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The balance between contraction and adhesion during cell division

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Abstract

The ability to divide is a fundamental property of a living cell. The 3D orientation of cell division is essential for embryogenesis, maintenance of tissue organization and architecture, as well as controlling cell fate. Much attention has been placed on the mitotic spindle's role in placing itself along the cell's longest axis, where a shape sensing mechanism between a population of microtubules extending from mitotic centrosomes to the cell cortex occurs. However, contractile forces at the cell cortex also likely play a decisive role in determining the final placement of

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¹Dix et al. This manuscript describes the interplay between actomyosin mediated contraction and adhesion mediated cell spreading in generating the forces required for cytokinesis. The authors show non-transformed cells such as RPE1 cells require cell-substrate adhesion to undergo abscission even in the presence of an intact contractile ring. Upon disruption of contractile ring assembly, these adhesions guide spreading to generate the tension required for cell abscission.

²Petridou et al. This manuscript describes a population of ligand-independent active integrin β -1 at the points of attachment of retraction fibers to the cortex of mitotic cells. The authors show this integrin activation is mediated by tension, and recruits spindle orienting cues to these points of tension. This study describes for the first time the molecular pathway between retraction fiber generated tension and spindle orientation.

³Roubinet et al. This manuscript describes the dynamics of myosin localization during asymmetric division of *Drosophila* neuroblast cells. The authors show using photo-conversion that two independent pathways drive stereotypical apical and basal flows of myosin to establish physical asymmetry in cleavage furrow positioning. Cell polarity cues direct basal myosin flow at anaphase onset, followed by mitotic spindle cues that direct myosin back apically to generate daughter size asymmetry.

⁴Taneja et al. This manuscript describes a population of focal adhesions underneath the cell body and retraction fibers that regulate the shape of dividing cells by physically opposing cleavage furrow ingression. These adhesions were regulated by FAK and vinculin, as well as integrin ligand concentration. In addition, the presence of more focal adhesions in a daughter cell dictated the positioning of the mother centrosome closer to the substrate.

⁵Farina et al. This manuscript describes for the first time the actin-nucleating ability of the centrosome. The authors show that purified centrosomes use an Arp2/3 dependent mechanism to nucleate actin networks. They further go on to show an elegant link between cell shape and actin nucleating ability of the centrosome, with rounder cells having more prominent actin networks surrounding centrosomes.

⁶Nam et al. This manuscript describes the changes in matrix deformation by cells during the cell cycle when confined in three-dimensional matrices. During early anaphase, spindle elongation contributes to matrix deformation while the contractile ring dominates matrix deformation during cytokinesis. Therefore, this study shows for the first time that force generation by the contractile ring is conserved in a three-dimensional environment.

⁷Jones et al. This manuscript describes the role of Cdk1 in orchestrating cell ECM adhesion remodeling with the cell cycle. Cdk1 promotes adhesion assembly during G1. The authors also report a surprising finding that adhesion remodeling by downregulation of Cdk1 activity is initiated several hours before mitosis, during G2.

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daughter cells following division. In this review, we discuss recent literature that describes the role of these contractile forces and how these forces could be balanced by mitotic adhesion complexes.

Introduction

Recent studies on mitotic spindle orientation have focused on the role of microtubules in spindle placement. The mitotic spindle is a microtubule-based structure composed of both central spindle microtubules as well as astral microtubules that extend from the centrosomes and interact with the polar cortex (Figure 1). Pulling forces generated by astral microtubules contribute to the placement and subsequent separation of chromosomes from the metaphase plate. However, additional mechanisms are likely needed to position the spindle in three-dimensional space beyond that of astral microtubules. Some of the earliest studies of spindle orientation focused on cell shape as the major driver in spindle placement, where the mitotic spindle is preferentially placed along the longest axis of a cell [1]. One key regulator in controlling cell shape is the actin cytoskeleton [2]. Actin-dependent structures, such as focal adhesions, the cleavage furrow [3], and actin clouds [4], have all recently been implicated in spindle positioning. Strikingly, many of the molecular players that regulate the actin cytoskeleton have been identified at the centrosome through proteomic analysis [5]. A recent study identified that not only is the centrosome a microtubule organizing center but is also an actin-nucleating center [6], suggesting that a crosstalk likely exists between the actin and microtubule cytoskeletons. The crosstalk between these two elements is likely an essential mechanism for spindle placement. An understanding of how this crosstalk is coordinated in space and time requires better elucidation of the molecular nature of contractile and adhesive actin-based structures during mitosis and cytokinesis. We will first discuss the primary contractile and adhesive structures that contribute to cell shape during mitosis. We will follow this with potential mechanisms that transmit cell shape sensing signals to and from the spindle.

Contractile forces within dividing cells

Upon mitotic entry, the actin cytoskeleton is re-organized to disassemble stress fibers to form an isotropic contractile cortical network, allowing the cell to increase surface tension and adopt a spherical shape (Figure 1) [7,8]. Upon completion of anaphase, accumulation of myosin II at the equator results in the formation of a contractile ring, the major contractile apparatus that drives cytokinesis (Figure 1) [9]. This accumulation can occur through both spindle dependent and independent mechanisms. The former is mediated through the centralspindlin complex, while the latter occurs through polarity cues, such as those mediated by Protein Kinase N in *Drosophila* neuroblasts [10–12].

While the mechanisms generating contractility at the cleavage furrow have been intensively studied, a second actomyosin network exists at the polar ends of the cell. The polar cortex, which usually retains low contractility during cytokinesis, can generate substantial forces that can cause spindle oscillations [13,14]. The adhesive actin structures that balance these contractile forces to modulate the final three-dimensional shape of the cell are less well understood.

The complex dynamics of cell-substrate adhesion during mitosis

Integrin based adhesion is the major mode of cell-substrate attachment employed by cells [15]. The canonical integrin-based adhesion is composed of the integrin receptor layer, that traverses the cell membrane, and links the cell to the extracellular matrix (Figure 2) [16]. Proteins such as focal adhesion kinase (FAK), talin and paxillin form a signaling layer that associates with the cytoplasmic tail of integrin β -subunits. The force transduction layer, composed of proteins such as zyxin, vinculin and p130Cas allow the physical coupling of the adhesion to the actin cytoskeleton (Figure 2). It has been long demonstrated that the majority of these focal adhesion complexes disassemble upon mitotic entry, and prevention of this disassembly leads to the activation of an adhesion dependent G2/M checkpoint [17,18]. Recent work has shed light on the molecular nature of what remains of these canonical focal complexes (Figure 2), with some interesting implications for both conserved and potentially unique mechanisms between interphase and mitosis. It is also unclear whether the perturbation of cell ECM adhesion primarily works through cell shape, and/or whether additional signaling pathways modulate this process.

Initial biochemical studies investigating the link between cell cycle and adhesion remodeling focused on mapping changes in phosphorylation of focal adhesion signaling layer proteins FAK, p130Cas and paxillin during mitosis [19,20]. How these changes were linked to cell cycle progression however was unclear. It was recently shown that Cdk1 is the master regulator of this process, with low Cdk1 activity during G2 promoting adhesion disassembly [21]. In further support of these findings, traction forces were found to peak during S-phase, subsequently decreasing during G2, a finding consistent even in epithelial sheets [22,23]. These studies have significantly advanced our understanding of adhesion remodeling leading to mitotic entry, while others have uncovered complex adhesion dynamics immediately following mitotic exit (Figure 2).

Early work using substrate wrinkling showed that mitotic cells exert forces on the substrate [14]. Interestingly, the greatest wrinkling was observed underneath the cleavage furrow during ingression, which then dissipated towards the cell periphery, corresponding to the initiation of cell spreading. This suggests a dynamic redistribution of cell-substrate adhesions during cytokinesis. Recent work has measured matrix deformation throughout mitosis in cell cultured in 3D matrices [24]. Notably, matrix deformation increased during mitotic progression, peaking during cytokinesis. This suggests that the contractile ring also generates significant forces in 3D environments. Transmission of such forces to the substrate would require cell-matrix contacts to be present immediately following mitotic exit.

We recently showed in dividing HeLa cells that the focal adhesion signaling layer protein, paxillin, localizes to adhesions under the cell body, and remains close to the ingressing cleavage furrow (Figure 2). We also found paxillin at the interface between the substrate and the ends of retraction fibers, which are actin-based tethers linking the side of the cell to the substrate [3]. Both FAK and vinculin regulate the adhesions under the cell body, which we termed “mitotic focal adhesions”. Our interpretation of this data is that adhesions under the cell body, while albeit smaller, are regulated similar to canonical focal adhesion complexes

present in interphase. However, another recent study has called into question whether focal adhesions exist during mitosis at all.

Baum and colleagues reported that “many components of focal adhesions present in interphase were lost upon entry into mitosis”, except for β -1 integrin [25]. The lack of canonical focal adhesion complexes led the authors to claim this as a fundamentally different mechanism of cell adhesion during mitosis, calling these “mitotic adhesions” [25]. However, we propose the possibility that canonical focal adhesion complexes do exist that are not necessarily unique in molecular composition but differ in their dynamics of assembly and spatial distribution. For instance, paxillin, a focal adhesion complex marker, was detected both underneath the cell body as well as underneath retraction fibers (Figure 1A in [25]). This localization was similar to the paxillin localization during metaphase we previously reported in HeLa cells and others in endothelial cells [3,26]. This consistent finding from two separate studies suggests that a similar mechanism of adhesion is likely present during interphase and mitosis but is redistributed during mitotic entry and exit. Furthermore, our studies identified a discrete distribution and assembly of paxillin positive focal adhesions following metaphase exit. For instance, during metaphase a few stable patches were identified underneath the metaphase plate and as the cells exited into anaphase, focal adhesions asymmetrically assembled under one daughter cell faster than the other (Figure 2) [3]. While differences in composition and dynamics have been reported [3,25], we speculate this might be due to differences in image acquisition. By utilizing total internal reflection fluorescence (TIRF) with a 30 sec image acquisition rate we were able to identify the dynamic nature of focal adhesions during division [3], compared to more traditional techniques that utilize low magnification confocal microscopy at lower temporal sampling (3 min) [25]. Thus, with the advance of live-cell imaging techniques we predict that the discrepancies between studies on focal adhesion assembly and/or disassembly during the cell cycle will be resolved, and novel spatial and temporal information identified.

An additional layer to investigate regarding focal adhesions is whether integrins at these sites are in an active or inactive state during the cell cycle. Multiple integrin paralogs (e.g., α V β 1 and α V β 5) have been localized underneath the cell body and retraction fibers [27,28]. Skourides and colleagues reported the localization of β -1 integrin, but did not detect any active integrins at retraction fibers, proposing that they only exist at the mid-lateral cortex [27]. In contrast to this report, Baum and colleagues showed a similar localization of active β -1 integrin, but proposed that active integrins do exist underneath retraction fibers [25]. Taken together, the presence of active integrin and other canonical focal adhesion complex markers reported in these studies support the existence of functional focal adhesions during mitosis. To yield further mechanistic understanding of cell substrate adhesion during mitosis, future studies will need to employ multiple focal adhesion markers, visualized with high temporal sampling and sensitive imaging.

Balance of contractile and adhesive forces as a determinant of cell shape

A balance between adhesion and contraction during cytokinesis was first proposed by Fishkind and Wang [29], and we now have a better molecular understanding of this force-balance and its effect on cell shape. Cells deficient in contractility were shown to rely more

on substrate adhesion at the polar regions of the cell to undergo cytokinesis [14,30]. Notably, Ect-2 depleted RPE1 cells failed cytokinesis when plated on micro-patterns that prevented cell spreading [25]. In our work, we showed that focal adhesions underneath the cell body regulated the three-dimensional shape of the cell by preventing ingression of the cleavage furrow from the bottom of the cell, strongly suggesting a mechanical link between mitotic adhesions and the actomyosin machinery (Figure 2). Deregulation of this link was later shown to reduce the fidelity of cytokinesis [31].

The exact nature of this link remains an area of speculation. It is possible that machinery similar to the one that links canonical focal adhesions to stress fibers may mediate this connection [32]. Indeed, the canonical Paxillin-FAK-vinculin signaling axis appears to regulate this process, suggesting the intriguing possibility that this pathway may be re-activated almost immediately after mitotic exit [3]. In interphase cells, connecting fibers, e.g. dorsal stress fibers, of actin filaments bundled by proteins such as α -actinin connect adhesions to stress fibers to regulate cell flattening [32,33]. We have localized α -actinin-4 structures extending from mitotic adhesions in HeLa cells (unpublished observations). Applying structured illumination microscopy (SIM) failed to resolve any layering within these adhesions; this is not surprising since SIM only has an axial resolution of ~ 250 nm [34]. Therefore, the elucidation of the ultrastructural organization of adhesions, α -actinin-4 and myosin II will likely require 3D single molecule imaging techniques such as iPALM or 3-D storm [35,36].

Interestingly, the cell shape changes upon modulation of cell adhesion corresponded with changes in the XZ orientation of the spindle; flatter, more adhesive cells presented with increased spindle angles ($9.7 \pm 3.6^\circ$) than rounder, less adhesive cells ($5.5 \pm 2.4^\circ$) (Figure 2) [3]. Cells under more adhesive conditions also showed an inherent asymmetry in daughter cell shape. One of the daughter cells made more cell-substrate attachments, which correlated with one of the mitotic centrosomes being oriented in closer proximity to the substrate. Although we have widely observed this asymmetry in numerous published images of dividing cells, this phenomenon has been largely ignored [25,26,37]. As such, how this asymmetry in the distribution of adhesions is established remains unknown. In the remainder of this mini-review, we will focus on the potential mechanisms that explain the interplay between cell shape, contractility and mitotic centrosome positioning.

Integrating cell shape into three-dimensional spindle placement

Taken together, recent data hint at the role of the actin-adhesion force balance in spindle placement, leading to the question: How do contractile and adhesive forces that determine cell shape communicate with the spindle? Most dividing cells follow Hertwig's rule, where the spindle aligns with the longest axis of the cell. Previous studies have tested the idea that astral microtubules sense the cortex as the "boundary" with which to interact to position the spindle [38,39]. An additional layer of regulation has been demonstrated where the adhesive microenvironment at the cell cortex provide additional cues to position the mitotic spindle [27,40,41]. In single cells, these points of mechanical tension correspond to the locations where retraction fibers contact the cortex. Interestingly, active integrin was recently found to localize to these points of contact, allowing the elucidation of the molecular pathway from

retraction fiber mediated tension to spindle orientation [27]. This localization is intriguing, since these active integrins are too far from the substrate to bind extracellular matrix proteins (Figure 2). These integrins recruit machinery similar to canonical focal adhesions, such as FAK, p130Cas and Src, and appear to be activated by tension, subsequently recruiting LGN, a component of the evolutionary conserved Gai/LGN/NuMA complex, to guide spindle orientation. The Gai/LGN/NuMA complex is an essential cortical force generator, where its molecular component, NuMA, plays an integral role in bridging the cortical membrane with astral microtubules. In epithelial cells, points of highest tension appear to correspond to tricellular junctions and recruit the cortical cue Mud (Drosophila homolog of LGN) [42]. However, recent studies suggest that this tension-dependent, astral pulling pathway may not be the only physical mechanism of communication between the cortex and the spindle.

Actomyosin contractility at the polar cortex can create significant intracellular pressure, which can lead to physical displacement of the spindle [13]. This phenomenon was first shown to occur upon deregulation of polar contractility, but may be employed by dividing cells in a highly regulated manner. An exciting study from Cabernard and colleagues has shown the presence of tightly coordinated cortical flows of myosin II during Drosophila neuroblast division [43]. The authors show induction of basally directed flow of myosin is determined by polarity cues and is then followed by spindle derived cues, directing myosin apically. The tight spatial/temporal control of contractility in this system may have interesting mechanical effects (e.g., changes in hydrostatic pressure) that could be directly effecting spindle placement.

Another potential source of mechanical force is the deformation of the cortex. In cells cultured on highly adhesive substrates, we observed an inherent asymmetry in the shape of the two daughter cells which correlated with an asymmetric distribution of mitotic focal adhesions [3]. Specifically, the daughter cell with more mitotic focal adhesions was flatter and contained a mitotic centrosome that was closer to the substrate. This observation raises additional questions about how cell geometry acts as a cue for spindle orientation. For example: Could it be possible that cortical contractility on top of the cell is simply pushing down on the spindle (Figure 2)? Or is asymmetric distribution of adhesions at the bottom of the cell creating a physical cue that activates astral pulling pathways? Both hypothetical mechanisms are likely playing a role in the final placement of the spindle. The former mechanism would likely require a physical link between the cortex and the spindle.

The mechanical link between the actin cytoskeleton and the spindle may be mediated by a population of actin that communicates or even is regulated by the centrosome (Figure 3). Indeed, the subcortical actin cloud, which is nucleated from centrosomes, has been implicated as a potential link between the actin cortex and the spindle [4]. Applying uniaxial stretch on the cortex during metaphase results in an enrichment of subcortical actin filaments in the direction of stretch, suggesting a link between cell shape and regulation of the actin cloud [40]. Indeed, cell shape was recently shown to be an integral determinant of the actin nucleating ability of the centrosome [6]. More rounded cells tend to display a more prominent actin cloud. It is interesting to speculate how cell flattening due to high adhesion during mitosis may alter the dynamics of the actin cloud. Specifically, the actin cloud may act as a conduit to transfer mechanical forces from the cortex to the spindle. Future

biophysical studies will shed light on the dynamics and mechanical properties of actin clouds, and how they influence the positioning of the spindle.

The ability of the centrosomes to directly nucleate actin filaments positions the centrosomes as a likely key player to regulate the cross-talk between the actin and microtubule cytoskeleton [6]. Interestingly, there is also an inherent asymmetry between the two mitotic centrosomes that occurs due to the nature of centrosome duplication during S-phase of the cell cycle [44]. The mother (older) mitotic centrosome has been shown to have distinct microtubule organizing and signaling activities compared to the daughter mitotic centrosome (younger) [45,46]. Given this asymmetry, it is interesting to speculate how different signals from two centrosomes might affect spindle positioning pathways. For example, Plk1 signaling from centrosomes has been shown to negatively regulate the recruitment of cortical dynein [47]. In addition, the mother centriole protein, Cenexin, a known Plk1 scaffold, also is an integral component in modulating appropriate spindle orientation [46,48]. It is also likely there are differences between the dynamics and mechanical properties of the actin cloud nucleated from the mother and daughter centrosomes. We recently showed that increasing the adhesiveness of the substrate results in preferential placement of the mother centrosome towards the substrate [3]. An important future direction would be to decouple the contributions of astral pulling forces versus the differential actin organizing ability of the centrosomes in explaining this phenomenon.

Conclusions and Future Directions

How the mitotic spindle is precisely oriented in three-dimensional space has now been investigated for more than a century. These studies have revealed a highly complex, regulatory network, with constant feedback between signaling pathways, mechanical forces and cell shape. Understanding this network will require the continued development of non-invasive biophysical tools that can measure multiple physical parameters in live cells, while simultaneously applying quantitative imaging techniques. Development of increasingly powerful light sheet microscopes should allow us to ask more ambitious questions inside live organisms. Ultimately, since the process of spindle movement is a physical one, these biological insights must be integrated to develop physical models that predict spindle positioning in response to all these complex cues. Only then can we understand how cells utilize this machinery during development to generate diverse tissues and morphologies.

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Figure 1.

A) Structured illumination microscopy micrograph of HeLa cell at metaphase, stained for α -tubulin (yellow), actin filaments (magenta) and myosin IIA (cyan). The mitotic spindle comprises spindle microtubules, that facilitate chromosome segregation and dictate furrow positioning, and astral microtubules that play a pivotal role in spindle positioning by interacting with the actin cortex. Myosin II is uniformly distributed at the cortex during metaphase. B) Upon anaphase onset, myosin II is enriched at the equator to ingress the cleavage furrow. Note the extensive contacts between the mitotic spindle and the contractile cortex, suggesting cross-talk between these two cytoskeletal networks. Note that the actin bundles protruding from the cells are not retraction fibers, as they are not attached to the substrate. Scale bar: 10 μ m.

Figure 2.

A) Side view of a cell during cytokinesis. Green arrows denote the location of active integrins. B) Known adhesion components localized to mitotic cells include active β -1 integrin and paxillin. Classical focal adhesion complex during interphase. C) Under high adhesive conditions, cleavage furrow ingression is delayed from the bottom of the cell, generating asymmetry in shape. In addition, the daughter cell containing the mother centrosome makes more adhesions to the substrate and is flatter compared to the daughter cell with the daughter centrosome. The mother centrosome is also closer to the substrate. Legend shows individual components.

Figure 3.

Cortical and cytoplasmic actin filaments during metaphase (A) and cytokinesis (B). Upon mitotic entry, stress fibers disassemble, and the majority of actin filaments are assembled at the cell cortex. Recent studies have focused on a second population of actin filaments in the cytoplasm that is nucleated and regulated by centrosomes. Note the extensive actin filament network in the cytoplasm. This network may play a role in shape sensing and transmission of mechanical forces from the cortex to the mitotic spindle. Scale bar: 10 μ m