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Review

Cytokinesis in development and disease: variations on a common theme

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Abstract. Cytokinesis is a crucial step in cell proliferation, and remarkably, it is also an important mechanism for developmental regulation in the generation of diverse cell types in eukaryotic organisms. Successful cytokinesis relies on the assembly and activation of an actomyosin-based contractile ring and membrane deposition/fusion in a spatially and temporally precise manner. As such, the molecular pathways governing cytokinesis are highly complex, involving a large number of components forming intricate interactive networks. The complexity of this system, however, may have also provided a rich platform for evolutionary 'tinkering' to achieve specific morphogenetic and developmental outcomes. Furthermore, failed or altered cytokinesis appears to contribute to the development of cancer in unexpected ways.

Keywords. Cytokinesis, asymmetric cell division, polar body extrusion, enucleation, polyploidization.

Introduction

Cytokinesis, the physical division of a cell into two, is an extraordinarily fascinating process to cell biologists, not only because of its crucial role in growth, but also because of the richness in the scientific disciplines that it brings together, from dynamic cytoskeletal rearrangements, full-scale force production, to cell cycle regulation and precise spatial patterning. Over the past decade, there has been an unprecedented energy in the field of cytokinesis. As a consequence, impressive progress has been made in deciphering the fundamental principles as well as the molecular pathways that control cytokinesis. In addition to understanding cytokinesis in the context of cell proliferation, there is also an increasing appreciation that cytokinesis provides a versatile means by which organisms achieve complex morphogenetic outcomes far beyond an increase in cell number.

The current state of the understanding of the basic process of cytokinesis has been thoroughly described and expertly synthesized in several recent reviews [1 – 5]. The focus of this review is on the less understood cytokinetic processes that lead to specialized physiological or pathological outcomes. Much remains to be learned about these processes, the study of which will provide insights into the question of how the basic cytokinetic machinery can be modified to bring about new functions. I will first summarize current understanding of the basic principles and molecular machinery governing animal cell cytokinesis and then describe the recent progress in studying cytokinesis in three developmental processes: asymmetric cell division in cell fate diversification; asymmetric cell division in genome extrusion; and blockage of cytokinesis in the generation of polyploids. Finally, I will venture into the elusive relationship between cytokinesis and cancer. Due to the broad scope of these topics, the discussion will center on how specialized

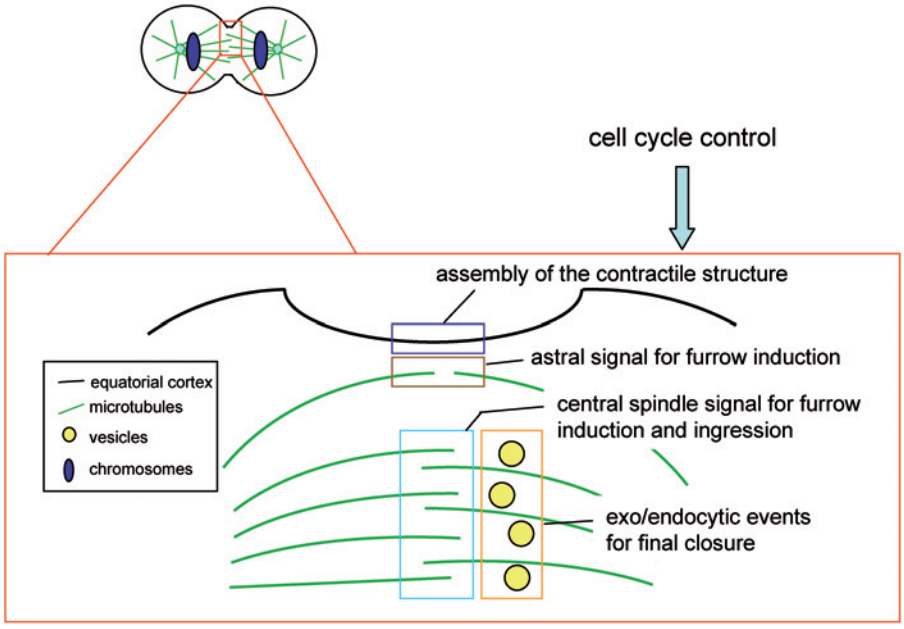

Figure 1. Structural and regulatory events that control cytokinesis. Successful cytokinesis requires highly coordinated events at the equatorial region of the cell (red box), including spatial positioning of the cleavage furrow by astral microtubule (brown box) and central spindle (light blue box) associated complexes, assembly and activation of the actomysoin contractile structure (dark blue box) to drive furrow ingression, and targeted exocytosis and endocytosis (orange box) to complete final closure. Many of these events are directly controlled by cell cycle regulators to ensure temporal coordination with chromosome segregation. During developmental processes, these subevents of cytokinesis are potential points of regulation in order to achieve specialized patterns of cell division.

cell divisions are achieved through variations of the common theme.

The basic mechanism: force production and physical separation

The mechanisms of cytokinesis have evolved to satisfy three basic requirements: 1) physical division of a cell to generate two topologically distinct progenies; 2) precise temporal control such that cell division does not occur until the completion of chromosome segregation; 3) precise spatial control such that the cleavage plane safely separates the two segregated masses of chromosomes. With this in mind, the study of cytokinesis has focused on three key questions: What is the physical machinery responsible for the generation of force and membrane partition that divide the cell? How is the timing of cytokinesis controlled in the cell cycle? And how is the plane of cytokinesis specified in a proper relationship with the spindle, the apparatus for chromosome segregation? This and the following sections are to highlight the recent discoveries and outstanding questions in regard to these problems.

In animal cells, cytokinesis occurs through 'pinching' along an equatorial plane to generate a cleavage furrow (Fig. 1). The furrow ingresses until the leading edge is closely surrounding a narrow mid-body structure, a remnant of the mitotic spindle, when membrane fusion occurs to close off the junction. Biophysical measurements have shown that the pinching force is produced directly at the equatorial furrow [6, 7], although relaxation of the polar cortex may also contribute to furrow formation and ingression [8, 9]. The main force producers in the cleavage furrow are filamentous actin (F-actin) and type II nonmuscle myosin, which in many cell types are assembled into a contractile ring [10–15]. Although the structural organization of the contractile ring may be different depending on the cell type, it is thought that the basic functional units are bipolar myosin-II filaments, which generate contractile force by sliding actin filaments that are attached to the cortex [16, 17]. Besides actin and myosin-II, the cleavage furrow is a region of compact localization of a large number of proteins [4]. A genome-wide localization study in budding yeast placed more than 80 different proteins at the bud neck during cytokinesis [18]. Genetic studies in model organisms, such as the slime mold *Dictyostelium* and the fission and budding yeasts [19–21], as well as recent high-throughput RNA interference (RNAi) screens in *Caenorhabditis elegans* embryos and cultured *Drosophila* and mammalian cells [22–26], have generated a nearly complete 'parts list' of the machinery that carries out cytokinesis. It is clear that cytokinesis is far more complicated than just a waltz between actin and myosin-II. A large number of proteins are involved to control the assembly and dynamics of the actomyosin structure and various other aspects of cytokinesis. Moreover, there is strong evidence that, in addition to the actomyosin-based force, alternative mechanisms of force production also exist and are capable of furrow production in cells attached to the substrate [27–30]. The molecular nature of these alternative cytokinetic mechanisms

remains elusive. A recent physical model of cytokinesis that integrates global and equatorial forces proposes that furrow ingression in the absence of myosin-II may occur as a result of the difference in Laplace pressure between the furrow and daughter cells [31]. An important question regarding the establishment of the cleavage site is how F-actin and myosin-II are localized to the equatorial region. Studies from various organisms have so far established that the formin-family proteins are critical for the nucleation of F-actin in contractile structures [32–35]. In addition to *de novo* nucleation, recruitment of existing actin filaments through cortical flow may also contribute to contractile ring formation [36–38]. Localization of myosin-II to the cleavage furrow requires assembly of myosin-II bipolar filaments, which in animal cells is controlled through phosphorylation of two sites on the regulatory light chain (RLC) of myosin-II [1]. However, this regulatory event, although required for myosin-II localization to the cleavage site, does not explain the specificity of this recruitment [39]. Moreover, studies of yeast myosin-II showed that tail regions devoid of the light chain binding sites are still recruited to the division site [40, 41]. Although the initial recruitment of myosin-II does not appear to depend on actin, formation of a stable contractile ring is accompanied by and requires formin-nucleated actin assembly [42, 43].

A fundamental difference between animal and plant cytokinesis was thought to lie in the direction in which the membrane partition grows [44, 45]. Plant cells accomplish cytokinesis mainly by addition of membrane and cell wall materials to construct a partition that grows centrifugally [44, 46]. However, classic and more recent studies have clearly indicated involvement of membrane addition at the cleavage furrow during animal cell cytokinesis [47, 48]. Consistent with cytological observations, a number of proteins involved in endocytosis, exocytosis and membrane fusion are on the 'cytokinesis parts list' [4]. In yeast it was shown that exocytosis is critical for the cleavage-site localization of certain trans-membrane proteins, such as Chs2 – a chitin synthase – which is required for the stability and productive force generation of the actomyosin ring [49, 50]. Studies in animal cells indicated that both exocytic and endocytic machinery plays important roles in the final closure of the junction between the daughter cells [48, 51, 52].

Basic questions regarding spatiotemporal regulation

Successful cell division is marked not only by the physical separation, but perhaps even more importantly by correct partition of genetic and organelle materials required for the survival and development of the progeny cells. The latter requires that the physical process of cell division be tightly coupled with other events in the cell cycle, especially chromosome segregation. This coupling is both temporal and spatial. Although some insights have been gained regarding the nature of the signals that determine the timing and position of cytokinesis, details are still lacking for a mechanistic understanding of the core regulatory events during cytokinesis.

Two issues regarding the cell cycle timing of cytokinesis have been raised: What controls the time of cytokinesis onset? and, Is there a distinct window in the cell cycle where cytokinesis is licensed to occur? Experiments in mammalian tissue culture cells demonstrated that cleavage furrow formation and cytokinesis onset require inactivation of the mitotic cyclin-CDK1 kinase complex [53]. Later work in yeast and echinoderm eggs found that both contractile ring activation and membrane transport and fusion at the cleavage sites are independent targets of this cell cycle regulation [49, 54–57]. Since in most cell types cyclin degradation is not complete until late anaphase, this requirement helps to ensure that cytokinesis does not initiate until sister chromosomes have successfully segregated. In regard to whether there is a set time window during which cells are competent for cytokinesis, experiments involving treatment with actin or myosin-II inhibitors in HeLa cells indicated that there is a time window of ~60 min after the onset of anaphase where the cell is competent to divide after drug washout [58, 59]. This time window roughly correlates with the persistence of components of the contractile ring and the spindle midzone. Disassembly of the cytokinetic structures, and hence the end of the cytokinesis competency phase, appear to require ubiquitin-mediated proteolysis [59]. Cyclin B degradation is also critical for the irreversibility of cytokinesis [60].

The proper location of the cytokinetic furrow is critical to successful cell division. At a basic level, the cytokinetic plane must be established obliquely, often perpendicularly, to the mitotic spindle in order to separate the two segregated masses of chromosomes. Elegant classical and more recent studies have demonstrated an unequivocal role for spindle microtubules in determining the placement of the cleavage plane [61–63] (Fig. 1). However, there was a debate regarding whether the inductive signal for furrow assembly came from astral microtubule arrays or the midzone microtubules and their associated proteins in telophase cells (termed the central spindle) [64]. A recent experiment in, *C. elegans* zygotes resolved this controversy by demonstrating the existence of two consecutive signals, emanating independently from

astral microtubules and the central spindle, which are both sufficient for cleavage furrow establishment [65]. It is likely that different cell types utilize these two signals to different extents. It remains an interesting question why these two partially redundant furrow specification mechanisms coexist, because these may not always converge to the same positions.

Core signaling pathways that control cytokinesis

Much remains to be learned about the molecular nature of the signals that provide spatiotemporal control over cytokinesis. In the *C. elegans* one-cell embryo, the astral microtubule-directed cleavage furrow formation is mediated through the heterotrimeric G protein GOA-1/GPA-16 and a regulator of G protein signaling, LET-99 [66]. LET-99 localizes to the cleavage site predicted by microtubule asters, and its inhibition prevents the aster-induced furrowing. As G protein signaling has been implicated in the regulation of microtubule pulling forces on the cortex [67], the authors hypothesized that such force could provide a mechanical signal for furrow positioning.

The existing data suggest that the central spindle stimulates furrow formation largely through regulation of the small GTPase Rho, which is a direct upstream regulator of the actomyosin-based contractile structure (Fig. 2). Rho regulates contractile ring assembly through at least two of its downstream effectors – Rho-activated kinase (ROCK) and the Diaphanous (Dia) type formins [1, 2]. ROCK promotes myosin-II activation by promoting RLC phosphorylation and at the same time inhibiting RLC phosphatase activity [68, 69], whereas formin activation by Rho leads to nucleation of the actin filaments that make up the contractile ring [70–72]. Activation of Rho during cytokinesis involves the Rho guanine nucleotide exchange factor (GEF) Ect2/pebble, which binds to and is possibly activated by one of the complexes associated with the central spindle, composed of MgcRacGAP/CYK-4 and microtubule plus end-directed motor protein – MKLP1/ZEN-4 (for review, see [2]). These interactions led to the hypothesis that microtubules could direct Rho activation and contractile ring formation at the equatorial cortex through kinesin-mediated transport of the GAP complex [73].

The Rho signaling module and the Ect2-interacting central spindle complex are targets of cell cycle kinases (Fig. 2). The kinesin MKLP1 is a substrate of mitotic Cdk1, and this phosphorylation inhibits motor activity by preventing microtubule binding [74]. Two mitotic kinases, Aurora B and Polo, have both been shown to phosphorylate MKLP1, and deficiency in this phosphorylation resulted in cytokinesis failure [75, 76]. Rho GEFs are also targets of Polo in yeast and mammalian cells, and this interaction is important for the localization of Rho GEF and Rho to the bud neck and equatorial cortex, respectively [77–79]. Both Aurora B and Polo are degraded at mitotic exit by APC^{Cdh1}-mediate proteolysis [80, 81], and hence it is possible that degradation of these kinases is a key event in ending the cytokinesis competency phase in G1.

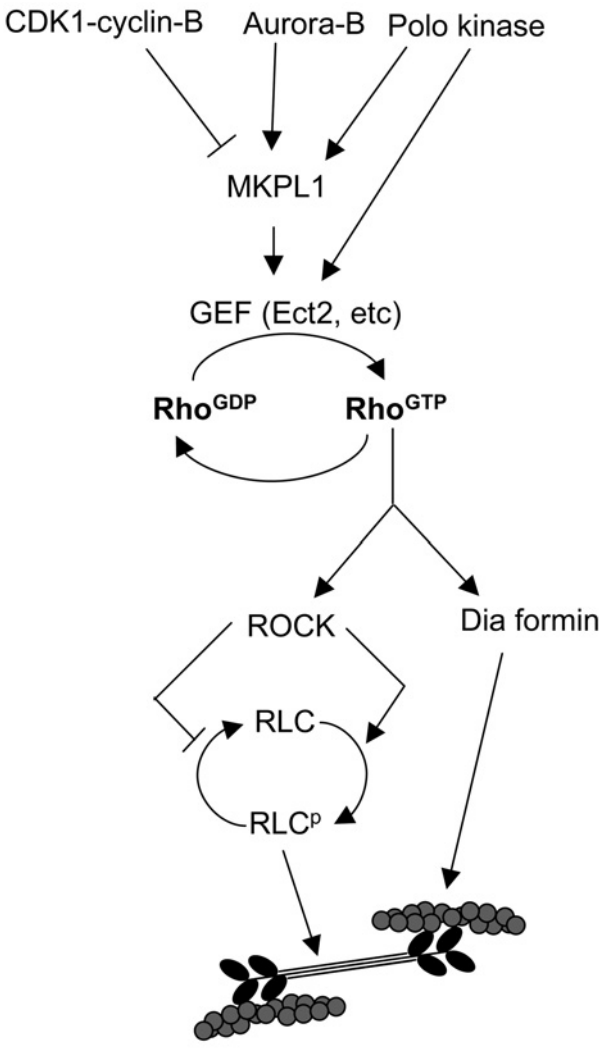

Figure 2. Rho GTPase controls actomyosin contractile ring assembly and is a major point of signal integration for spatiotemporal control of cytokinesis. The diagram shows a simplified version of a complicated and only partially known signaling pathway. The activated Rho stimulates myosin activation through regulating RLC phosphorylation, and actin polymerization through activation of the Dia-type formin proteins. Rho activation is controlled by GEFs such as Ect2, which is a target of the central spindle-associated mgcRacGAP-MKLP1 complex and several mitotic kinases, including CDK1, Aurora and Polo.

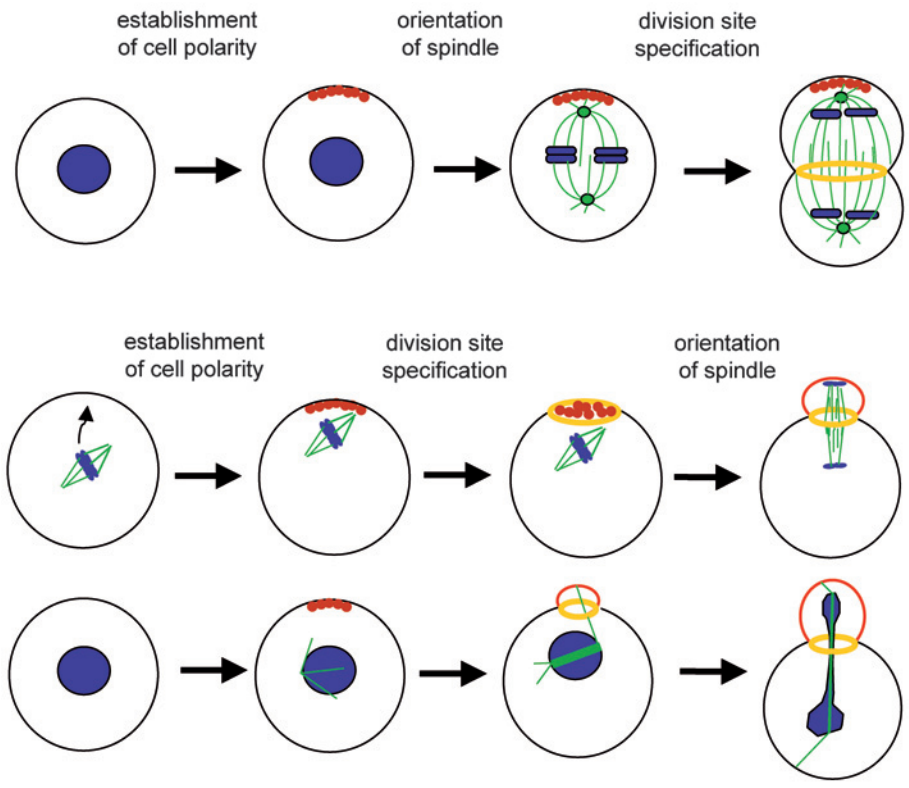

Figure 3. Comparison of the various schemes in asymmetric cell division. Top row: Pathway of mitotic asymmetric cell division in animal organisms. Cell polarity determines the orientation of the spindle, which in turn determines the position of the cleavage plane. Middle row: Polar body extrusion in mammalian oocytes. Cell polarity is established through asymmetrically located meiotic chromosomes. An actomyosin ring self-organizes around the polar cortical domain and roughly predicts the position of cleavage furrow during anaphase. The spindle is often not oriented until after anaphase onset in an actin-dependent manner. Bottom row: Asymmetric cell division in budding yeast, during which the division plane is also specified early as a direct consequence of polarity establishment and the spindle is aligned later during mitosis. Red marks the polar cortex; green, microtubules; blue, chromosomes; yellow, contractile ring.

Asymmetric cytokinesis – an evolutionarily conserved mechanism for cell fate diversification

Despite a lack of understanding of all the details in the molecular pathways, the emerging theme in the regulation and execution of cytokinesis suggests many potential points of regulation to manipulate its outcome during developmental processes. A much appreciated example of regulated cytokinesis as a major developmental mechanism is asymmetric cell division, a process where cytokinesis contributes to the generation of two different cells from a single progenitor cell. Decades of studies from model organisms, such as *C. elegans* and *Drosophila*, have led to insights into the general mechanisms that govern asymmetric cell division [82, 83]. The asymmetry in the fate of the daughters comes from the polarity of the progenitor cell, which serves two important purposes: asymmetric localization of cell fate determinants and orientation of the cell division machinery, including the spindle and cleavage furrow. In most mitotic systems, there is a clear hierarchy in the patterning processes during asymmetric cell division: cell polarity dictates the orientation and position of the mitotic spindle, which in turn through its microtubules determines the placement of the cleavage furrow (Fig. 3). Powerful genetic analyses in these model systems have led to the identification of many molecular components and various regulatory and structural modules important for the establishment of cell polarity and asymmetric cell division. As these molecular details can be found in several excellent reviews [84–89], this review will focus on some of the new findings in the field.

Asymmetric cell division may give rise to progeny cells with different cellular contents, such as cell fate determinants, or cell size, or both. As spindle position ultimately determines the placement of the contractile ring, the critical issue in whether cytokinesis occurs symmetrically or asymmetrically falls squarely on the orientation of the spindle axis relative to the axis of cell polarity. This criterion has been used in several recent studies examining the role of symmetric versus asymmetric cell division in stem cell or progenitor cell proliferation and differentiation during mammalian development. Experiments in the epidermis [90, 91], dermomyotome [92], nervous system [93, 94] and immune cells [95] have led to the conclusion that asymmetric cell division provides a universal mechanism in the generation of differentiated cell types while replenishing progenitor cells. It is important to note that the symmetry in cell division *per se* does not necessarily predict the fate of the progeny cells. Although symmetric cell divisions often lead to proliferation of stem/progenitor cells, there are also clear examples where symmetric cell divisions can

result in daughter cells with either differential fates or both going on to differentiation [96–98]. Nonetheless, at distinct developmental stages, the decision to undergo symmetric or asymmetric cell divisions is often critical for the correct developmental fate of the progeny cells.

Central roles of the centrosomes in asymmetric cell division

The centrosomes, which are microtubule organizing centers at the poles of the spindle in most mitotic cell types, play multiple roles in asymmetric cell division. A well-known role for centrosomes is in spindle placement and orientation (Fig. 4a), the process that is pivotal to the success of asymmetric cell division. Spindle position determines not only the orientation of the cleavage plane but also the sizes of the daughter cells. *C. elegans* zygotes divide asymmetrically along the anterior-posterior (AP) polarity axis to give rise to two blastomeres of different sizes and fates. The spindle is aligned along the AP axis. During anaphase, the elongating spindle oscillates, and its posterior pole exhibits greater movement toward the posterior cortex, resulting in an off-centered spindle and hence asymmetrically placed cleavage furrow [86]. The centrosomes are points of force anchorage by motor proteins, such as the minus-end-directed microtubule motor dynein, which pulls on astral microtubules at the cell cortex. The posterior translocation of the spindle is due to a larger force on the posterior centrosome than that on the anterior one, and this force imbalance is attributed to proteins that regulate AP polarity [99, 100] (Fig. 4a). A recent mathematical model suggests that an increase in the processivity of the motor protein can explain all the observed features of spindle movement and oscillation [101]. At the molecular level, superior motor force at the posterior cortex requires the interaction of LIN-5, a centrosome and cortex-associated protein related to vertebrate NuMA, with the Gi/o heterotrimeric G protein regulatory module, which is enriched on the posterior cortex [102–104]. Studies in *Drosophila* and mammalian cells suggest that this molecular system of spindle positioning is highly conserved [87, 97, 103–106]. At a mechanistic level it remains to be determined how the interaction between NuMA and components of the Gi/o module regulates the processivity of dynein motor activity along microtubules. The mechanism discussed above emphasizes the contribution of polarized distribution of cortical signaling molecules in asymmetric force generation and spindle positioning. However, there is evidence that the asymmetry may also lie in the composition of

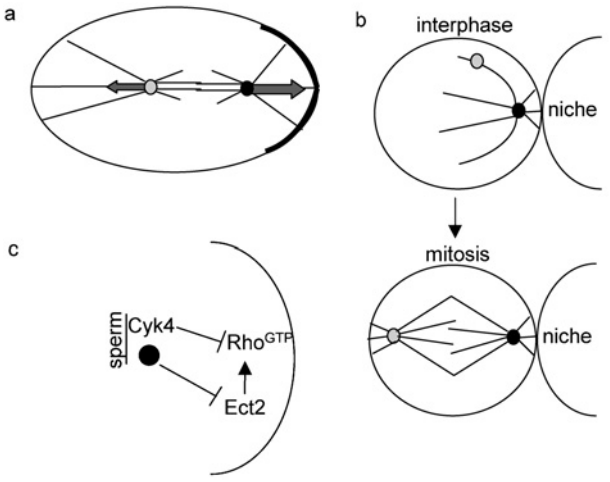

Figure 4. Three different roles of the centrosome in asymmetric cell division. (*a*) The centrosome's role in mediating asymmetric forces that lead to asymmetric spindle positioning. This force asymmetry is a result of the interaction of astral microtubules nucleated from one of the centrosomes (black dot) with the polar cortex (thick black line) toward which the spindle moves. (*b*) Anchorage of the mother centrosome (black dot) to the stem cell cortex juxtaposing the stem cell niche contributes to spindle orientation required for asymmetric cell division. An outcome of this process is asymmetric inheritance of daughter (gray dot) versus mother centrosomes between the two progenies of this cell division. (*c*) The sperm-associated centrosome (black dot) triggers cell polarity in *C. elegans* zygotes. A target of this process is Rho: the centrosome excludes ECT-2, a Rho GEF, from the posterior cortex. The sperm also provides a high local concentration of Cyk-4, a GAP for Rho. A local reduction in RhoGTP results in imbalanced actomyosin contractility and cortical symmetry breaking (not depicted in the diagram).

the two centrosomes that organize the spindle poles. Centrosomes duplicate conservatively, generating a daughter centrosome using new protein components next to the mother centrosome. Recent work in *Drosophila* male germline stem cells [107] and larval brain neuroblasts [108] revealed that the stem cell always retain the mother centrosome, whereas the daughter centrosome is inherited by the cell destined for differentiation. This asymmetric inheritance stems from a delay in the maturation of the newborn centrosome such that the mother centrosome is preferentially tethered to the stem cell cortex opposite from the differentiating cell (or the side close to the stem cell niche) through an abundance of astral microtubules (Fig. 4b). Due to a lack of anchorage, the newborn centrosome, migrates to the opposite side of the nucleus. Anchorage of the mother centrosome was proposed to serve as the first step in the proper alignment of the mitotic spindle relative to the axis of polarity of the stem cell. An intriguing parallel of this phenomenon has been studied in budding yeast [109], which undergoes asymmetric cell division during the vegetative cell cycle. The bud is stem cell-like in that it is always a newborn with high replicative

potential, whereas the mother is aged with more limited replicative life span. To ensure alignment of the spindle along the mother-bud (polarity) axis, the old spindle pole body (the centrosome equivalent in yeast) is preferentially anchored to the bud cortex through astral microtubules, and this preference is due to a delay in maturation of the new spindle pole body [110]. The S phase cyclin-associated CDK1 complex is critical for this centrosomal asymmetry [111].

Centrosome's role in asymmetric cell division is not limited to spindle alignment: a more unexpected role in the establishment of cell polarity has been reported in recent studies with, *C. elegans* zygotes (Fig. 4c). The sperm entry site is well known to be important for the establishment of AP polarity in the one-cell embryo [112]. At least one of the critical factors provided by the sperm is the centrosome it brings, whose migration and contact with the posterior cortex initiates the polarization process [113]. Cell polarization is driven by actin- and myosin-II-based contractile movement toward the anterior pole, resulting in segregated localization of polarity determinants, such as PAR-3 and PAR-2, to separate domains along the AP axis [114]. Laser ablation of the centrosome inhibited the establishment but not maintenance of polarity, and interestingly, the essential function of the centrosome in polarity establishment does not require microtubule assembly [113]. A recent study showed that the centrosome excludes the Rho GEF Ect2 from the posterior cortex [115] (Fig. 4c). This event, coupled with a local concentration of Cyk-4, a Rho GAP that is also supplied by the sperm [116], results in local decline of Rho activity and hence weakening of the myosin-II contractile network at the posterior cortex. Interestingly, the ability of centrosomes to induce cell polarity is regulated by cyclin E-Cdk2: cyclin E-Cdk2 knockdown by RNAi prevented the establishment of polarity in, *C. elegans* embryos, and this defect is likely due to failed recruitment of certain critical centrosomal components [117].

Polar body extrusion – an extreme example breaking the common rules

Whereas most insights into asymmetric cell division have come from studies in mitotic systems, a most extreme case of asymmetric cell division occurs during oocyte meiotic maturation. In animal sexual reproduction, female gametes are matured through two consecutive rounds of meiotic cell divisions, the products of which are a single mature oocyte, with a genome reduced to half that of a somatic cell, and two polar bodies that rapidly degenerate. These divisions are not only highly asymmetric in cell fate; the cell size asymmetry is also important: cytoplasmic material must be preserved as much as possible in the oocytes in order to support robust embryonic development after fertilization. Like asymmetric mitotic divisions, three events govern the process of polar body extrusion: cell polarity, spindle orientation and cleavage plane positioning. However, the means by which these processes relate to each other appear quite different in the meiotic process. The cortical polarity required for this asymmetric cell division is established upon migration of the meiotic chromosomes and spindle from the center of the oocytes to a subcortical location, where a contractile cortex forms overlying the meiotic chromosomes [118] (Fig. 3). In mouse oocytes, the chromosome/spindle migration is an actin-driven process but is independent of microtubules [119–121], whereas in *C. elegans*, the movement is clearly dependent on microtubules, the microtubule severing protein katanin and the motor protein kinesin-1 [122, 123]. It remains unclear how force is produced to drive the chromosome movement in the mammalian process. Formin-2, a member of the formin family that potentially nucleates actin filaments, is required for mouse meiotic chromosome movement [124, 125], but it is unclear whether this requirement involves formin-dependent formation of actin tracks that enable a myosin motor-driven motility, or reflects more direct force production through formin-stimulated actin polymerization.

Once in close vicinity to the cortex, the meiotic spindle induces the formation of a cortical domain competent for polar body extrusion. Recent work in mouse oocytes has shown that this cortical domain consists of a ring of myosin-II surrounding an actin cap [126]. The myosin ring contains a distinct set of actin filaments and constricts during anaphase to extrude a set of the segregating chromosomes into the polar body. Thus the meiotic and mitotic contractile ring formation differ at two levels: the former is induced as early as metaphase and is a direct product of cortical polarity, not a consequence of spindle orientation. In fact, in meiosis II it is not until mid-to-late anaphase that the spindle aligns in an actin-dependent manner along an axis perpendicular to the cleavage plane for polar body extrusion [127]. The early determination of the cleavage plane and a later adjustment in spindle orientation are strikingly similar to the characteristics of the general scheme for budding yeast cytokinesis [128] (Fig. 3). The most remarkable aspect of the process in mammalian oocytes is that the signal governing asymmetric cell division comes directly from the meiotic chromatin [126, 129]. Even DNA-coated beads are fully capable of inducing cortical actomyosin cap in the absence of microtubules. The size of the cortical cap responds quantitatively to the

amount of the DNA present, and the efficiency of its formation is inversely related to the minimum distance between the chromatin and the cortex [126]. These relationships potentially allow the size of the polar body to be tailored based on the size of the genome to be disposed and prevent symmetric cell divisions that could lead to a large loss of oocyte cytoplasm.

Much remains to be learned about the molecular pathway underlying the unique scheme of meiotic asymmetric cell division. The Rho family small GTPases Cdc42 and Rac are implicated in the asymmetric movement and cortical attachment of the meiotic spindle, respectively, and intriguingly, both GTPases appear to play important roles in spindle assembly and microtubule dynamics [130, 131]. Perhaps even more unexpected is the involvement of the small GTPase, Ran, which was not previously known to regulate cortical events. However, based on its known role in spindle assembly and nuclear envelope formation, Ran is perfectly suited as a chromatin signal that can measure distance [132, 133]. The spatially segregated Ran GEF and GAP distribution results in a gradient of Ran-GTP emanating from the chromatin [134–136]. Two recent studies provide complementary evidence that a Ran-GTP gradient indeed exists around the meiotic chromatin in mouse oocytes and that Ran-GTP is required for assembly of the chromatin-induced actomyosin cap, and also the meiotic spindle [126, 137]. Myosin-II assembly appears to be a downstream event induced by the chromatin. It remains to be tested whether Rho relays the Ran signal to myosin-II. Importantly, Mos, a mitogen-activated protein (MAP) kinase kinase kinase that plays critical roles in meiotic cell cycle [138], regulates the meiotic asymmetric cell division process. Mos-deficient mouse oocytes exhibit strong defects in spindle migration to the cortex and in the establishment of cortical polarity in response to the chromatin signal [121, 126, 129].

Enucleation and polyploidization – creative tinkering in the hematopoietic lineage

The hematopoietic lineage has two interesting examples where cytokinesis is controlled in unusual ways to generate specialized cell types (Fig. 5). Erythroblasts, the immediate precursor for mature reticulocytes, undergo asymmetric cell division during final maturation, a process referred to as enucleation (or denucleation). This cell division, however, breaks all the common rules because it does not partition the genetic material and it occurs during interphase. This unusual cell division gives rise to a cell with only the cytoplasm (the reticulocyte), and a cell with just the nucleus surrounded by a plasma membrane that is quickly engulfed by phagocytic macrophages [139–141]. Our understanding of this remarkable process is mostly limited to descriptive data from classical cytology studies, which showed that the process is initiated by nuclear movement to one side of the erythroblast [142, 143], during which key plasma membrane and cytoskeletal components required for reticulocytes are sorted to the cytoplasmic side of the cell [144, 145]. Enucleation appears to be accomplished through constriction at the base of the nucleus, where a concentration of F-actin was observed [146, 147]. Consistent with a role for F-actin, cytochalasin completely blocked the enucleation process, whereas microtubules inhibitors had no effect [146]. Whether actin's role reflects the function of a contractile ring remains to be determined, as immunocytochemistry staining showed that myosin-II localizes to the entire cortex engulfing the protruding nucleus [147]. A better understanding of the organization and function of actin and myosin-II during enucleation requires analysis using more contemporary approaches.

In addition to a possible involvement of the contractile ring, the enucleation process, like cytokinesis, appears to involve local vesicle fusion, as a large number of coalescing vesicles were observed at the base of the extruding nucleus, resulting in convoluted membranes connecting the nucleus and the incipient reticulocyte [143]. Attachment to the extracellular matrix also appears to be critical for enucleation [148]. If erythroblast enucleation truly uses the same physical mechanism as that in cytokinesis, the control of this mechanism must be quite different from the common pathways described above, as this process is independent of microtubules and is not coupled with chromosome segregation. In addition to erythrocyte enucleation, programmed removal of other major cellular parts also occurs in specialized developmental programs, such as the process of residual body detachment during sperm maturation, where a major portion of the cytoplasm, as opposed to the nucleus, is discarded [149] (Fig. 5). It will be interesting to investigate if the cytokinetic machinery is employed during this process.

In contrast to erythroblasts, megakaryocytes, which are derived from the same myeloid progenitors, skip cytokinesis in order to achieve differentiation [150] (Fig. 5). Megakaryocytes are highly polyploid cells, each of which can generate a large number of platelets through fragmentation of the cytoplasm. Polyploidization is a normal physiological process observed in many tissues and organs and can be achieved through a variety of mechanisms that in general involve DNA replication without performing all the subsequent

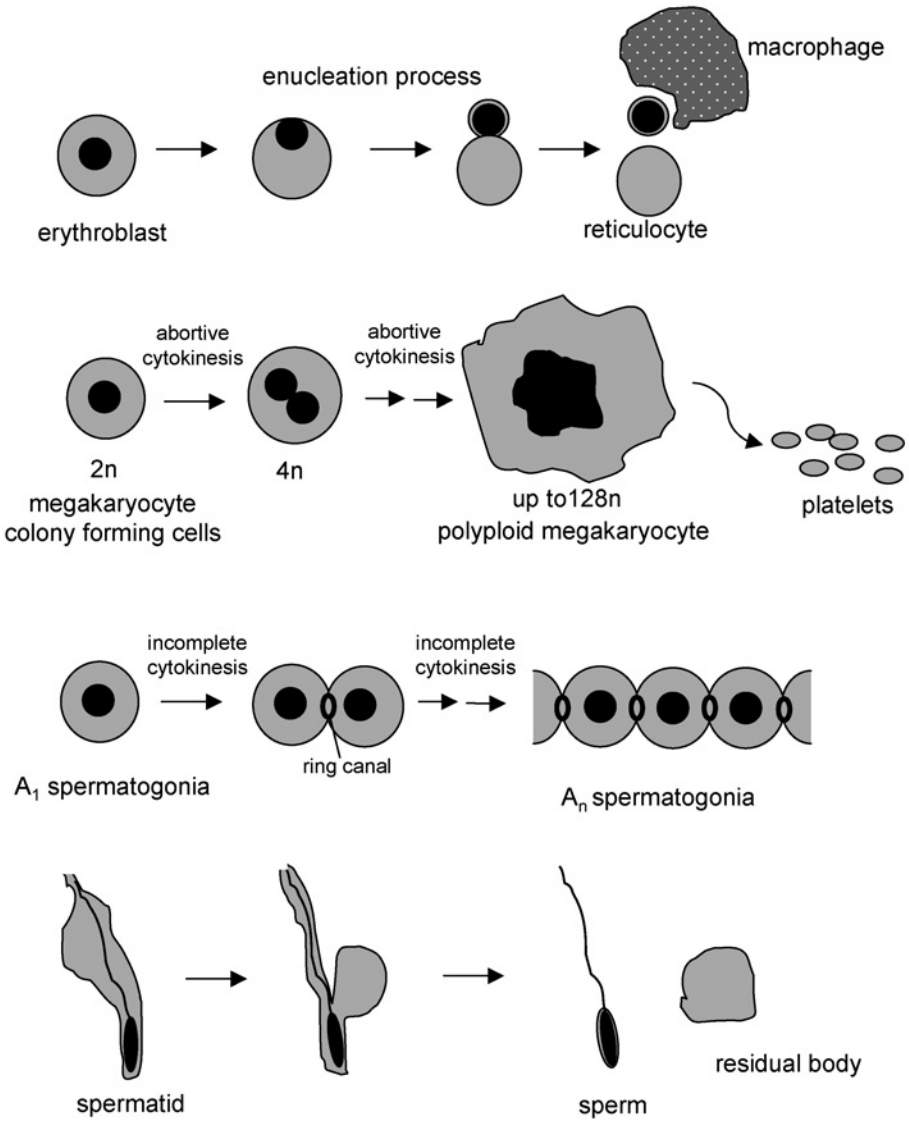

Figure 5. Unusual cytokinetic events (or a lack of) in the formation of specialized cell types during the differentiation of blood and germ cell lineages.

events in mitotic cell division [150, 151]. During megakaryocyte polyploidization, DNA replication, mitotic entry and chromosome segregation all seem to occur normally, but cytokinesis fails. Time-lapse microscopy analysis revealed that a cleavage furrow forms initially, ingresses to some extent and then regresses [152]. Similar abortive cytokinesis was also observed in liver hepatocytes that initiate polyploidization [153]. Thus, it appears that a late event in the completion of cytokinesis but not the initial contractile ring formation is the target of regulation to achieve polyploidization in these cell types. Late-stage cytokinesis failure is often observed in cells deficient for central spindle components [4]. Indeed, Aurora-B kinase and its functional partner, survivin, were reported as missing or underexpressed in megakaryotes undergoing polyploidization [154, 155]. Consistently, overexpression of survivin antagonized megakaryocyte polyploidization [155]. However, a different study found that central spindle formation and localization of functional Aurora B and survivin are apparently normal in megakaryocytes with abortive cytokinesis [156].

While the above discrepancy remains to be reconciled, given the knowledge of all the requirements for successful cytokinesis, what else could be inhibited to achieve polyploidization by blocking the completion of cytokinesis? As mentioned earlier, completion of cytokinesis requires local delivery and insertion of membrane, and therefore those proteins specifically involved in membrane fusion in the cleavage furrow are candidates in addition to central spindle components. Another possibility arises from the idea that there is a limited cell cycle window that allows cytokinesis. Polyploidizing megakaryocytes are known to have altered cell cycles with short gap

phases [157]. Indeed, numerous studies suggest that polyploidization involves altered regulation of A-, D- and E-type cyclins [150]. It is possible that an unusual oscillation of certain cell cycle regulators does not permit sustained activation of the cytokinetic machinery to complete cell division in megakaryocytes.

Abortive cytokinesis does not always lead to polyploidization: in certain cell types the partially ingressed furrow can be stabilized, resulting in formation of a sustained intra-cellular bridge connecting the daughter cells [158–160]. A relatively well studied example is the formation of ring canals in male and female germline divisions, involving a series of incomplete cell divisions that give rise to either connected spermatogonia and spermatocytes or an oocyte connected with surrounding nurse cells [161, 162] (Fig. 5). Such intercellular bridges are thought to be important for the germ cells to share cell cycle regulators and other developmental factors [163]. Midway through furrow constriction, certain key components of the contractile ring, such as myosin-II and actin (in the case of male ring canals), disassemble from the cytokinetic furrow [164, 165]. The mature ring canal is lined by remaining cytokinetic proteins and additional structural proteins, and the final compositions of male and female ring canals are quite different [165–167]. A testis-specific protein, called Tex14, was identified in mammalian male germ cells and was shown to be critical for ring canal formation and male fertility [168]. Tex14 is an ankyrin repeat-containing protein and may thus play a scaffolding role. Indeed, Tex14 localizes to the ring canal and is important for recruitment of central spindle components, such as MacRacGAP and MKLP1, to form stable intracellular bridges [169]. It is puzzling why during normal cytokinesis these central spindle components promote the final closure, whereas in germ cell divisions these proteins function to maintain the junctions between the daughter cells.

Cytokinesis in cancer: a double-edged sword?

Summarizing the information at hand, cytokinesis is not only critical for cell proliferation but is also delicately regulated in diverse developmental processes. It is thus not difficult to imagine that disease states could arise when aspects of cytokinesis control goes awry. There is in fact an enigmatic relationship between cytokinesis and cancer. As a hallmark of cancer is uncontrolled cell division, cytokinesis may be a target for cancer treatment. However, recent evidence suggests that such an approach may be problematic, since defects in cytokinesis may promote cancer development through at least two mechanisms.

The first mechanism relates to asymmetric cell division: since this is a critical step in the commitment to differentiation, defects in asymmetric cell division could result in drastically elevated proliferation potential [98]. In *Drosophila*, many genes required for asymmetric cell division, such as disc large (Dlg), lethal giant larvae (Lgl) and scribble (Scrib), are tumor suppressors, mutations which lead to invasive tumors in the imaginal epithelia and the nervous system in the larva stage [170]. Several recent studies have clearly suggested a link between their tumor suppressor function and role in asymmetric cell division. It was found that Brat and Prospero, two proteins that inhibit proliferation and promote neuron differentiation, are segregated to the daughter cell destined to become a ganglion mother cell (GMC) during neuroblast asymmetric cell division [171, 172]. Failure to restrict these proteins to the basal cortex (the GMC side) in *lgl* mutant neuroblasts results in hyperproliferation of neuroblast in the larval brain. Another experiment involved transplantation of neuroblasts from larval brains of mutants defective in asymmetric cell division to wild-type hosts. These neuroblasts, but not those from a wild-type donor, grew into invasive tumors that eventually led to host death [173]. Observations similar to those described in *Drosophila* have also been made in mouse retina, where inhibition of mammalian Inscuteable, a protein that regulates spindle orientation during asymmetric cell division, also results in hyperproliferation of neural progenitor cells [174].

A less expected mechanism by which defects in cytokinesis contribute to cancer progression is the generation of polyploid cells. A recent study found that tetraploid, p53-deficient cells, generated with transient blockage in cytokinesis, led to tumor formation after injection into nude mice, whereas diploid cells did not have this effect [175]. How might polyploid cells develop into cancer? Tumors generated from p53-deficient tetraploid cells exhibited high levels of whole chromosome aneuploidy, gross chromosome rearrangements and amplification of regions enriched for genes whose overexpression had been implicated in mammary tumors. At a basic level, polyploidy can result in high-level genomic instability, which creates heritable variations that enable cancer evolution and adaptation [176, 177]. Interestingly, processes that result in genomic instability, such as chromosome non-disjunction, have been reported to correlate with cytokinesis failure and polyploidization [178]. Therefore, cytokinesis defect, polyploidization and erroneous chromosome segregation may constitute positive feedback that could drastically accelerate the development of aggressive tumor phenotypes.

A third potential mechanism by which polyploidy could contribute to tumorgenesis is a poorly understood process termed neosis. In neosis, giant mononucleate polyploid cells, formed due to DNA damage and destined for apoptotic death, undergo a peculiar process of nuclear budding and splitting off small mononucleate cells called Raju cells [179]. Raju cells that survive give rise to transformed cell lines. This process may represent yet another altered scheme of cytokinesis decoupled from proper chromosome segregation. It is not known whether such a process indeed contributes to tumor growth *in vivo*. In summary, cytokinesis, because of its critical role in cell proliferation, is a plausible target for cancer chemotherapy. However, due to the intricacies and flexibility in cytokinesis regulation and the consequence of cytokinesis failure on genomic stability, incomplete inhibition of cytokinesis without rapid cell death may in fact promote, rather than delay, cancer progression.

Perspective

Cytokinesis is a process of intricate spatiotemporal regulation and large-scale, dynamic cytoskeletal rearrangement. Cytokinesis is not only a critical event a cell must accomplish over and over again in proliferative divisions, but more interestingly, it is a focal point of developmental regulation. From an evolutionary perspective, perhaps the molecular complexity inherent in the cytokinesis process provides the useful 'substrates' that enable the cytokinetic machinery to be 'tinkered' in various ways to satisfy specific development objectives. This ability to evolve may also underlie the robustness of the cytokinetic process observed in yeast, *Dictyostelium* and cultured mammalian cells. Although tremendous progress has been made in identifying the molecular 'nuts and bolts' that constitute the cytokinetic machinery, there is still a way to go to achieve a conceptual and quantitative understanding of the cytokinetic process as a whole, which might enable explanation and prediction of the emergent phenotypes in both physiological and pathological settings.

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