Review

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Mechanisms of daughter cell-size control during cell division

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Daughter cell size is tightly regulated during cell division. In animal cells, the position of the anaphase spindle specifies the cell cleavage site to dictate the relative size of the daughter cells. Although spindle orientation is regulated by dynein-dependent cortical pulling forces exerted on astral microtubules in many cell types, it was unclear how these forces are precisely regulated to center or displace the spindle. Recently, intrinsic signals derived from chromosomes or spindle poles have been demonstrated to regulate dynein-dependent pulling forces in symmetrically dividing cells. Unexpectedly, myosin-dependent contractile forces have also been shown to control spindle position by altering the cellular boundaries during anaphase. In this review, I discuss how dynein- and myosin-dependent forces are coordinately regulated to control daughter cell size.

Daughter cell size is defined by anaphase spindle position

Cell division is the fundamental process by which two daughter cells are produced from a single progenitor. In animal cells, the site of cell cleavage to 'cut' the cell in two is specified during anaphase [1–3] by signals derived from the spindle midzone, which is formed between the separating chromosomes (Figure 1A) [4]. This mechanism coordinates chromosome segregation with cytokinesis and ensures the equal distribution of the duplicated chromosomes into daughter cells to maintain the genomic information. By contrast, other factors such as polarized cell-fate determinants and extrinsic niche signals can be symmetrically or asymmetrically distributed between daughters by controlling spindle orientation (Figure 1A, left and center; Figure 1B) (reviewed in [5]). Because the distribution of these polarized factors is critical to determine the fate of the daughter cells, and thus the cell division type (symmetric or asymmetric cell division) [6], the mechanisms of spindle orientation have been extensively studied in several organisms during development [7–13] and in *in vitro* cell culture [14]. These studies have established a key concept that polarity signals assemble force-generating machineries at specific sites at the cell cortex to properly orient the spindle along the polarity axis [5].

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Similarly to the way in which the distribution of polarity factors can be controlled by modulating spindle orientation, the physical size of the daughter cells is varied by controlling spindle position (Figure 1A, center and right). However, compared with the detailed understanding that exists for the basis of spindle orientation, the mechanisms and roles of spindle positioning and daughter cell-size control were poorly understood. In most vertebrate cells, the spindle is positioned in the center of the cell resulting in equal-sized cell division (Figure 1B, I,III). By contrast, the spindle is displaced to generate unequal-sized daughters in several different cell types, such as the *Caenorhabditis elegans* early embryo [8], *Drosophila* neuroblasts [7], sea urchin micromeres [2], and mouse oocytes [15–17]. These unequally dividing daughters display different cell fates due to both differences in cell size and asymmetric distribution of cell-fate determinants as a result of controlled spindle orientation (Figure 1B, IV). However, a difference in cell size is not always required for asymmetric cell fate during asymmetric cell division (Figure 1B, III) and the contribution of the relative daughter cell size to defining cell fate was unclear.

Nonetheless, daughter cell size appears to be tightly regulated during both symmetric and asymmetric cell division. The difference in cell volume or mass between two daughter cells in symmetrically dividing L1210 lymphoblasts is less than 10% [18,19]. Daughter cell size affects the relative amount of cytoplasmic factors and organelles, such as mitochondria, which is critical for cell function and survival [20]. Furthermore, daughter cell size may have critical roles in early interphase events such as nucleus formation and may affect the relative volume of the nucleus and cytoplasm, which is maintained as a constant ratio during the cell cycle [21]. Thus, it is plausible that daughter cell-size control plays a critical role in cell physiology. Recent studies indicate that altering daughter cell size results in differential behavior of daughter cells in both symmetrically and asymmetrically dividing cells [22–24].

To understand the mechanisms of spindle positioning, it is critical to define the forces acting on the spindle to control its position. Accumulating evidence indicates that the minus end-directed microtubule-based motor cytoplasmic dynein [25,26] (hereafter called dynein), generates cortical pulling forces that act on astral microtubules to control spindle orientation and position [8,27,28]. However, the mechanisms that precisely regulate cortical dynein localization and activity to control spindle position is

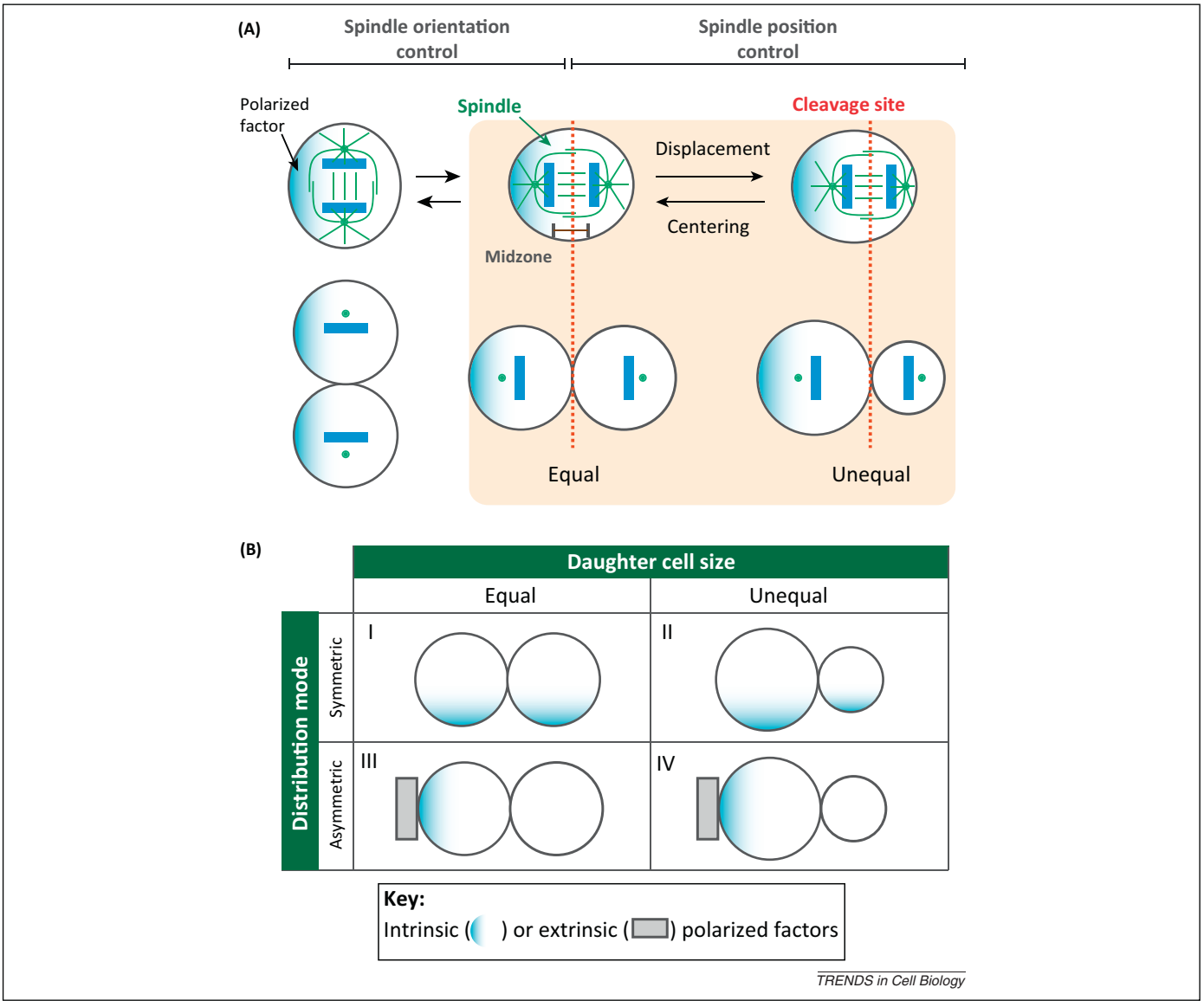

Figure 1. Daughter cell-size control by spindle positioning. **(A)** Spindle orientation controls the distribution of polarized factors (compare left with center), whereas spindle position defines daughter cell size (compare center with right). Left: During symmetric cell division, the spindle is centrally positioned and all cellular components are equally distributed between daughter cells. Center: During asymmetric cell division in most vertebrate cells, the spindle is oriented parallel to the polarity axis to asymmetrically distribute polarized factors, whereas the spindle is positioned in the center of the cell to divide equally in size. Right: In a subset of asymmetrically dividing cells, the spindle is displaced and both daughter cell size and the distribution of polarized factors become asymmetric. The blue line and green circle indicate chromosomes and centrosomes, respectively. **(B)** Cell division can be classified into four groups in terms of daughter cell size and distribution of polarized factors.

poorly understood, especially in symmetrically dividing cells. Here, I review recent advances in understanding how dynein-dependent cortical pulling forces are regulated during metaphase and anaphase to center or displace the spindle, thus generating equal- or unequal-sized daughters, respectively.

Direct contacts between astral microtubules and the cell cortex act to generate a physical connection and generate force to move the spindle in most cell types. However, in extremely large cells such as *Xenopus* zygotes [29] and in cells with anastral spindles such as mouse oocytes [15–17] or plant cells [12], astral microtubules do not reach the cell cortex. In these cells, spindle position must be regulated by different mechanisms such as length-dependent astral microtubule pulling in the cytoplasm [29–32] or actin-based forces both in the cytoplasm [16,33] and at the cell cortex [34]. As these mechanisms have been reviewed extensively [15,17,35,36], I instead focus on the mechanisms of spindle positioning by cortical pulling forces during metaphase and anaphase.

Cortical dynein recruitment in unequally dividing cells

Over the past few decades, the mechanisms of spindle displacement and the resulting unequal-sized cell division have been extensively studied in the asymmetrically dividing one-cell *C. elegans* embryo (reviewed in detail in [8,28]). In these cells, the maternal and paternal pronuclei and their associated centrosomes are initially positioned in the center of the cell during interphase by microtubule-length-dependent pulling mechanisms [31]. Subsequently, the spindle forms and is displaced toward the posterior cell cortex during anaphase (Figure 2A). Dynein is a key player in the generation of asymmetric pulling forces that act on astral microtubules [8,28]. In *C. elegans* embryos, a