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Force and length regulation in the microtubule cytoskeleton: lessons from fission yeast

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How does a living cell deal with basic concepts of physics such as length and force? The cell has to measure distances and regulate forces to dynamically organize its interior. This is to a large extent based on microtubules (MTs) and motor proteins. Two concepts are emerging from recent studies as key to the positioning of cell components: preferred disassembly of longer MTs and preferred detachment of motors under high load force. The role of these concepts in nuclear centering and nuclear oscillations is coming to light from experimental and theoretical studies in fission yeast. These universal concepts are likely crucial for a variety of cell processes, including nuclear and mitotic spindle positioning, control of spindle length, and chromosome congression on the metaphase plate.

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Introduction

A living cell is not a bag full of randomly distributed bits and pieces — molecules, molecular assemblies, and organelles. The cell interior is instead neatly organized in a dynamic yet controlled manner. Dynamic organization of the cell interior requires constant exploration of the intracellular space to adjust the position of cell components in a response to changes such as cell growth, progression through the cell cycle, and signals from the environment. To this aim the cell uses microtubules (MTs) and actin filaments, motor proteins, and other cytoskeleton-associated proteins.

MTs are dynamic polymers, which can be in a growing or a shrinking state. Growth and shrinkage are more pronounced at one (plus) MT end, compared to the other (minus) end. The switch from growth to shrinkage is called catastrophe, while the switch from shrinkage to growth is rescue. Catastrophe and rescue are stochastic events, which together with growth and shrinkage belong to intrinsic properties of MTs [1]. Cells use MTs to carry out a variety of functions, such as transport of organelles and molecular assemblies, segregation of chromosomes, and positioning of the nucleus and of the mitotic spindle. To perform these different tasks, the cell regulates the intrinsic properties of MTs according to the specific task, using MT-associated proteins.

Dynamic spatial organization of the cell interior requires forces to move and position organelles [2]. Force is generated when MT growth and shrinkage is hindered by objects such as the cell cortex and organelles. MTs growing against an obstacle produce pushing force [3], while shrinking MTs pull on structures that remain attached to the MTs as they shrink [4]. In addition, MTs transmit the force generated by motor proteins [5].

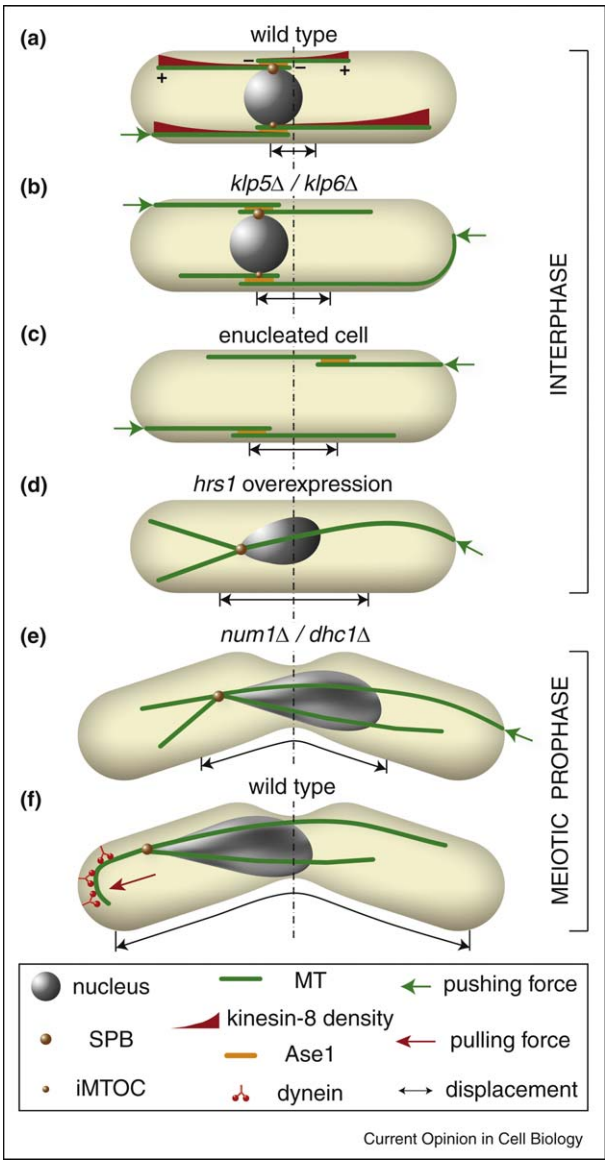
MT-based movements of the nucleus are extensively studied in fission yeast as a model system. An advantage of this system is its genetic amenability, which allows for fluorescent tagging and deletion of proteins involved in nuclear movements. Moreover, tracking and manipulation of single MTs is possible because of the small number of MTs in these cells [6]. The cells are rod-shaped and the nuclear diameter is only slightly smaller than the diameter of the cell. Hence, one-dimensional models are appropriate theoretical descriptions of nuclear movements. Because of the low number of important degrees of freedom in the theoretical models, the underlying mechanisms can be easily understood. A combination of modeling and experimental work has recently provided the understanding of several mechanisms driving nuclear movements, from nuclear centering [7•,8•] to pole-to-pole nuclear oscillations [9••].

Nuclear centering

In interphase fission yeast cells as well as in many other cell types, the nucleus is found at the geometric center of the cell. This central location of the nucleus in fission yeast ensures symmetric cell division, because the cell divides at the site where the nucleus is positioned in early mitosis [10,11]. Between two divisions, the cell grows more at the old pole, which existed previously, than at the new pole, which was created during the latest division [12,13]. The nucleus must be, therefore, recentered continuously as the cell grows.

During interphase, the nucleus is linked to MTs, which are organized in three to five bundles extending along the cell axis [8•,14,15] (Figure 1a). Each bundle consists of several antiparallel MTs [16,17]. Their plus-ends point toward the opposite cell poles, while the minus-ends are located near the nucleus. Overlapping minus-end regions of antiparallel MTs are bound together by the Ase1 protein (Figure 1a) [18,19]. The plus-ends grow toward the cell pole, and generate pushing forces as they continue growing against the cell pole [8•]. After pushing for about a minute or two, MTs undergo catastrophe and shrink back to the nuclear region. This retraction is followed by new growth.

Figure 1



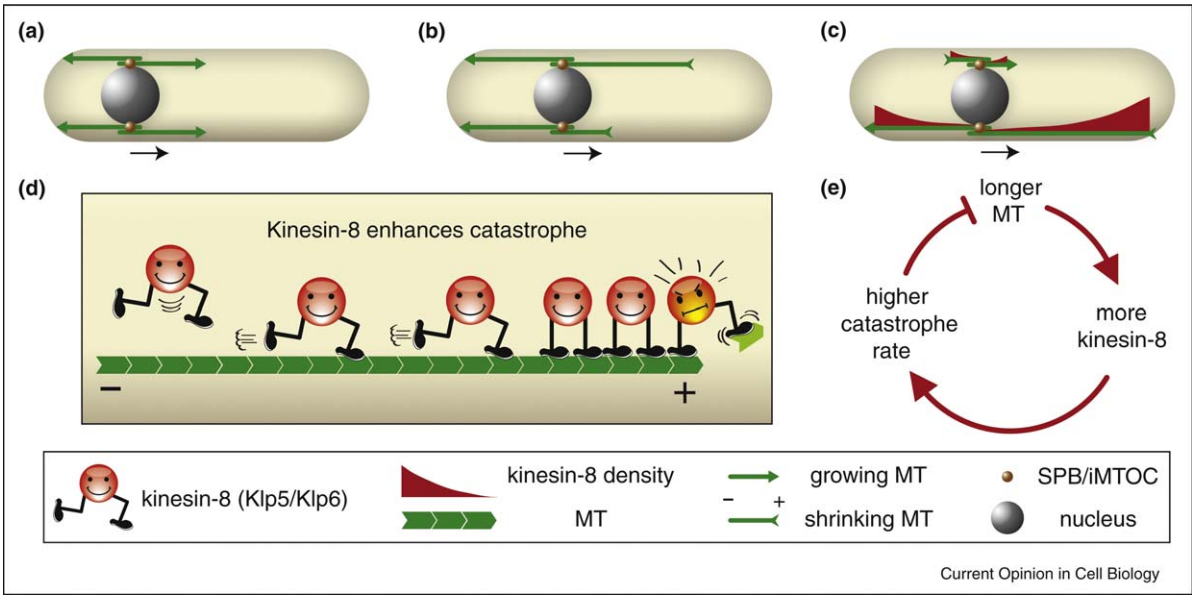
From nuclear centering to pole-to-pole nuclear oscillations in fission yeast. Conditions that increase the amplitude of nuclear movements. **(a)** Nuclear centering in interphase fission yeast cells. For simplicity, only two bundles are shown, each consisting of two antiparallel microtubules (MTs). MTs push against the cell ends, thereby moving the nucleus. Kinesin-8 motors (red) increase MT catastrophe frequency in a MT length-dependent manner, which facilitates nuclear centering. **(b)** Nuclear centering by MT pushing with length-independent catastrophe frequency, as in cells lacking kinesin-8 motors Klp5/6. **(c)** Centering of MT bundles in enucleated cells. **(d)** Nuclear movement driven by MT pushing in interphase cells where MTs grow in an aster configuration, as in cells overexpressing Hrs1. **(e)** Nuclear movements in meiotic prophase driven by MT pushing in a cell that lacks dynein heavy chain (Dhc1) or dynein anchors (Mcp5/Num1). **(f)** Nuclear oscillations in meiotic prophase driven by pulling forces exerted by dynein motors (red) in wild-type cells.

MT pushing forces are required for the positioning of the nucleus and the mitotic spindle [7•,8•,10,20]. When an interphase nucleus is artificially displaced by optical tweezers [10] or centrifugation [7•], MTs push against the cell poles and thereby recenter the nucleus within 10–20 min. Moreover, in early prophase, the nascent spindle grows adjacent to the overlap zone of one MT bundle, thus both the position of the spindle at the cell center and the alignment of the spindle along the cell axis depend on MT pushing forces against the cell poles [21–23]. Similarly in anaphase B, pushing forces exerted by astral MTs help spindle alignment along the cell axis, but in this case the MTs push against the lateral sides of the cell [20]. Recent findings suggest a mechanism by which MT pushing forces, together with length-dependent regulation of MT dynamics, may lead to accurate nuclear and spindle positioning [7•,24••].

How does a cell center its nucleus? Let us imagine a nucleus that is displaced from the cell center (Figure 2a–c). For the nucleus to return to the cell center, MTs should push more against the closer cell pole than against the farther cell pole. How can a cell generate such a difference in pushing forces? For example, MT nucleation at the nuclear region may be asymmetric in such a way that more MTs grow toward the closer than the farther cell pole. Further, proteins that promote MT growth may be loaded asymmetrically to the MTs growing into opposite directions, so that MTs on the closer side grow faster than those on the farther side. However, asymmetry in MT nucleation and growth rates has not been experimentally observed.

Even with equal MT nucleation and dynamics on both sides, the pushing forces generated at the opposite cell poles will be different if the nucleus is positioned away from the cell center. There are two reasons for this asymmetry. First, MTs growing toward the closer cell pole reach the pole more often than those growing toward the farther pole because of the difference in the distance to the cell poles (Figure 2a). Second, assuming a constant frequency of MT catastrophe, MTs growing toward the closer pole have a higher probability to reach the cell pole than those growing toward the farther pole, because the probability to undergo catastrophe before reaching the cell pole is proportional to the time needed to reach the pole (Figure 2b). These two effects result in a net

Figure 2



Nuclear centering in interphase is facilitated by preferred disassembly of longer MTs. **(a)**–**(b)** Kinesin-8-independent effects that result in nuclear centering. **(a)** MTs growing toward the closer cell pole reach the pole faster, and thus more often, than those growing toward the farther pole. **(b)** MTs growing toward the closer pole have a higher probability to reach the pole without undergoing catastrophe, than those growing toward the farther pole. **(c)** Kinesin-8 motors (Klp5/6 in *S. pombe*) produce an additional centering effect: MTs pointing toward the closer pole accumulate less motors, undergo catastrophe less often, and thus push on the nucleus for a longer time, than those pointing toward the farther pole. **(d)** Kinesin-8 motors bind along the MT and move processively toward the MT plus-end. The more the motors accumulate at the plus-end, the higher the MT catastrophe frequency. **(e)** The feedback cycle that results in preferred disassembly of longer MTs.

pushing force on the nucleus in the direction of the cell center [25•].

Yet, there is something suboptimal in this scenario: MTs do not 'know' how long they are. When in contact with a cell pole, MTs exert pushing forces on the nucleus for the same amount of time, irrespective of MT length and thus of the distance between the nucleus and the cell pole they are pushing against. Nuclear centering would be more efficient if short MTs, which are in contact with the closer cell pole, would push for a longer time than long MTs, which are in contact with the farther pole.

The contact time between a MT and the cell pole was, indeed, experimentally shown to depend on MT length in fission yeast cells [7•,24••]. When the nucleus is displaced by centrifugation, shorter MTs, which are in contact with the closer cell pole, stay in contact for a longer time than long MTs, which are in contact with the farther pole [7•]. Moreover, even in nonmanipulated cells in which the nucleus is at the center, shorter MTs (in shorter cells) contact the cell poles for a longer time than longer MTs (in longer cells) [24••]. Computer simulations have shown that increasing the contact time of short MTs increases the efficiency of nuclear centering [26].

Microtubule length-dependent effects: buckling and catastrophe frequency

How is MT behavior regulated in response to MT length? Buckling force depends on MT length: longer MTs buckle at a lower force than shorter MTs. Under compressive forces of 5–10 pN, which are typically found in cells, buckling starts when MTs are 4–8 μm long [27]. Buckling can affect centering: MT asters in microfabricated chambers, which mimic the confining geometry of large cells, are not centered if the catastrophe frequency is small, because MTs reaching the chamber edge keep growing and buckle. As their length increases, the buckling force and thus the pushing force decreases [28,29]. The role of buckling in nuclear centering in fission yeast is still unclear.

A difference in MT length can also result in a difference in catastrophe frequency and thus in the contact time between the MT and the cell edge. MT dynamics, including the occurrence of catastrophes, is to a large extent regulated by proteins bound at the plus-end of the MT. Among the regulators of MT dynamics are the plus-end-directed motors from the kinesin-8 family, which promote MT catastrophe. Deletion or depletion of the kinesin-8 Kip3 in budding yeast [30–32], Klp5/6 in fission yeast [33], KipB in *Aspergillus* [34], KLP67A in flies [35],

and Kif18A in humans [36] results in longer MTs (Figure 1b). Experiments *in vitro* have shown that the budding yeast kinesin-8 Kip3 moves processively toward the plus-end [37•,38•] and depolymerizes longer MTs faster than shorter ones [38•]. Similarly, in fission yeast cells, kinesin-8 motors Klp5/6 increase the catastrophe frequency of longer MTs more than that of shorter ones [24••].

How can events at the plus-end depend on the length of the whole MT? Regulatory proteins could produce such a MT length-dependent effect if they would accumulate at the plus-end in an amount that depends on MT length. This could be achieved by binding of the protein along the whole MT, and the subsequent movement of the protein toward the plus-end (Figure 2d) [37•,38•,39]. If the motor movement is faster than the growth of the MT, motors accumulate at the plus-end of the MT. Once there, the motors may enhance the catastrophe frequency of the MT: the more motors accumulate at the plus-end, the higher is the catastrophe frequency (Figure 2d,e). Since in this scenario the number of motors at the plus-end increases with MT length, the catastrophe frequency also increases with MT length (Figure 2e). Consequently, the contact time between a MT and the cell edge decreases with MT length.

The length-dependent contact time improves the efficiency of nuclear centering. If the nucleus is not at the cell center, MTs pointing toward the closer cell pole accumulate fewer motors, undergo catastrophe less often, and thus push on the nucleus for a longer time, than those pointing toward the farther pole (Figure 2c). The length-dependent contact time helps centering in addition to the two motor-independent centering mechanisms described above and depicted in Figure 2a,b. The three effects together result in a net force on the nucleus directed toward the cell center (Figure 2a–c). It will be interesting to see whether kinesin-8 motors increase the efficiency of nuclear centering in fission yeast cells by enhancing catastrophe of longer MTs.

Role of the nucleus and microtubule arrangement in centering

MT bundles center the nucleus in interphase fission yeast cells, but does the nucleus also stabilize the central position of the overlap zones of the MT bundles? Two studies have shown that in a cell devoid of a nucleus, antiparallel MT bundles are still formed and behave similarly to those in normal cells [40,41]. Bundles in enucleated cells have normal dynamics, alignment along the long axis of the cell and orientation with plus-ends pointing toward the cell poles. The overlap zones of the bundles are found in the central region of the cell, though the distribution of the overlap zone position is wider in enucleated than in normal cells with a nucleus (Figure 1c) [41]. This suggests a feedback between MTs and the nucleus, where MTs center the nucleus, while the nucleus stabilizes the position of the overlap zones of the MT bundles close to the cell center.

Is MT arrangement in antiparallel bundles important for nuclear centering? When the antiparallel MT configuration is remodeled by ectopic expression of the meiotic protein Hrs1 into an aster arrangement, the nucleus starts to oscillate around the cell center (Figure 1d) [42]. These oscillations are more pronounced than wild-type interphase nuclear movements (Figure 1a), but less extensive than meiotic nuclear oscillations (Figure 1f). The amplitude of the aster-driven oscillations in interphase is similar to that of the movement of a nucleus in meiotic prophase in cell lacking dynein or dynein anchors Mcp5/Num1 [43–45], where the nucleus is also pushed by MTs in an aster configuration (Figure 1e).

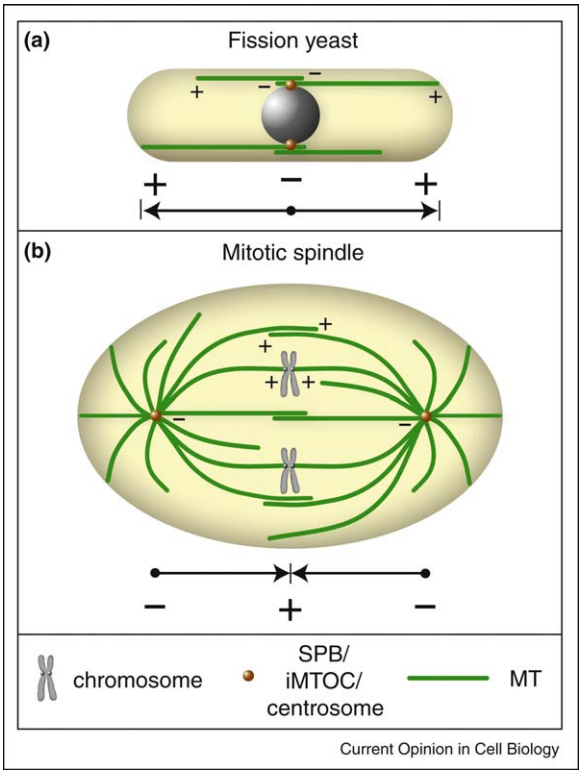
Microtubule length-dependent catastrophe in the mitotic spindle

In addition to their function in regulating MT length in interphase, kinesins play an important role in regulating MT length in the mitotic spindle and thus the length of the spindle as a whole, in cells ranging from yeast to human. Deletion of the kinesin-8 in *Drosophila* S2 cell line makes the spindles longer, while overexpression makes the spindles shorter [46]. Moreover, kinesin-8 motors regulate chromosome positioning in the mitotic spindle. A major question here is how the MT plus-end dynamics is regulated to achieve chromosome alignment on the spindle equator. The human kinesin Kif18A has been shown to reduce the amplitude of chromosome oscillations, thereby helping chromosome congression on the metaphase plate [47]. In budding yeast, kinesin-5 motors Cin8p and Kip1p mediate chromosome congression by suppressing MT plus-end growth of longer MTs [48••]. In both cases, kinesin-mediated chromosome centering in the spindle and centering of the fission yeast interphase nucleus may be driven by a similar mechanism based on MT length-dependent catastrophe (Figure 3).

Nuclear oscillations: mechanical feedback on motor activity

As described above, the nuclear position fluctuates only slightly around the cell center during interphase. In meiotic prophase, on the contrary, the nucleus travels from one cell pole to the other and back (Figure 1f). This striking oscillatory nuclear movement in meiosis also depends on MTs [49]. While MTs push on the nucleus in interphase, in meiotic prophase MTs are being pulled by dynein motors [9••,45]. In order to exert force on the MT, dynein motors are anchored to the cell cortex by the membrane protein Mcp5/Num1 [43,44]. Nuclear oscillations have a period of about 10 min and last for several hours [50]. These oscillations are crucial for proper chromosome pairing and recombination [45,51], which is most likely a conserved phenomenon [52–55].

Figure 3



Fission yeast interphase MT arrangement is equivalent to a mitotic spindle turned inside out. **(a)** In fission yeast, MT minus-ends are near the cell center and plus-ends at the cell periphery, whereas **(b)** in the mitotic spindle, plus-ends are at the center and minus-ends at the centrosomes. The arrows illustrate the overall MT orientation. MT pushing against the cell poles centers the fission yeast nucleus, while MT pushing and pulling on the chromosomes centers them on the metaphase plate in the spindle. The two centering mechanisms may be based on kinesin-mediated preferred disassembly of longer MTs.

Nuclear oscillations are led by the motion of the spindle pole body (SPB) [50], from which MTs extend with their minus-ends at the SPB and the plus-ends pointing toward the opposite cell poles [56•]. As the SPB moves toward one cell pole, dynein is found mainly along the MTs extending in front of the SPB, whereas MTs trailing behind the SPB have fewer dyneins [9••]. This asymmetry of dynein distribution results in a stronger pulling force by the leading than by the trailing MT and, consequently, in persistent nuclear movement toward one cell pole. As the nucleus moves, the leading MT shrinks and eventually disappears. Afterwards, the MT directed toward the opposite cell pole starts to lead the SPB movement and the oscillations are established.

A key question is which mechanism creates the oscillations. There are several possibilities. First, it has been proposed that the SPB sends a signal [56•]: when the SPB reaches one cell pole, it may deactivate a cortical component required for force production, for example, the cortical anchor proteins for dynein, in that region. The anchors are in the meantime reactivated at the opposite cell pole, resulting in pulling toward that side [56•]. A different scenario may be envisioned based on the measured speeds of MT growth and of the SPB movement [56•]. The assumption here is that MTs interact only with dynein motors anchored at one cell pole. At the same time, MTs pointing toward the opposite cell pole are not able to reach this pole, as well as the motors anchored there, because MT growth is slower than the speed of the SPB movement. Only when the SPB pauses at one cell pole, MTs reach the opposite pole and start pulling the SPB in the opposite direction. Though these scenarios seem plausible, they lack experimental support. In contrast to the possibilities described above, oscillations may be driven by mechanical cues [57], where dynein detachment under high load forces plays a key role.

Load-dependent detachment of dynein motors

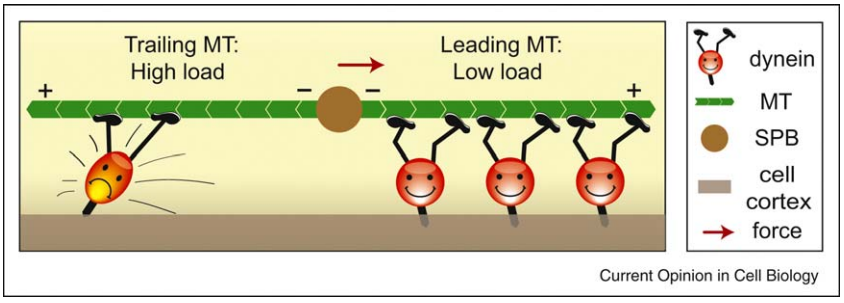
The probability of breaking a bond between two objects, such as between a motor protein and a MT, is increased by an external pulling force [58,59]. This process is known as load-dependent detachment. Detachment of motors from MTs in response to load forces has been studied theoretically [60], *in vitro* [61], and has been suggested to play a crucial role in bidirectional transport processes and spindle and chromosome oscillations [62,63•,64,65].

In general, a MT motor protein walks either to the plus-end or to the minus-end of a MT (depending on the motor type), and the walking velocity depends on the load force exerted on the motor. As the resisting load force increases, the motor velocity decreases; when the load exceeds a certain value the motor moves in the opposite direction. If the tail of the motor is fixed to a surface and its head attached to a MT, the direction and the velocity of the motor can be determined from the movement of the MT. Hence, the load force on the motor depends on the movement of the MT.

In a meiotic fission yeast cell, two populations of cortically anchored dynein motors can be defined: the population on the leading MTs walks toward the minus-end of the MTs while the other one on the trailing MTs is forced, by the movement of the trailing MTs, to walk toward the plus-end of those MTs. Therefore, during the SPB movement, the dynein population on the trailing MTs is under higher load force and thus has a higher probability to be detached from the MTs [9••] (Figure 4).

As the SPB moves, the load on the motors on the leading MTs is low. Thus, the probability of their detachment is also low (Figure 4). Because of the different detachment probability on the leading and the trailing side, the

Figure 4



Nuclear oscillations in meiotic prophase are based on preferred detachment of motors under high load force. During the SPB movement, the load on the cortically anchored dynein motors on the leading MT is low. Thus, these motors remain attached and keep pulling the SPB. Simultaneously, the load on the motors on the trailing MT is high, which enhances their detachment.

asymmetry in the number of motors on the leading and the trailing MTs grows, resulting in a faster SPB movement. The faster movement further increases the asymmetry in the load on the motors, creating a positive feedback between the SPB movement and the number of motors on the leading MTs [9••]. However, as the SPB moves, the leading MTs shrink and thus lose motors. When the number of motors on both sides of the SPB is equal, the SPB stops.

Microtubule length-dependent attachment of dynein motors

Dynein motors from the cytoplasm can attach along the MTs and the number of attachment sites depends on the length of the MTs. During the oscillations, length-dependent attachment of dynein is necessary for the change of direction of the SPB movement [9••]. When the movement of the SPB stops near a cell pole, the MTs extending toward the opposite cell pole are longer than those pointing to the closer cell pole. Owing to the length-dependent attachment of dynein, more motors will accumulate on the longer MTs. Thus, a movement starts in the direction of the longer MTs. Once the movement has started, the motors on the longer MTs experience lower load forces, the motor detachment rate thus decreases and the motors accumulate on the longer MTs, thereby the change of direction is completed. Afterwards, the MT length does not play a key role in dynein accumulation and the resulting force.

Conclusion

Cells can change nuclear movements between nuclear centering and pole-to-pole nuclear oscillations by rearranging MTs and using specific motor proteins [2]. Two concepts are crucial for the regulation of these movements: preferred disassembly of longer MTs (for nuclear centering) and preferred detachment of motors under high load (for nuclear oscillations). MT length feeds back on itself via motors, resulting in nuclear centering. Force exerted by motors also feeds back on itself, generating instability and thus nuclear oscillations. These simple concepts, emerging from a combination of experimental and theoretical work, can explain the basis of how the cell regulates the size of MT-based structures and how it positions and moves the nucleus, spindle, and chromosomes on the spindle. Studies on model systems such as fission yeast will likely bring about further simple and universal concepts of cell organization.

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