tropomodulin	Unknown	Kong and Kedes (2004)
NUANCE	Linkage to cytoplasmic actin filaments	Zhen *et al.* (2002), Libotte *et al.* (2005)
hnRNP U	RNA polymerase II transcription	Kukalev *et al.* (2005)
DNA helicase II/ RNA helicase A	RNA polymerase II transcription and RNA processing	Zhang *et al.* (2002)

tions of these various nuclear actin-binding proteins have not been comprehensively studied in all cases, and those functions listed should be viewed as simply the current snapshot.

WHAT DO WE MOST NEED TO KNOW NEXT?

There is presently no experimental evidence for the existence of filamentous structures at sites of gene transcription, notwithstanding controversial claims of an in vivo "nuclear matrix," which did not invoke actin in any case (Pederson, 1998, 2002). Nevertheless, a recent study suggests that nuclear actin might be a determinant in the partitioning of certain proteins between the soluble or residual fraction when nuclei are extracted to produce the nuclear matrix biochemical fraction (Andrin and Hendzel, 2004).

A major issue then is to define the stoichiometry and molecular organization of actin at sites of gene transcription. One possibility is that to perform its role in gene transcription, actin assembles into some sort of unconventional oligomeric or polymeric structure that has not yet been observed in ultrastructural studies of active genes. The finding that (presumably monomeric) actin forms complexes with hnRNP proteins (Percipalle *et al*., 2001, 2002, 2003; Kukalev *et al*., 2005) suggests that numerous actin subunits might be brought into proximity along a single nascent Pol II transcript, a situation possibly conducive to promoting a template-mediated actin polymerization process yielding conventional F-actin filaments or perhaps an unconventional form of actin, such as the lower dimer, for example (Millonig *et al*., 1988; Steinmetz *et al*., 1997; Bubb *et al*., 2002; Schoenenberger *et al*., 2002; Reutzel *et al*., 2004).

The second area in which much more needs to be learned is how actin interacts with all three transcription machineries. This includes both the many subunits of all three polymerases, already well done for Pol III (Hu *et al*., 2004), and the many transcription factors and other accessory proteins for each polymerase. At the least, this may help to define how actin works in each case, and, at the most optimistic, such studies may reveal common features that will provide a fundamental insight as to how this ancient protein has collaborated with gene transcription during eukaryotic evolution.

The third frontier concerns the PLFs (Kiseleva *et al*., 2004) as well as nuclear actin rods. Their existence in other cell types needs to be scrutinized and their molecular architecture must be dissected. The elegantly studied *Chironomus* BR2 mRNP (Daneholt, 1999) would seem to be a perfect system for investigating this issue, hopefully capturing temporal events just before the remarkable nuclear pore transits of this RNP already captured (Stevens and Swift, 1966; Daneholt, 1999).

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