HHS Public Access

Author manuscript

Semin Cell Dev Biol. Author manuscript; available in PMC 2019 October 01.

Published in final edited form as:

Semin Cell Dev Biol. 2018 October ; 82: 3–16. doi:10.1016/j.semcdb.2017.10.024.

Nuclear movement in fungi

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Abstract

Nuclear movement within a cell occurs in a variety of eukaryotic organisms including yeasts and filamentous fungi. Fungal molecular genetic studies identified the minus-end-directed microtubule motor cytoplasmic dynein as a critical protein for nuclear movement or orientation of the mitotic spindle contained in the nucleus. Studies in the budding yeast first indicated that dynein anchored at the cortex via its anchoring protein Num1 exerts pulling force on an astral microtubule to orient the anaphase spindle across the mother-daughter axis before nuclear division. Prior to anaphase, myosin V interacts with the plus end of an astral microtubule via Kar9-Bim1/EB1 and pulls the plus end along the actin cables to move the nucleus/spindle close to the bud neck. In addition, pushing or pulling forces generated from cortex-linked polymerization or depolymerization of microtubules drive nuclear movements in yeasts and possibly also in filamentous fungi. In filamentous fungi, multiple nuclei within a hyphal segment undergo dynein-dependent back-and-forth movements and their positioning is also influenced by cytoplasmic streaming toward the hyphal tip. In addition, nuclear movement occurs at various stages of fungal development and fungal infection of plant tissues. This review discusses our current understanding on the mechanisms of nuclear movement in fungal organisms, the importance of nuclear positioning and the regulatory strategies that ensure the proper positioning of nucleus/spindle.

Keywords

Yeast; filamentous fungi; nuclear migration; spindle orientation; dynein

Introduction

Nuclear movement within a cell occurs in a variety of eukaryotic organisms during different developmental stages. For example, after fertilization, the female and male pronuclei in a fertilized egg must move toward each other before fusing into a zygotic nucleus [1, 2]. During skeletal muscle development, hundreds of myoblasts (single-nucleated cells) fuse with each other, leading to the formation of multi-nucleated muscle fibers. Within a functional muscle fiber, nuclei move around to be properly positioned, and some nuclei are clustered underneath the synapse at the neuromuscular junction [3]. Another interesting

example of nuclear movement is the interkinetic nuclear migration within a pseudostratified epithelium, which is important for neuroepithelial development. Specifically, while a nucleus at the G2 phase of the cell cycle moves from the basal side to the apical side where it undergoes mitosis, a G1/S nucleus moves towards the basal side where it undergoes DNA replication [2, 4]. While the detailed mechanisms of nuclear migration and positioning differ in different cell types, our understanding on this topic has been influenced by the early genetic data from fungal model organisms. For example, studies in the budding yeast *Saccharomyces cerevisiae* and filamentous fungi such as *Aspergillus nidulans* and *Neurospora crassa* have first identified cytoplasmic dynein, a minus-end-directed microtubule motor, as a critical player in nuclear migration and spindle orientation [5–8]. This review will discuss studies in several fungal model organisms, highlighting original discoveries that have provided insights into the mechanism of nuclear movement. It also aims to cover the importance of nuclear positioning or movement in various fungal organisms and regulatory strategies that control the proper positioning of nucleus/spindle.

1. Cytoplasmic dynein plays a critical role in nuclear migration in fungi

1.1 Discovering the importance of microtubules and cytoplasmic dynein in nuclear migration

Using *Aspergillus nidulans*, a filamentous fungus with multinucleated hyphae, Ron Morris pioneered the genetic study on nuclear positioning [9]. Upon germination of a single-nucleated *A. nidulans* asexual spore, rounds of nuclear divisions occur within the germ tube and the multiple daughter nuclei are positioned at about equal distances from each other (Fig. 1A; Movie 1). During an effort to genetically dissect mitosis by isolating mitotic mutants, Ron Morris collected several temperature-sensitive (ts) nuclear distribution (*nud*) mutants [9]. In the ts *nud* mutants grown at the restrictive temperature, nuclei are able to divide but they form an abnormal cluster at the spore end of the germ tube (Fig. 1A) [9, 10]. This study first suggested that products from specific genes are required for nuclear distribution in fungi.

The requirement of microtubules for nuclear movement was first revealed in *A. nidulans,* using the microtubule-depolymerizing drug benomyl and different tubulin mutants with different sensitivity to benomyl [10]. Because benomyl blocked both nuclear division and nuclear migration, a ts mitotic mutant was used to show that nuclear division is not a prerequisite for nuclear migration. In addition, after shifting a ts *nud* mutant germinated at a restrictive temperature to a permissive temperature, nuclei initially clustered at the spore end were able to move into the germ tube, but the movements are blocked by benomyl [10]. These results first established the notion that nuclear migration is a microtubule-dependent process.

In the budding yeast *S. cerevisiae*, proper orientation of the anaphase spindle along the mother-bud axis ensures that the mother cell and the bud would each receive a single nucleus after nuclear division. Prior to anaphase, the nucleus within the mother cell must move towards the bud neck so that one of the spindle pole bodies would be positioned at or across the bud neck (Note that *S. cerevisiae* has closed mitosis and thus the mitotic spindle is within the nucleus). Using microtubule drugs as well as tubulin mutants, it was found that

nuclear migration in *S. cerevisiae* depends on microtubules [11, 12]. By using a cell cycle mutant to synchronize the cells before anaphase, the role of astral microtubules in spindle orientation was revealed [13].

The importance of cytoplasmic dynein in spindle orientation was first discovered in *S. cerevisiae* (Movie 2) [5, 6]. Cytoplasmic dynein is a multi-subunit complex containing two heavy chains (HCs) with motor domains (simply called as "dynein" in many places of this review), two intermediate chains (ICs), two light intermediate chains (LICs) and several light chains (LCs) [14, 15]. In the dynein HC deletion/disruption mutants, a fraction of mother cells contain both daughter nuclei after mitosis (in contrast to wild type in which one daughter nucleus enters the bud) (Fig. 1B), and the whole anaphase spindle can be seen to locate inside the budding mother cell [5, 6].

In filamentous fungi, genetic studies on the *nud* mutants in *A. nidulans* and the *ropy* mutants in *Neurospora crassa* led to the identification of dynein (*nudA* in *A. nidulans* and Ro-1 in *N. crassa*) as a critical factor for nuclear distribution (Fig. 1A and Fig. 1C; Movies 3 and 4) [7, 8]. The role of dynein in positioning nuclei/spindles has subsequently been found in other fungal organisms including *Nectria haematococca*, *Ustilago maydis*, *Ashbya gossypii*, *Aspergillus oryzae*, *Candida albicans* and *Schizophyllum commune* [16–23]. Interestingly, in the dynein-null mutant of *A. gossypii*, multiple nuclei form a cluster at the hyphal tip [16] (Fig. 1D), which is in contrast to the formation of nuclear cluster at the spore end in *A. nidulans* [8] (Fig. 1A). In the fission yeast *Schizosaccharomyces pombe*, dynein plays a role in the so-called "horsetail nuclear movement" that moves the prophase nucleus back and forth during meiosis [24]. It also functions in parallel with Klp2 (a kinesin-14 family member) to cause nuclear congressional during mating [25].

1.2 Identifying cytoplasmic dynein regulators involved in nuclear migration/spindle orientation

Cytoplasmic dynein is a multi-subunit complex whose function in vivo requires the dynactin complex, LIS1 and NudE/Nudel [15, 26, 27]. Fungal genetic studies on nuclear movement paved the way leading to the identification of dynein regulators such as LIS1 and NudE/Nudel [28–32]. In *A. nidulans*, the first cloned *nud* gene was *nudC*, which encodes a protein important for the stability of NudF/LIS1 [33, 34]. The *nudF* gene product shows 42% sequence identity to the product of human Lis1, a causal gene for lissencephaly (smooth brain) [28, 35]. Because lissencephaly is a brain development disorder caused partly by a defect in neuronal migration, the similarity between NudF and LIS1 supported the idea that "nucleokinesis" (the movement of the nucleus within a migrating cell) is important for certain types of cell migration [36–38]. The *nudE* gene was cloned in *A. nidulans* as a multi-copy suppressor of a *nudF*/Lis1 mutant [31], and the NudE protein interacts with NudF/LIS1 [31]. Note that NudE is the homolog of *N. crassa* RO11 [30], and *N. crassa* contains two LIS1 homologs [39]. In *S. cerevisiae*, Pac1/LIS1 was identified in a screen for mutations synthetically lethal with a loss-of-function mutation in Cin8 (kinesin-5) [29], and the NudE homolog Ndl1 was found in a screen for cold-sensitive haploid null mutants with a higher than normal percentage of bi-nucleated cells [32]. In both *A. nidulans* and *S. cerevisiae*, NudE/Ndl1 is less critical than NudF/Pac1/LIS1 for nuclear distribution or spindle

orientation, and the defect caused by NudE/Ndl1 deletion can be rescued by overexpression of NudF/Pac1/LIS1 [32, 40, 41]. The mechanisms of actions of LIS1 and NudE/Nudel in dynein function have been studied intensively, and the readers are referred to several most recent papers covering these topics [15, 42–45].

The dynactin complex was purified as a complex required for in vitro vesicle transport by dynein, and its largest p150 subunit (Drosophila Glued protein) binds dynein IC [46–52]. The complex contains the Arp1 (actin-related protein 1) mini-filament (37 nm) whose barbed end is occupied by capping proteins and whose pointed end occupied by pointed-end proteins Arp11, p62, p25 and p27, and it also contains p50/Jnm1 and p24 on top of the Arp1 filament [15, 53, 54]. Studies in *S. cerevisiae* and *N. crassa* first revealed the role of Arp1 in dynein-mediated spindle orientation/nuclear migration, demonstrating that dynactin is required for the in vivo function of dynein [7, 55]. Multiple other dynactin components such as p150, p50, p24, Arp11 and p62, as well as multiple components of the dynein complex such the ICs, LICs, and LCs, are also required for nuclear migration [29, 30, 56–69]. It should be pointed out that not all dynactin-dynein components are required for nuclear migration. For example, the p25 subunit of dynactin is required for vesicle transport but not nuclear distribution in filamentous fungi [59, 70, 71].

2. Importance of nuclear movement in different fungal organisms

In some fungal organisms, nuclear movement/positioning is linked to cell cycle progression or cell division. In *S. cerevisiae*, the cell division site is determined prior to mitosis, and thus, proper positioning of the nucleus/spindle across the bud neck prior to chromosome segregation is necessary for the proper segregation of genetic materials. If the spindle fails to move into the neck, the spindle-position checkpoint remains active to prevent mitotic exit and cytokinesis, and only when one SPB enters the bud, mitotic exit and cell division can occur [72–75]. The dynein pathway is partially redundant with the Kar9 pathway or the “early” pathway, which uses multiple proteins including Kar9 and Kip3 to function before anaphase for nuclear migration toward the bud [76–79]. While these two pathways compensate for each other, loss of both results in lethality [76, 79].

In the fission yeast *S. pombe*, the position of the nucleus determines the position of the cell division plane, a notion best illustrated by experiments in which the nucleus is displaced by centrifugation [80]. Microtubule growth-generated pushing force is used for centering the nucleus, which ensures fission yeast cells to divide in the middle [81, 82]. During meiosis in *S. pombe*, dynein is required for the back-and-forth oscillatory movements of the prophase nucleus, and these movements are thought to be important for the initial pairing of homologous chromosomes and their proper segregation [83–85].

It should be pointed out that many ascomycete fungal organisms, including *S. cerevisiae* and *S. pombe*, undergo closed mitosis, and although *A. nidulans* undergoes a partially open mitosis following the partial disassembly of the nuclear pore complex, the mitotic spindle is still contained inside the nucleus by the nuclear envelope [86]. However, *U. maydis*, a dimorphic basidiomycete fungus and a plant pathogen, undergoes open mitosis, and during

its “yeast-like” phase, it is the dynein-mediated movement of the pre-mitotic nucleus into the bud that helps to strip off the nuclear envelope [22].

Proper distribution of multiple nuclei in filamentous fungi is important for hyphal extension and colony growth. In *A. nidulans*, *nud* mutants form colonies that are abnormally compact and without asexual spores, a phenotype that can be used for isolation of additional *nud* mutants or suppressors [8, 31, 57, 87–92]. In the *nud* mutants, empty segments of hyphae without any nucleus can be seen, and the spore end that contains a nuclear cluster often sends out multiple short germ tubes, presumably as a way of compensating for the lack of nuclei to support hyphal tip extension [28]. In addition, septa are often positioned abnormally [90, 93]. In many filamentous fungal organisms including *U. maydis* and *A. nidulans*, dynein is required not only for nuclear distribution but also for transporting early endosomes and other cargoes, and early endosome motility helps to distribute a variety of hitchhiking organelles/vesicles and proteins/RNAs in hyphae [94–101]. The *A. nidulans* null mutant of p25, a dynactin component important for dynein-mediated transport of early endosomes and post-Golgi vesicles but not for nuclear distribution [59, 70, 71], exhibits a much milder defect in colony growth than that exhibited by a *nud* mutant [70], consistent with a critical role of nuclear distribution in colony growth. In *N. crassa*, mutants in the dynein pathway exhibit abnormally curly hyphae, which is why they are called the “*ropy*” mutants [7, 30, 56, 59, 102, 103]. The ropy phenotype is unlikely caused by a nuclear-distribution defect, because p25 (or Ro-12), originally discovered in *N. crassa* as a protein important for vesicle transport but not for nuclear distribution, was identified from a collection of *ropy* mutants [59].

The importance of nuclear distribution for fungal colony growth is best demonstrated in *A. gossypii*, a filamentous fungus evolutionarily close to *S. cerevisiae*. Similar to *S. cerevisiae, A. gossypii* microtubules are organized for nuclear division and distribution but not for vesicle transport, and thus, *A. gossypii* dynein does not play a role in vesicle transport [16, 104–108]. In the dynein-null mutant of *A. gossypii*, multiple nuclei are clustered at the hyphal tip [16], and the mutant colony is significantly compact (~14% of wild type size) [16], similar to that formed by *A. nidulans nud* mutants [8]. More interestingly, partial depolymerization of microtubules using benomyl suppresses the nuclear-distribution defect in the dynein-null mutant, and it also results in the formation of a normal-sized colony [16].

Nuclear migration is important for asexual spore development in fungi such as *A. nidulans* because the process consists multiple steps of budding like yeast budding and one daughter nucleus has to enter the asexual spore (conidium) [28, 92, 109–112]. In addition, the transcription factor FlbB required for the development of conidiophore, the asexual spore-bearing structure, localizes at the hyphal tip before its activation [113–115]. In this context, proper nuclear distribution may be important for ensuring that the apical nuclei are not too far away from the hyphal tip so that hyphal tip-nuclei communication can occur efficiently.

Nuclear movements are important for mating and the subsequent nuclear fusion (Karyogamy) in fungal organisms, and minus-end-directed microtubule motors such as dynein and kinesin-14s are involved in these processes [23, 25, 116–118]. In some filamentous fungi, such as *N. crassa* and the plant pathogen *Fusarium oxysporum*, fusion of

vegetative hyphae (termed “anastomosis”) occurs during colony formation [119], and hyphal fusion is often followed by nuclear migration, which may be important for colony formation and/or fungal infection [120, 121]. Nuclear migration in hyphae of chimeric colonies composed of genetically different nuclei may increase the chance of occasional genetic material exchange, thereby promoting genetic diversity within a fungal species [122].

Nuclear migration also occurs during infection of plants by fungal organisms including the rice blast fungus *Magnaporthe oryzae* [123, 124]. Penetration of plant tissues by *M. oryzae* is facilitated by the formation of a specialized fungal cell called “appressorium” that contains huge turgor, and the appressorium is developed at the tip of a germ tube formed on top of rice leaf [124]. In the germ tube, one of the post-mitotic nuclei moves into the developing appressorium and the other three nuclei enter the conidial cell at the spore end where they are degraded [123]. After infection, the nucleus in the appressorium migrates down into the primary hypha penetrating the plant tissue [125], and the directional movements of these nuclei may positively regulate the efficiency of infection [123–128].

There are other examples of nuclear movement/positioning in fungi [111, 129]. Most interestingly, one early experiment done in *A. nidulans* suggests that nuclei are not positioned randomly within a hyphal segment where they undergo synchronous division [129, 130]. In the experiment, the single nucleus within an asexual spore was labeled during spore development by a radioactive DNA precursor, and subsequently, multiple nuclei produced after germination of the spore in a nonradioactive medium were observed [130]. Astonishingly, within a short hypha (or germ tube) containing four or eight nuclei, the labels were not distributed randomly among the nuclei, and instead, the two most apical (or hyphal tip-proximal) nuclei were much more heavily labeled compared to other nuclei. In other words, the relatively “old” nuclei are positioned near the hyphal tip [130]. The non-random distribution of the labels is consistent with an intriguing phenomenon of non-random segregation of sister chromatids during mitosis, which is thought to happen during nuclear division of some stem cells for preventing the stem cell genomes from acquiring mutations [130–133]. In *A. nidulans*, it is unknown whether the “old” nuclei would be the ones that enter the process of asexual spore development, and this would be an interesting topic for future studies.

3. Mechanisms of dynein-mediated nuclear movement

3.1 Dynein exerts its pulling force from the cell cortex via its anchoring protein Num1/ApsA/Mcp5

Microtubules are polarized polymers whose plus ends face the cell periphery and minus ends are at the centrosome in most cell types, and the plus ends are highly dynamic, undergoing alternative phases of growth (polymerization) and shrinkage (depolymerization) [134]. In ascomycete fungi including *S. cerevisiae, A. gossypii* and *A. nidulans*, the minus ends of microtubules are linked to gamma tubulins at the centrosome-equivalent spindle-pole bodies (SPBs) that are physically connected to the nucleus [135–140], and importantly, the minus ends are not dynamic as shown in *S. cerevisiae* [140]. Since dynein is a minus-end-directed motor, it was proposed that dynein must be anchored at the cell cortex to pull the astral microtubules generated from the SPBs to move the nuclei/spindles [5, 6, 141, 142]. In *S.*

cerevisiae, a cortical dynein-interacting protein Num1 has been found to be required for both dynein localization to cortical foci and dynein-mediated microtubule sliding against the cortex, which powers nuclear migration/spindle orientation (Fig. 2) [143–146]. Num1 is a large coiled-coil protein whose interaction with the cell membrane is mediated by its C-terminal pleckstrin homology (PH) domain, which can be functionally substituted by a different membrane-interacting motif [147]. Its N-terminal Bin/Amphiphysin/Rvs (BAR)-like domain is responsible for the assembly of cortical patches and for interacting with dynein [148].

Num1 orthologs are present in various fungal organisms. Its *A. nidulans* homolog is the cortical protein ApsA, which is important for spindle movement and nuclear positioning in hyphae as well as nuclear migration during asexual spore development (a process consists a series of budding events reminiscent of the asymmetric cell division of budding yeast) [110, 111, 149]. In *Ashbya gossypii,* multiple nuclei in hyphae can be seen to undergo dynein-mediated bidirectional movement and bypass each other (Movie 5), and Num1 is important for these movements [150, 151]. Recently, a simulation of nuclear movement in *A. gossypii* has been done based on the idea that dynein anchored at the cortex pulls on microtubules [151]. By varying the density of the cortical anchor, the simulation can produce a nuclear movement pattern similar to what happens in real cells [151]. Interestingly, while dynein pulls the spindle toward the bud mainly during anaphase in budding yeast [152, 153] (In metaphase, dynein is required for oscillatory spindle movements across the bud neck [153]), it pulls on nuclei during all stages of the *A. gossypii* cell cycle as suggested by the model [151].

In the fission yeast *Schizosaccharomyces pombe*, dynein plays a role in moving the prophase nucleus during meiosis [24, 60, 83], and the *S. pombe* Mcp5, a Num1 homolog, is important for this process [154–157]. Recently, it has been shown that Mcp5/Num1 binds to phosphatidylinositol 4,5-bisphosphate, and its membrane localization is enhanced by myosin I [157].

3.2 Recruitment of dynein to the cortex from microtubules

Dynein and its regulators, such as dynactin and LIS1, all accumulate at the dynamic plus ends of microtubules, similar to the microtubule “plus-end-tracking proteins” (+TIPs) such as CLIP-170 and EB1 [39, 158–165]. Plus-end accumulation of dynein in *A. nidulans* and *U. maydis* depends on Kinesin-1 and dynactin [62, 162, 163, 166–168] while that in *S. cerevisiae* depends on LIS1, the CLIP-170 homolog Bik1 as well as the transporting function of Kip2 (kinesin-7) [164, 165, 169–171]. In addition to kinesin-based transport, dynein can also be recruited directly from the cytosol to the plus ends [62, 71, 169, 172].

In *S. cerevisiae*, the plus-end accumulation of dynein is enhanced upon loss of the cortical Num1 protein, and this finding led to the idea that dynein molecules at the plus end are offloaded to the cortical Num1 site [164, 165]. Dynactin is implicated in the offloading process [65, 164, 165], and it accumulates at the microtubule plus ends mainly at anaphase; in the *she1* null mutant, dynactin accumulates at the plus ends ahead of schedule, leading to spindle movement toward the bud before anaphase [173]. The actual dynein off-loading process has been observed in yeast cells containing a mutant dynein HC and also in *she1*-

null cells at preanaphase [174]. It should be noted that offloading only occurs for full-length dynein on a microtubule, as the dynein tail domain (without the microtubule-binding motor domain) can be directly recruited from the cytosol to the cortex in a Num1-dependent manner [146]. In *U. maydis*, offloading of plus end-associated dynein to the cell cortex has been implicated in dynein-mediated pulling force that powers rapid elongation of mitotic spindle during late anaphase [175].

In both the budding and fission yeasts, the cortical anchor Num1/Mcp5 has been implicated in activating the minus-end-directed motility of dynein [165, 176, 177], but the mechanisms used for targeting dynein to the cortical anchor differ from each other [176]. In the fission yeast *S. pombe*, dynein molecules diffuse along a microtubule instead of undergoing kinesin-based transport to the microtubule plus end, and when a dynein motor encounters its cortical anchor, it gets activated to undergo minus-end-directed movement that drives the movement of prophase nucleus during meiosis [176].

3.3 The postulated antiparallel microtubule-sliding mechanism for nuclear distribution in filamentous fungi

In filamentous fungi, dynein is the most critical factor for nuclear distribution, and dynein-mediated pulling force is also important for spindle elongation [175, 178]. However, the Num1-dependant microtubule sliding along the cortex may not be the only major pulling mechanism in filamentous fungi. In *S. cerevisiae*, the num1-null mutant produces a phenotype similar to that exhibited by a dynein-null mutant [144]. However, although the *A. nidulans* Num1 homolog ApsA is important for spindle movement, loss of ApsA has a much less deleterious effect on nuclear distribution or colony growth compared to that caused by loss of dynein [110, 111, 149, 179]. In *A. gossypii*, Num1 plays an important role in dynein-mediated bi-directional nuclear movements [150, 151]. However, a loss-of-function mutation (N- or C-terminal deletion) of Num1 has little effect on colony growth and a much less dramatic effect on nuclear distribution compared to that caused by loss of dynein [16, 150]. Thus, there could be either additional cortical anchors for dynein or mechanisms of dynein-dependent nuclear distribution that are independent of dynein's cortical anchors.

In one model proposed previously to explain nuclear distribution in filamentous fungi, dynein molecules are located along antiparallel cytoplasmic microtubules whose minus ends are at the SPBs of adjacent nuclei, and the minus-end-directed motility of dynein pulls the adjacent nuclei toward each other (Fig. 3) [7] (Note that this is similar to minus end motor-driven yeast karyogamy after mating during which the two zygotic nuclei move toward each other [25, 117]). In this model, the farther apart the two nuclei, the longer the overlapping microtubules and more dynein molecules on them, whose collective action leads to a stronger pulling force, and this self-organization of dynein distribution allows multiple nuclei to be distributed evenly along hyphae [7]. In a slightly modified version of this model depicted in Fig. 3, the SPBs from the two newly divided daughter nuclei face opposite directions and thus no antiparallel microtubules are present in between them right after nuclear division. In contrast, antiparallel microtubules can be formed between one of them and another nearby nucleus, bringing closer these two connected nuclei while driving the two daughter nuclei apart (Fig. 3). In *A. nidulans*, two nuclei can sometimes be seen to move

together as a cluster in the absence of any obvious microtubule-cortex interaction, consistent with the idea that nuclei are connected by microtubules [149]. It should also be pointed out that non-SPB microtubule-organizing centers are found at the septa in *A. nidulans* [180, 181], but it is unclear whether they contribute in any way to nuclear movement.

In filamentous fungi, neither the plus-end accumulation of dynein nor the maximal dynein motor activity seems to be critical for nuclear migration toward the hyphal tip [167, 182, 183]. In *A. nidulans*, a mutation in dynactin that diminishes plus-end dynein accumulation only had a mild effect on nuclear distribution [167]. In addition, nuclear movement still occurs when dynein's motor activity is significantly decreased, as evidenced by the result that an *A. nidulans* mutant dynein whose yeast counterpart walks with a significantly lowered speed in vitro (a 94% reduction from wild type) is still able to support nuclear migration toward the hyphal tip [182]. Thus, although dynein motor function is needed for nuclear distribution and various dynein heavy chain mutations affect this process [102, 182, 184], dynein's maximal motor activity is not absolutely required for nuclear migration toward the hyphal tip [182].

In the budding yeast, dynein has also been implicated in the microtubule plus end "capture/shrinkage" mechanism of SPB movement [152, 185], and this will be discussed in more detail in a later section.

4. A pulling mechanism for nuclear movement based on microtubule plus end-linked myosin motor walking on actin cables

During *S. cerevisiae* cell cycle, the Kar9 pathway functions before the dynein pathway, and this "early" pathway relies on the cortical actin cables for nuclear migration to the bud neck (Fig. 4) [76–79, 153, 186–190]. The kar9 mutant was originally isolated as a karyogamy mutant [191], and Kar9 was subsequently identified as a cortically localized protein that also plays an important role in nuclear migration during the mitotic cycle [79]. The kar9 deletion mutant is synthetically lethal with null mutants of dynein and dynactin components, and this result first defined two partially redundant pathways for nuclear migration/spindle positioning in *S. cerevisiae* [79]. The importance of the actin filaments for this "early" pathway but not for the dynein pathway was revealed via an analysis on the deletion mutant of Bni1, a formin critical for actin cable assembly, and the notion was supported by experiments using the actin polymerization inhibitor latrunculin [186, 187, 192–196]. A subsequent series of elegant analyses in *S. cerevisiae* indicate that Kar9, via its interaction with both the microtubule plus-end protein Bim1 (EB1 homolog) and the actin-based motor Myo2 (myosin V), links the microtubule plus ends to the cortical actin cables, and the movement of Myo2 along the actin cable pulls the microtubule-attached nucleus towards the bud neck (Fig. 4) [188–190, 197–201].

The Kar9 pathway also contains Kip3 (kinesin-8) [76–78], which prevents the nucleus from being pushed back to the mother cell [202]. The function of Kip3 will be discussed in more detail in the next section.

In *S. cerevisiae*, the Kar9 pathway may modulate dynein-mediated spindle positioning to keep the spindle close to the bud neck before anaphase [153]. Specifically, dynein mediates oscillations of the preanaphase spindle across the bud neck, and the movements become much more dramatic (span about 3–4 times longer distances) in the absence of Kar9 [153].

In filamentous fungi, the Kar9 pathway is not critical for nuclear distribution. In *A. nidulans*, neither MigA/Kar9 nor KipB/Kip3 affects nuclear distribution in any obvious way [183, 203, 204], although loss of MigA/Kar9 reduces spindle motility [204] and loss of KipB/Kip3 enhances spindle motility [203]. EBA/EB1 in *A. nidulans* is not important for nuclear distribution either, and the triple EBA/EB1, CLIPA/CLIP-170 and NUDA/dynein null mutant grows like a single dynein null mutant [183]. In *A. gossypii*, nuclei undergo oscillating back-and-forth movements and sometimes pass each other [16, 150], and the bi-directional movements depend on dynein [150]. Neither Kar9 nor Bim1/EB1 is important for nuclear distribution in *A. gossypii* [150]. Interestingly, although *A. gossypii* Kar9 is not required for nuclear movement toward the hyphal tip, its loss results in more backward movements and bypassing events, suggesting that Kar9 may antagonize dynein function in a way similar to what has been found in *S. cerevisiae* [150, 153].

5. Microtubule dynamics is important for nuclear movement

5.1 Pushing force generated from microtubule growth at the cortex

In both the budding and fission yeasts, microtubule polymerization at the cortex can generate pushing force for nuclear positioning [81, 152, 153]. In *S. pombe*, microtubule plus ends are at the two ends of the rod-shaped cell, and their polymerization at the cortex generates pushing forces to center the nucleus at interphase [81]. In *S. cerevisiae*, microtubule growth at the cortex pushes the nucleus toward the center of the mother cell at an early stage of the cell cycle [153]. Importantly, microtubule polymerization-generated pushing force needs to be regulated, because excess microtubule growth can push the nucleus to a wrong position. This is illustrated by the work on Kip3 (kinesin-8), which functions in the “early” pathway of nuclear migration toward the bud neck in *S. cerevisiae* [76–78, 153, 186, 202]. Kip3 is a microtubule plus-end depolymerase and also promotes the rescue of shrinking microtubules [202, 205–209]. Because Kip3 walks to the plus end as a plus end-directed motor, a longer microtubule tends to have a higher Kip3 concentration at the plus end [205], where Kip3 senses the curved tubulin conformation and switches to a depolymerase [209]. In vivo, when a relatively long astral microtubule contacts the cortex at the bud tip, the plus-end accumulated Kip3 initiates microtubule depolymerization [185, 202]. In the absence of Kip3, the abnormally long microtubules can push the preanaphase nucleus to the mother cell [202].

For a microtubule to grow continuously at the cortex, a cortical protein may be needed for capturing the plus end to stabilize the microtubule-cortex interaction. Indeed, the abnormal microtubule growth at the cortex in the absence of Kip3 requires both the microtubule plus end protein Bim1/EB1 and the cortical protein Bud6 [185]. Bim1/EB1 is a microtubule plus-end-tracking protein that promotes plus end dynamics [197], and Bud6 is a cortical protein that uses its C-terminal region to interact with formins, thereby helping to organize the actin cables [194, 210–212]. Bim1/EB1 and Bud6 are known to participate in the Kar9 pathway as

Bim1/EB1 links Kar9 to microtubule plus end and Bud6 is involved in actin cable assembly [188–190, 194, 198–200, 210], but they also function at an even “earlier” stage of the cell cycle. Right after the previous cell cycle, the “old” SPB (daughter-bound or destined to enter the bud) has astral microtubules attached, and the Bud6-mediated microtubule capture serves to “prime” the spindle polarity early in the cell cycle [185, 213–215]. Mechanistically, Bud6 localizes at the cortex of the emerging bud during the G1/S stage of the cell cycle and relies on the direct interaction between Bim1/EB1 and the N-terminus of Bud6 to capture the plus ends of microtubules [185, 216]. While the absence of Kip3 results in abnormal microtubule growth at the cortex, which generates pushing force, the normal function of Kip3 is required for the Bud6-dependent the “capture/shrinkage” mechanism of SPB movement (discussed in more detail in Section 5.2) [185].

5.2 Pulling force generated from microtubule shrinkage at the cortex

Microtubule plus-end depolymerization at the cortex can generate pulling force if the plus end remains linked to the cortex while shrinking. This has been termed as the “capture/shrinkage” mechanism, which differs from the dynein-Num1-dependent pulling mechanism in which the minus end-directed movement of cortically anchored dynein causes the attached microtubule to slide along the cortex [152]. This mechanism has been implicated in Kar3 (kinesin-14) mediated coupling of microtubule plus ends with the shmoo tip for nuclear positioning in mating yeast cells [217, 218]. During G1/S of yeast cell cycle, the “capture/shrinkage” mechanism is implicated in moving the daughter-bound SPB, and several proteins are involved, which include Kip3, dynein, Bim1/EB1 and Bud6 but not Num1 or Kar9 [185]. In this mechanism, a growing microtubule plus end is captured at the cortex by Bud6 via Bud6-Bim1/EB1 interaction, and the plus-end-accumulated Kip3 initiates microtubule shrinkage by using its depolymerase activity, but the function of Kip3 seems to be limited to the initiation stage of catastrophe as it disappears quickly from the shrinking end [185]. In contrast, dynein is present at the shrinking end contacting the cortex, and it is needed for the coupling between the cortex and the shrinking end [185]. In vitro, when dynein is attached to a cortex-like barrier, it pulls on a microtubule and causes shrinkage when the plus end of the microtubule hits the barrier, and if the connection of the shrinking end with the barrier is maintained, a pulling force of several pN can be generated [219, 220]. In vivo, dynein-mediated “capture/shrinkage” at G1/S needs more players such as Kip3, Bim1/EB1 and Bud6, and as dynein’s cortical anchor Num1 is not required at this stage for “capture/shrinkage”, exactly how dynein interacts with the cortex still needs to be studied [185, 221].

5.3 Dynein, microtubule stability and nuclear distribution

In fungi, microtubule dynamics are important for nuclear migration [16, 77, 87, 152, 153, 179, 222, 223]. In theory, microtubule dynamics may not only generate pulling and pushing forces, but they may also help the plus ends to search for the cortical anchor of dynein or an antiparallel microtubule. In addition, in context of the Num1-based pulling mechanism, the stability of the microtubule along the cortex may possibly affect the duration of dynein-mediated pulling, thereby affecting spindle positioning [223].

One intriguing phenotype produced by loss-of-function dynein mutations in budding yeast and filamentous fungi is that cytoplasmic/astral microtubules appear abnormally long, stable, curved and sometimes curled along the cortex, and a similar but less severe change in microtubule dynamics also happens upon loss of Num1 or its homologs [144, 149, 150, 163, 222–224]. It seems possible that the interaction between the plus-end dynein and the cortical Num1 is important for microtubule dynamics, and in its absence, the frequency of microtubule catastrophe (the switch from growth to shrinkage) is reduced. However, a recent study in budding yeast suggests that the motor activity of dynein is required for destabilizing microtubule plus ends regardless of their cortex interaction [223].

In *A. nidulans*, a β-tubulin mutation that causes hyperstabilization of microtubules blocks nuclear migration [225], suggesting that the abnormal stability of microtubules impairs nuclear movements. The clusters of multiple nuclei are formed at the opposite ends in *A. nidulans* and *A. gossypii* dynein mutant hyphae, i.e., at the spore end in *A. nidulans* and at the hyphal tip in *A. gossypii.* It is still not clear why nuclei accumulate at the hyphal tip upon loss of dynein in *A. gossypii*, but microtubules that are stably growing may push the nuclei all the way towards the hyphal tip [16, 150]. Interestingly, although microtubule deploymerization quickly stops nuclear movements [10, 16], microtubule destabilization by benomyl at the concentration that supports colony growth suppresses completely the nuclear-distribution and colony-growth defects in *A. gossypii* dynein-null mutant [16]. In *A. nidulans*, the nud phenotype is partially suppressed by a low concentration of benomyl as well as by an ApsB mutation that causes a deficiency in the generation of microtubules from the SPBs [87, 149]. Thus, the presence of hyperstable microtubules in the absence of dynein may impede nuclear distribution by other forces. Some nuclear migration events in fungi may not be powered by dynein, for example, nuclei from *N. crassa* dynein mutants defective in nuclear distribution can still migrate after hyphal fusion [120].

In both filamentous fungi and *S. pombe*, the internal turgor pressure is important for tip growth [226–229]. In filamentous hyphae, the difference in turgor pressure in different regions forms a pressure gradient that can result in cytoplasmic streaming toward the hyphal tip, which affects the positioning of nuclei or carries the nuclei toward the hyphal tip in *N. crassa* [226, 228, 230, 231]. In *A. gossypii*, nuclei can also be carried toward the hyphal tip by cytoplasmic streaming in the absence of microtubules [139].

6. Regulations on nuclear or spindle positioning

In theory, directional movement can be caused by a difference in the pushing or pulling force on the front verses that on the back of the nucleus/spindle, which may simply be due to an asymmetrical distribution of microtubules or their motors. In *S. pombe*, centering of the nucleus after being displaced by centrifugation of the cell results from the pushing force generated at the cortex by microtubule polymerization, and asymmetry in the number, length and dynamics of microtubules at the two ends of the cell causes the directional movement of the nucleus [82]. The oscillatory movement of the prophase nucleus during *S. pombe* meiosis is driven by dynein-mediated pulling force, and it needs a special astral microtubule array whose assembly requires the Hrs1p/Mcp6p protein on the meiotic SPB [232]. It is likely to be caused by the dynamic asymmetric distribution of dynein molecules on the

microtubules in the front verses the rear of the moving nucleus, which could be self-organized based on how the dynein motor responds to force [233, 234].

In the budding yeast *S. cerevisiae*, the bud-ward movement of the nucleus/spindle is facilitated by the asymmetric loading of proteins such as Kar9 in the "early" pathway and dynein in the "late pathway" at the daughter-bound SPB, which, in conjunction with kinesin-mediated transport, could result in the preferential accumulation of these proteins at the microtubule plus ends extending into the bud [165, 169, 171, 213, 235–246]. She1 has recently been revealed as a microtubule-crosslinking protein required for spindle integrity during spindle movement [247]. She1 inhibits dynein motility in vitro, and loss of She1 enhances microtubule-cortex interaction specifically in the mother cell, suggesting that She1 may inhibit dynein activity in mother cells, thereby allowing spindle movement toward the bud [248]. Moreover, stability of the microtubule pulled by dynein may also be regulated by dynein, which may facilitate spindle movement toward the bud [223]. Additional regulatory mechanisms must also exist to ensure that the mother-directed pulling force balances the bud-directed pulling force so that the spindle will be across the bud neck instead of entering completely into the daughter cell [249–251]. In this context, it is interesting to mention that in the "yeast-like" stage of the dimorphic *U. maydis*, dynein-mediated pulling force (possibly in combination with other forces) moves the pre-mitotic nucleus all the way into the daughter cell, which is followed spindle elongation across the mother-bud neck [22]. A recent study combining imaging and modeling suggests that the number of astral/cytoplasmic microtubules is higher in basidiomycete budding yeasts (such as *U. maydis* and *Cryptococcus neoformans*) than that in ascomycete budding yeasts (such as *S. cerevisiae* and *Candida albicans),* which could explain why the whole nucleus/spindle is pulled into the daughter cell in basidiomycete budding yeasts [252].

In *S. cerevisiae,* different mechanisms of nuclear movement have been found to operate at different stages of the cell cycle [136, 213, 246, 253, 254]. While it is not well understood how different pathways in *S. cerevisiae* coordinate with each other, it is known that some proteins participate in more than one pathway. For example, Bik1/CLIP-170, which functions in the dynein pathway [165], binds to Kar9 and promotes Kar9 phosphorylation and its asymmetric loading on the two SPBs [255]. In addition, while Bud6 and Bim1/EB1 are in the Kar9 pathway, they are also critical for the Kar9-independent capture of astral microtubules at G1/S, and Bim1/EB1 is able to bind both Bud6 and Kar9 [153, 185, 188, 189, 198–201, 216]. The localization or activity of proteins in these pathways may be regulated by post-translational modifications, as several of them undergo phosphorylation, sumoylation and/or ubiquitylation, and multiple kinases (including a cyclin-dependent kinase CDC28 and aurora B kinase Ipl1) and at least one phosphatase (Glc7p) are implicated in regulating the localization or function of Kar9, dynein or other proteins in these pathways [213, 235, 236, 238–240, 242, 244, 245, 247, 256–264]. It also appears that timely degradation of proteins may be important for proper spindle positioning, for example, if Kar9 is not degraded properly, the whole spindle tends to be pulled into the daughter cell [251].

Perspectives

More than 20 years ago, fungal molecular genetic studies led to the identification of cytoplasmic dynein as a main microtubule motor for nuclear migration/spindle orientation [5–8]. Studies in the budding yeast *S. cerevisiae* have first suggested that dynein exerts its pulling force on the nucleus/spindle by being anchored at the cortex via its interacting protein Num1 and walking toward the minus end of the astral microtubule linked to the spindle/nucleus [136, 143, 145, 148, 253]. Although Num1 is not a highly conserved protein, the concept that dynein exerts its pulling force from the cortex to drive nuclear migration is applicable to higher eukaryotic cells [265–267]. In addition, it was shown in yeasts that the movements of nuclei or SPBs can be driven by cortex-linked microtubule dynamics or by protein-mediated microtubule-actin interactions, and the same principle also governs nuclear or centrosome positioning in higher eukaryotic cells [79, 81, 152, 153, 185–187, 189, 267–270]. Thus, detailed studies on these mechanisms should continue to provide insights into the mechanistic understanding of nuclear migration or spindle orientation in general.

While the studies on yeast dynein have shed light on the understanding of nuclear movement, detailed mechanisms still remain to be revealed. For example, it remains incompletely understood how pulling forces from the mother and daughter cells balance each other to ensure that spindle is positioned across the bud neck of *S. cerevisiae*. In addition, although it has been a well-accepted idea that dynein at the microtubule plus end is offloaded to the cortical anchor Num1 where it exerts pulling force on the spindle, the offloading process has not yet been observed in wild type cells and its mechanism remains to be further studied. In addition, it is not clear whether the offloading is coupled to the pulling on the same microtubule that had delivered dynein to the Num1 site or results in pulling on a different microtubule that would encounter the cortical dynein at a later stage.

Mechanisms of dynein-mediated nuclear distribution in filamentous fungi need to be further studied. Filamentous fungi as a whole group are of significant importance to economy and medicine, and great cell biological work has been done to understand hyphal growth and organelle transport in these organisms [228]. Different fungal organisms may offer different advantages for the study of nuclear distribution. For example, the asynchronous cell cycle progression in a hyphal segment of *A. gossypii* could allow examination on the motility of nuclei at different cell cycle stages simultaneously [105, 271], if differential labeling can be used to indicate the cell cycle stages of the nuclei. In *A. nidulans*, where nuclei divide in synchrony within a hyphal compartment, a variety of cell cycle mutants are available for us to examine nuclear movement during different stages of the cell cycle [9, 272]. Hyphae of *N. crassa* are significantly wider than those of *A. nidulans*, and this organism is well suited for studying how dynein mediates nuclear distribution under the influence of cytoplasmic streaming [231]. Combining quantitative data with modeling will continue to be a very useful approach [151, 252], and in this context, a better understanding of dynein distribution in vivo and its force production will also enhance our understating of nuclear movement.

Studies on nuclear movement may also contribute to the understanding of dynein regulation. Previously, genetic studies contributed to the discovery of dynein regulators, including NudE

and a human disease protein LIS1, whose deficiency causes lissencephaly, a brain developmental disorder [28–31, 35, 37, 273]. Because the screen for nuclear-distribution mutants has not yet been saturated, additional regulators could potentially still be discovered. In addition, as nucleus is considered as a heavy cargo, studies on nuclear movement should shed light on dynein regulation and/or force production under high-load conditions [274].

Finally, the intriguing phenomenon of non-random sister chromatid segregation during mitosis in *A. nidulans* provides an opportunity for dissecting its mechanism as it may benefit the understanding of a similar phenomenon in some stem cells [129–133]. In this context, studying the positioning and developmental fate of nuclei of different “ages” within the fungal hyphae would also be an exciting future direction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

I would like to dedicate this review to my postdoctoral mentor Ron Morris who initiated the genetic study on fungal nuclear distribution. I am grateful to the two anonymous reviewers for helpful suggestions, and I apologize for not citing or covering in detail some studies due to word limit. I thank Rosa Mouriño-Pérez for unpublished *Neurospora crassa* images and movies, Wei-Lih Lee and Safia Omer for unpublished budding yeast images, Kerry Bloom, Reinhard Fischer and Peter Philipson for providing or giving permission for using published movies. For the *Aspergillus nidulans* images, I thank Berl Oakley, Samara Reck-Peterson and Martin Egan for sharing/sending the GFP-Histone H1 strains. The author’s lab is currently supported by a grant from the NIH (R01GM121850-01A1).

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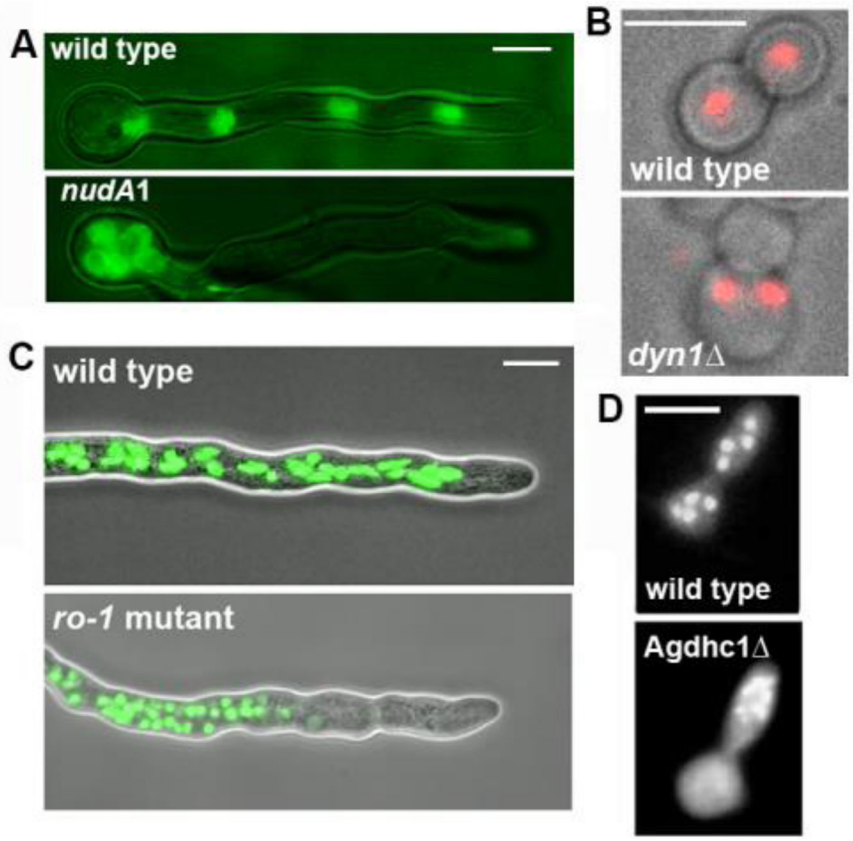

Fig. 1.

Nuclear distribution in wild type and dynein mutants in different fungi. (A) Nuclei labeled with GFP-Histone H1 in wild type and the dynein heavy chain mutant *nudA*1 in *A. nidulans.* Bar, ~5 μm. (B) DAPI-stained nuclei in wild type and a dynein heavy chain null mutant (*dyn1*Δ) of *S. cerevisiae.* Bar, ~7 μm. Images kindly provided by Wei-Lih Lee and Safia Omer. (C) Nuclei labeled with GFP-Histone H1 in wild type and the *ro*-1 (dynein heavy chain) mutant in *N. crassa.* Bar, ~10 μm. Images kindly provided by Rosa Mouriño-Pérez. Also see Movies 3 and 4. (D) DAPI-stained nuclei in wild type and a dynein heavy chain null mutant (Agdhc1Δ) of *A. gossypii.* These images were originally published in [16] (with permission from the *Journal of Cell Science*). Bar, ~10 μm.

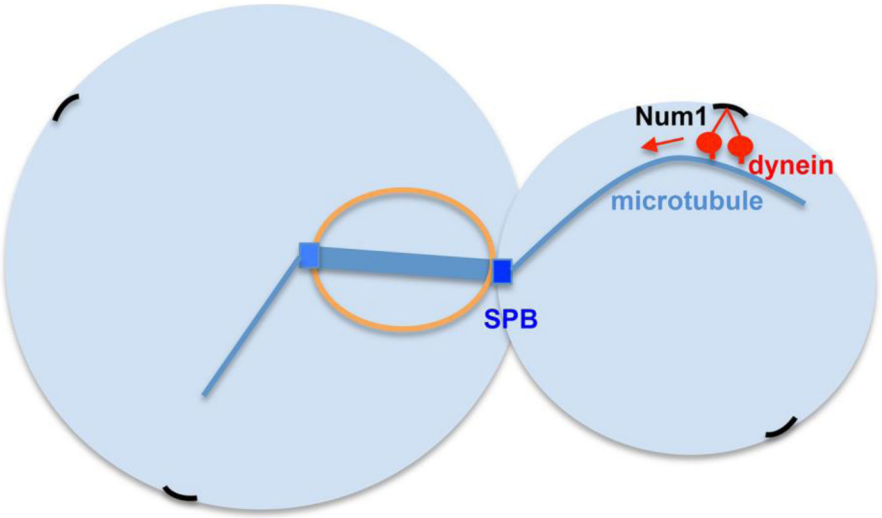

Fig. 2.

A cartoon illustrating that *S. cerevisiae* dynein anchored at the cortical Num1 site walks on an astral microtubule towards its minus end at the spindle-pole body (SPB), causing the microtubule to slide along the cortex. This action of dynein serves to position the anaphase spindle across the bud neck.

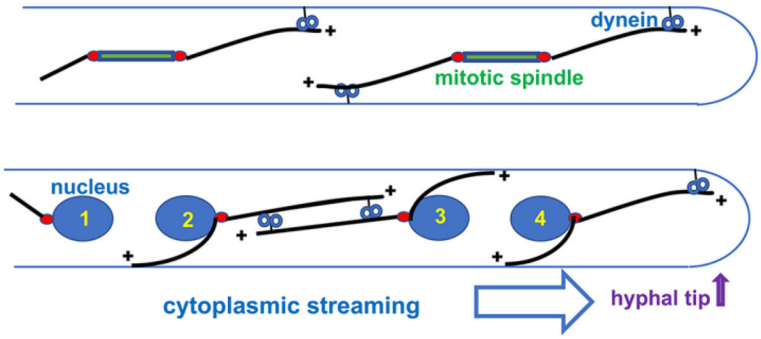

Fig. 3.

A cartoon illustrating postulated mechanisms of nuclear distribution in filamentous fungi. During mitosis (upper hypha), the mitotic spindles are mainly moved by dynein-mediated astral microtubule sliding against the cortex in a Num1/ApsA-dependent manner [149]. Two spindles are depicted, and the red dots represent the spindle pole bodies (SPBs). The plus end of a microtubule is labeled as "+". Dynein-based pulling force on astral microtubules has been demonstrated in filamentous fungi for spinel elongation [175, 178]. In this cartoon, dynein at the plus end is offloaded to the cortex to power spindle movement. The direction of the movement is determined by the difference in the pulling force on either end of the spindle, depending on the number of active dynein molecules at the cortex, their efficiency in engaging a microtubule as well as the stability of the engaged microtubule. Shortly after nuclear division (lower hypha), two pairs of daughter nuclei are generated, 1–2 and 3–4. The SPBs are positioned in opposite directions within each pair, and thus, there could be no overlapping microtubules between nuclei 1 and 2 or between 3 and 4 within a short time window after their division. In contrast, there are overlapping cytoplasmic microtubules between nuclei 2 and 3, and dynein anchored on one microtubule could walk toward the minus end (SPB) of an antiparallel microtubule, bringing the two nuclei toward each other. In the original model raised by Plamann et al. to explain an even nuclear distribution in hyphae [7], nuclei closer to each other have shorter overlapping microtubules and fewer dynein molecules on them, and thus, dynein-mediated pulling force is stronger between two more distant nuclei than between two more adjacent nuclei. Cortical sliding mechanism may also work in the same hypha, especially at the hyphal tip area. In addition to dynein-driven nuclear movement, cytoplasmic streaming toward the hyphal tip also pushes the nuclei toward the hyphal tip [226, 228, 230, 231].

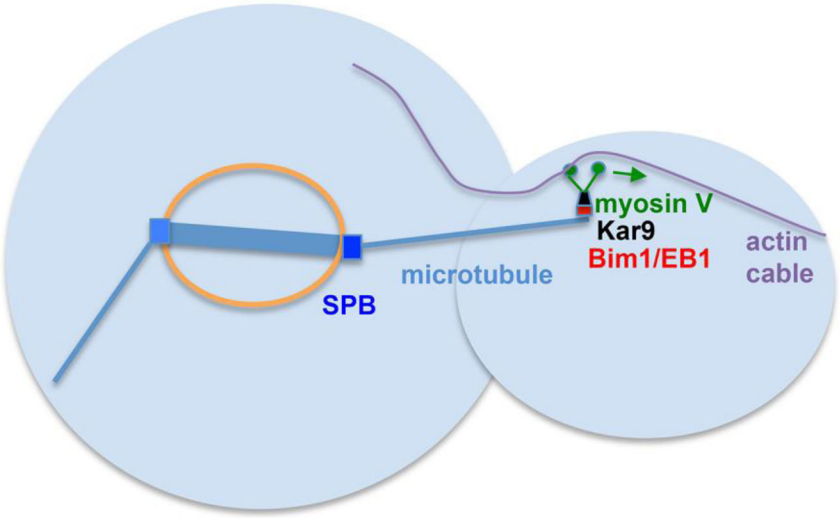

Fig. 4.

A cartoon illustrating how a preanaphase spindle is moved toward the bud neck in *S. cerevisiae*. Bim1/EB1 at the microtubule plus end interacts with Kar9, which interacts with the myosin V motor, and myosin V walks along the actin cable generated from the bud cortex, thereby moving the spindle/nucleus toward the bud neck.