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Review

Nuclear movement in fungi

Xin Xiang*

Department of Biochemistry and Molecular Biology, Uniformed Services University of the Health Sciences – F. Edward Hébert School of Medicine, Bethesda, MD, USA

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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.

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* Corresponding author.
E-mail address: Xin.xiang@usuhs.edu

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1. 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.

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

2.1. 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 congression during mating [25].

2.2. 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 binucleated 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

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