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Review

Actin cytoskeleton dynamics and the cell division cycle

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ABSTRACT

The network of actin filaments is one of the crucial cytoskeletal structures contributing to the morphological framework of a cell and which participates in the dynamic regulation of cellular functions. In adherent cell types, cells adhere to the substratum during interphase and spread to assume their characteristic shape supported by the actin cytoskeleton. This actin cytoskeleton is reorganized during mitosis to form rounded cells with increased cortical rigidity. The actin cytoskeleton is re-established after mitosis, allowing cells to regain their extended shape and attachment to the substratum. The modulation of such drastic changes in cell shape in coordination with cell cycle progression suggests a tight regulatory interaction between cytoskeleton signalling, cell–cell/cell–matrix adhesions and mitotic events. Here, we review the contribution of the actin cytoskeleton to cell cycle progression with an emphasis on the effectors responsible for the regulation of the actin cytoskeleton and integration of their activities with the cell cycle machinery.

Contents

1. Introduction

The actin cytoskeleton of eukaryotic cells undergoes drastic changes and remodelling during cell division. Interphase cells usually contain an extensive actin network but this network is rapidly dismantled and rearranged when cells enter mitosis, giving mitotic cells their characteristic round shape. At the end of mitosis, actin rearranges at the cleavage furrows and forms part of the contractile ring, which is central to the process of cytokinesis. Another mitotic

Abbreviations: APC, adenomatous polyposis coli; CDK1, cyclin-dependent kinase 1; ECM, extra cellular matrix; FAK, focal adhesion kinase; GAP, GTPase-activating protein; GEF, guanine nucleotide exchange factor; MLCK, myosin light chain kinase; PAK, p21-activate kinase; Plk1, polo-like kinase 1; ROCK, p160-Rho-associated coiled-coil-containing protein kinase.

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event in which the actin network plays an important role is the separation of centrosomes, which is dependent on the cortical flow of cortical actin and the myosin network. Disruption of the actin and myosin II networks by inhibitory drugs such as latrunculin, ROCK (p160-Rho-associated coiled-coil-containing protein kinase) inhibitor and myosin II RNA interference (RNAi) causes failure in centrosome separation and proper spindle assembly (Rosenblatt et al., 2004; Uzbekov et al., 2002).

Thus, the regulation of the actin cytoskeleton and of cell cycle progression appears to be connected. However, the nature of their functional integration is not well understood. Here, we review the current state of knowledge concerning the regulatory links between these two activities in proliferating cells. The emphasis is on proteins known to regulate the actin cytoskeleton and are implicated in cell cycle control. Our discussion on the actin cytoskeleton will not be limited to the acto-myosin filament or filamentous actin (F-actin) but will also encompass proteins associated with the modulation of the actin cytoskeleton such as the Rho GTPases and their regulators. We will also discuss cell adhesions and their effect on the cell cycle.

2. Actin cytoskeleton, myosin and the cell cycle

2.1. Actin cytoskeleton in cell cycle control

Actin is a highly conserved globular protein found in almost all eukaryotic cells. It forms cellular scaffold structures that provide cells with their shape, tension support, intracellular vesicular transport, cell attachment, adhesion properties and the ability to move. Apart from these well-studied mechanical functions, actin also plays a more subtle role in chemical signal transduction. It was once thought that the cell cycle machinery controls the state of actin organization within the cell via an "inside-out" signalling mechanism (Wang, 1991; Yamashiro et al., 1991). However, retrograde signalling where the state of actin organization within the cell controls cell cycle progression has proven to be important as well (Assoian and Zhu, 1997; Thery and Bornens, 2006). The significance of the actin cytoskeleton for cell cycle progression can be easily gleaned from experiments using drugs or chemicals that interfere with the actin filament in the cells. Depolymerization of actin filaments by toxins such as cytochalasin D and latrunculin B has been reported to delay progression of mitosis in primary cells and fission yeast, suggesting that an intact actin cytoskeleton may be required for the efficient onset of mitosis (Gachet et al., 2001; Lee and Song, 2007). A summary of the different drugs and chemicals and their effect on the actin cytoskeleton is listed in Table 1. While a morphogenesis checkpoint has been proposed in budding yeast which is activated in response to perturbation of the actin cytoskeleton leading to delays in chromosome segregation (McMillan et al., 1998), a similar actin regulated checkpoint control has not been established in mammalian cells. Apart from causing a delay in mitosis, disruption of actin filaments also leads to G_1 arrest. This actin cytoskeleton dependent arrest has been linked to cyclin expression and cyclin-dependent kinase (CDK) activation (Reshetnikova et al., 2000). In a study in which disruption of the actin cytoskeleton was induced by the over-expression of cofilin, a member of the actin depolymerization factor (ADF)/cofilin family, more than 90% of H1299 lung carcinoma cells arrested at G_1 phase of the cell cycle (Lee and Keng, 2005). Excessive polymerization of F-actin by a mutant WASP or the drug Jasplakinolide, which interferes with actin depolymerization, causes an increase in multinucleate cells suggesting a possible defect in cytokinesis (Moulding et al., 2007). Similarly, expression of mutant $WASP^{I294T}$ which mis-regulates the Arp2/3 complex and enhances F-actin polymerization, results in abnormal accumulation of F-actin around the mitotic chromosomes and may possibly lead to the observed cytokinesis defects. These observations demonstrate actin's involvement in cell cycle progression. Various proteins known to function in both the regulation of the actin cytoskeleton and the cell cycle progression are summarized in Table 2. Many of these proteins change their cellular localization at different phases of the cell cycle (Fig. 1 and Table 3).

Recently, cortactin, an actin-binding protein, has been identified as an anchor between the centrosome and F-actin and is essential for F-actin driven centrosome separation during mitosis. The triply phosphorylated form (Tyr421-, Tyr466- and Tyr482-) of cortactin is found to be localized exclusively to the spindle poles during transition to anaphase. Truncated cortactin lacking its actin-binding domain inhibits centrosome separation (Wang et al., 2008). Interestingly, cortactin has also been identified as a substrate of CDK1 at serine 405 (Blethrow et al., 2008). Although the significance of this phosphorylation of cortactin during mitosis has not been examined, it raises the possibility of a link between CDK1 signalling and cortactin-mediated centrosomes separation during mitosis.

Links between actin cytoskeleton and transcription control have also emerged. Disruption of the actin cytoskeleton during mitosis leads to changes in the G- to F-actin ratio and hence in transcription activities mediated by the myocardin-related transcription factor and serum response factor, MAL/SRF (Miralles et al., 2003). It is possible that cell cycle progression could be affected by the status of actin polymerization via MAL/SRF mediated transcription. A recent report shows that in human uterine leiomyosarcoma cells, down-regulation of MAL leads to reduction of p21 CDK inhibitor (Kimura et al., 2010). However, work by Triesman's group has shown that depletion of SRF or MAL affects cell spreading and adhesion without affecting cell proliferation or apoptosis (Medjkane et al., 2009).

2.2. Actin, myosin and the regulation of the mitotic spindle

In mitosis, microtubules have hogged the limelight with their beautiful arrays and precisely choreographed functions in organising events from the establishment of the bipolar spindle to the capturing, alignment and accurate segregation of chromosomes. Most importantly, mitotic spindle assembly and chromosome segregation can be reconstituted *in vitro* in cell free extract. The studies on actin in mitosis have remained focused almost solely on its mechanical function during cytokinesis until recently, where actin's role in the biogenesis of the mitotic spindle has gained increasing attention. Using different methods of interference with actin polymerization and actin-myosin at the cell cortex, two earlier papers clearly showed the requirement of myosin II and actin in centrosome separation in higher eukaryotic and mammalian cells (Rosenblatt et al., 2004; Uzbekov et al., 2002). Upon actin depolymerization with latrunculin treatment, centrosome separation is blocked and a proper spindle cannot be assembled (Uzbekov et al., 2002). Proper spindle assembly is also disrupted when myosin II is inhibited through the use of the ROCK inhibitor – Y26732, which prevents ROCK-mediated phosphorylation of myosin light chain phosphatase, eventually blocking myosin activity. A similar effect is seen in cells treated with blebbistatin which inhibits the ATPase activity of non-muscle myosin II (Rosenblatt et al., 2004). Silencing of non-muscle myosin II heavy or light chain using RNA interference also disrupts spindle formation. When the cortical flow of acto-myosin filaments is prevented by cross-linking the cell surface with lectins such as concanavalin A, centrosome separation and movement are impeded, which results in a lopsided spindle (Rosenblatt et al., 2004).

More recent studies have illustrated a closer direct link between the actin filaments and the mitotic spindles where F-actin was found localized to the mitotic apparatus (Woolner et al., 2008; Yasuda et al., 2005). Additional reports have also suggested that the stability of the cortical actin network is crucial in establishing