Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Cell Biology

Dynamizing nuclear actin filaments

Matthias Plessner and Robert Grosse

While it is long known that actin is part of the nuclear proteome, its properties and functions as regulated, functional and dynamically assembled actin filaments are only recently emerging. Thus, newly uncovered roles for intranuclear actin filaments are opening new perspectives on how the nucleus and its genomic content may be organized in particular with regard to a given stage of the cell cycle. Here, we summarize recent studies on actin filament polymerization and turnover within the nuclear compartment of mammalian cells. We emphasize and discuss novel findings, in which transient and dynamic nuclear actin filaments have been visualized in physiological contexts, and focus on aspects of signalling mechanisms, chromatin reorganization and DNA repair. Further, a better understanding of the spatiotemporal control of nuclear actin-regulating factors in mammalian cells will ultimately provide a more detailed view on how the nuclear F-actin cytoskeleton contributes to genome organization and nuclear architecture.

Address
Institute of Pharmacology, Medical Faculty, University of Marburg, Karl-von-Frisch-Str. 2, 35043 Marburg, Germany

Corresponding author:
Grosse, Robert (robert.grosse@staff.uni-marburg.de)

Current Opinion in Cell Biology 2019, **56**:1–6

This review comes from a themed issue on **Cell architecture**

Edited by **Johanna Ivaska** and **Manuel Théry**

https://doi.org/10.1016/j.ceb.2018.08.005

Introduction

A great deal is known about the precise molecular mechanisms as well as the cellular and physiological functions of actin polymerization and actin filament dynamics. However, whether a functional and regulated actin filament cytoskeleton operates in somatic cell nuclei is not well understood. As cell biologists adhere to the credo 'seeing is believing', they expect to be given solid evidence of the existence of the actin cytoskeleton in the nucleus by means of crystal clear live fluorescence microscopy images. However, F-actin visualization is challenging and difficult in the nucleus. Thus, researchers studying what is widely called 'nuclear actin' frequently face scepticism and disbelief. Actin is actively transported between cytoplasm and nucleus [1], and hence the molecule to be visualized is the same in both compartments. In that regard, it should also be considered that endogenous filamentous actin (F-actin) structures are generally rather difficult to visualize, particularly in living cells due to their highly dynamic turnover as well as the size and width of actin filaments in comparison to microtubules or intracellular membranes. In addition, actin concentrations in somatic cell nuclei are significantly lower when compared to the cytoplasm while at the same time actin and actin regulatory factors are constantly shuttling between both compartments [1]. Recent advances allowing for controlled visualization of actin filaments in cell nuclei have now paved the way for a better understanding of the roles and properties of nuclear actin dynamics [1–3] and permit the discussion of new concepts [4].

In this short review, we will emphasize the most recent discoveries and observations on intranuclear actin filaments exerting physiological cellular functions, which may open novel directions of research to better understand nuclear architecture and organization. Due to space limitations, we will not discuss bottlenecks and advantages of nuclear actin probing concepts, which have been reviewed very recently [5]. As a variety of actin-regulating proteins has been identified to play a functional role in the nucleus, we will further highlight recent progress on mammalian nuclear actin regulators and their functions (Table 1).

Physiological F-actin structures form in somatic cell nuclei

Although the presence of monomeric actin in somatic cell nuclei was long appreciated, it was generally assumed that F-actin only dynamically forms in the cytoplasm. Studies from *Xenopus laevis* oocytes showed that nuclear F-actin can promote gene regulation, transcriptional reprogramming and chromatin tethering to the nuclear envelope [6,7]; however, oocyte nuclei are large with high nuclear actin concentrations, thus it remained unclear whether such processes take place in somatic cells.

The breakthrough leading to somatic intranuclear actin visualization came with the idea of targeting commonly used actin probes to the nuclear compartment, finally allowing F-actin structures to be studied in intact living cells [8,9]. Thus, it could be shown that serum stimulation leads to a rapid and transient actin network assembly, which promoted MRTF-A (MAL) nuclear retention for transcriptional regulation of serum response factor (SRF), an essential and core regulator of extracellular signal-controlled gene expression [8]. This study further

Table 1

Recently described nuclear actin regulators and their functions in mammalian cells. This table summarizes selected mammalian actin-regulating factors, for which nuclear functions were identified

Factor	Function
Arp2/3 complex (ARPC2 and ARCP4)	Nuclear F-actin assembly for DSB clustering and repair (by HDR) [25••,26••]
Cofilin-1	Disassembly of nuclear F-actin during early G1 [19••]
Filamin A	MRTF/SRF-dependent transcription [17]
FMN2	Nuclear accumulation in response to DNA damage [9]
	Nuclear F-actin assembly during DNA damage [9]
	DSB clustering [23]
mDia2	CENP-A loading and nucleosome maintenance (actin assembly function) [14•]
	Nuclear F-actin assembly during cell spreading, fibronectin [11] and serum [8] stimulation (with mDia1)
Myo1A, Myo1B MyoV	DSB clustering (motor function) [25••]
Myo1C	Nuclear import dependent on ER interactions and phosphoinositide binding [30]
SCAI	DSB repair [29]
	Meiotic recombination [29]
Spire1, Spire2	Nuclear actin assembly during DNA damage [9]
SUN2	DSB clustering [23]
	Nuclear actin assembly during cell spreading and fibronectin stimulation (with SUN1) [11]
WASP	Nuclear Arp2/3 complex activation during DNA repair [26••]

demonstrated that the activation of endogenous Diaphanous formins (mDia1 and mDia2) using an optogenetic trigger for release of protein autoinhibition lead to dynamic and transient intranuclear actin polymerization. The reversibility and repeatability of optogenetically controlled intranuclear actin polymerization provided proof of concept that somatic cell nuclei retain the capacity to polymerize actin through regulation and activation of actin nucleation factors [8].

The actin assembly factors mDia1 and mDia2 were also found to be important for intranuclear actin assembly and MRTF activation upon integrin activation during cell spreading, which depended on the functional integrity of the LINC complex [10,11]. Hence, this study demonstrated that extracellular signals can be transduced via the LINC complex leading to intranuclear formin-dependent F-actin assembly and subsequent MRTF activation.

In another effort to visualize intranuclear actin it was shown that actin foci can be detected in the interchromatin space when a derivative of the actin binding probe Utrophin was targeted to the nuclear compartment by a nuclear localization signal (NLS) [12], suggesting that short F-actin structures are present even in unstimulated interphase cell nuclei. While above mentioned studies evidenced the presence of endogenous F-actin structures using nuclear targeted actin-binding probes, they did not clarify whether actin filaments exert any 'F-actin typical' functions, for example transport, scaffolding, or mechanical properties within the nuclear compartment. Of note, it was recently shown that baculoviral nuclear egress requires intranuclear F-actin-dependent nuclear protrusions to disrupt the nuclear envelope [13•], suggesting that actin polymerization can be a nuclear force generator. Another question was whether dynamic nuclear actin assembly is involved in any cellular process or in spatio-temporal nuclear organization.

Cell cycle and chromatin organization

Formins have now emerged as important intranuclear actin regulating factors [9,11,14•,15••,16–18]. Indeed, it was shown that mDia2 promotes CENP-A loading onto centromeres downstream of MgcRacGap [14•], suggesting that cell cycle-specific nucleosome organization is formin-dependent. Whether this requires locally regulated actin polymerization remains to be shown, although an actin assembly-deficient mDia2 mutant failed to rescue the reduced CENP-A loading upon mDia2 depletion [14•].

Two recent studies demonstrated cell cycle-regulated intranuclear actin assembly. Fisher and colleagues identified F-actin formation to be critical for cyclin-dependent kinase (CDK) and proliferating cell nuclear antigen (PCNA) loading onto chromatin [15••]. Inhibiting or overactivating formin proteins interfered with initiation of DNA replication, implicating a critical role for dynamic F-actin assembly in this process [15••]. Precisely how actin filaments facilitate PCNA loading onto chromatin or how they affect DNA synthesis remains to be studied further. Additional reported functions of nuclear actin filaments in this study included nuclear transport and cargo release from RanGTP-importin complexes, whereas global transcription was affected by application of the formin inhibitor SMIFH2, but not by efforts to activate endogenous formins (Figure 1).