# Hyphal tip growth and nuclear migration

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Recent molecular and cytological studies have greatly advanced our understanding of hyphal tip growth and nuclear migration in filamentous fungi. Mutants involved in various aspects of hyphal tip growth have been isolated. Genes involved in nuclear migration continue to be identified, including putative regulators. The role of microtubules and microtubule motor proteins in hyphal tip growth has also been studied.

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**Abbreviation**
**MTOC** microtubule organization center

## Introduction

Tip growth is the dominant growth form of filamentous fungi. In filamentous fungi, such as *Aspergillus nidulans*, upon inoculation of a dormant spore into a nutritional medium, the spore first undergoes isotropic growth. During this period, cell-wall materials are added uniformly and the cell becomes significantly larger than the spore. This process of isotropic growth is accompanied by one to two rounds of nuclear division during which the single nucleus in the spore divides to become two to four nuclei. This phase of isotropic growth is then followed by the polarized growth of a germ tube. How a cell determines the timing of switching to polarized growth from isotropic growth is not known. Whether there is a cell-autonomous cue to determine the position of the initial emergence of a germ tube is also not known, although such a cue has been found in the budding yeast in which the position of the new bud depends on the position of the bud scar formed during the previous budding cycle [1].

Filamentous fungi grow by apical extension, localized apical synthesis that creates a tubular hyphal morphology. Besides linear tip extension, filamentous fungi branch to form new growing tips, and they also lay down septa to divide the old and the new hyphal compartments [2]. Another essential feature of the filamentous growth is the distribution of multiple nuclei along the growing hyphae. This review covers recent studies on hyphal tip growth and nuclear migration in filamentous fungi, mainly *A. nidulans* and *Neurospora crassa*, although insightful discoveries from other fungal species are also cited.

## Hyphal tip growth

In filamentous fungi, a germ tube grows by apical extension, which is characterized by the addition of new cell-wall materials specifically at the apex [3]. The tip growth is also correlated with a tip high calcium gradient [4,5] and a pH gradient [6]. Although it has been proposed that turgor pressure is important for driving tip extension [3], the molecular mechanism that governs apical extension remains largely unknown.

Cytological studies have identified a phase-dark structure near the apex named the 'Spitzenkorper', whose position is correlated with hyphal growth direction, which is consistent with the presumption that it represents a collection of vesicles required for tip growth [7,8,9••]. Microtubule poisons as well as kinesin and dynein mutants in different filamentous fungi show a defect in the Spitzenkorper structure, indicating that microtubules could be the track for the long range transport of these tip vesicles [10–13,14••]. On the other hand, the actin cytoskeleton is highly localized at the growing tip and could also participate in initiating new tip formation [15•,16,17]. In *A. nidulans*, a *myoA* conditional null mutant is defective in polarized growth and secretion, which suggests a role for type I myosin in tip vesicle transport [18].

Besides the cytoskeletal elements, genetic studies have also identified additional proteins involved in the polarized growth of filamentous fungi. The primary defects of most of these mutants are in cell-wall synthesis (discussed in [19]). Examples of recently identified genes involved in various aspects of hyphal tip growth in *A. nidulans* include *nudC* (a nuclear migration gene) [19], and *samB* [20]. In *N. crassa*, proteins involved in hyphal tip growth include a regulatory subunit of cAMP dependent protein kinase [21], the catalytic subunit of calcineurin encoded by *cna-1* [5] and protein phosphatase 2A, encoded by *pph-1* [22•]. Protein phosphatase 1 is also involved in tip growth in *A. nidulans* [23]. Recent genetic studies in *A. nidulans* have identified mutants defective in various aspects of hyphal tip growth, which includes the *swo* mutants [24••], the *hyp* mutants [25••], *sepA*, *hypA* and several *pod* mutants [26••]. Molecular characterization of these mutants should lead to a better understanding of the hyphal growth phenomenon. Presumably, some of them will represent the small G proteins that are known to participate in polarized growth in other systems.

## Nuclear migration

Nuclear migration is an essential feature that accompanies the growth of filamentous fungi. Upon germ-tube formation, multiple nuclei migrate into the germ tube to achieve relatively equal spacing of the individual nuclei. The migration distance of individual nuclei is different.

The nucleus closest to the tip moves a long distance, whereas the nucleus near the spore end moves only a short distance [27].

Molecular studies on nuclear migration started initially from the isolation of the *nud* (nuclear distribution) mutants in *A. nidulans* [28]. Characterization of the *nud* gene products in *A. nidulans*, as well as the *ropy* gene products of *N. crassa*, has identified cytoplasmic dynein as a major motor for nuclear migration in filamentous fungi [29,30], although kinesin-like proteins are also involved in nuclear migration in *Saccharomyces cerevisiae* [31,32]. Cytoplasmic dynein is a microtubule stimulated ATPase that can translocate towards the minus ends of microtubules [33]. Mammalian cytoplasmic dynein is a 20S complex containing heavy chains, intermediate chains, light intermediate chains and light chains. The heavy chain contains the ATP-binding activity, whereas the other subunits may regulate activity or target the motor to different cargos [33]. A dynein accessory complex, the dynactin complex, has also been identified and shown to be required by dynein to move vesicles *in vitro* [33]. The dynactin complex also contains multiple subunits, such as dynactin and the actin-related protein Arp1 [33]. In *A. nidulans*, genes affecting nuclear migration include those that encode a cytoplasmic dynein heavy chain (*nudA*) [29], a cytoplasmic dynein intermediate chain (*nudI*) (X Xiang, NR Morris, unpublished data), the 8 kDa cytoplasmic dynein light chain (*nudG*) [34] and an Arp1 homolog (*nudK*) [35]. In *N. crassa*, genes encoding components of the dynein complex and the dynactin complex have also been identified. These include *ro-1*, which encodes a cytoplasmic dynein heavy chain [30], *ro-4*, which encodes an Arp1 homolog [30,36], and *ro-3*, which encodes dynactin [37].

Several models have been proposed to explain dynein-mediated nuclear migration in filamentous fungi [28,30,38]. The existing experimental data are not sufficient, however, to prove or disprove any of these models. Since dynein is a minus-end microtubule motor, one obvious issue concerns the location of microtubule minus ends in the hyphae. Inside a cell, the minus ends of microtubules are generally embedded in a γ-tubulin containing structure called the microtubule organization center (MTOC) [39]. In *A. nidulans*, evidence indicates that the spindle pole body is the MTOC that generates cytoplasmic microtubules since γ-tubulin has only been found at the spindle pole body [40]. However, in *Allomyces macrogynus* and *Ustilago maydis*, data support the existence of a MTOC at the apex [41••,42]. Depending on the need for different microtubule polarities in the cell, different fungi may use different mechanisms to move their nuclei in the hyphae. Besides the action of motors on microtubules, microtubule dynamics itself, which can be affected by motor proteins, could also generate the force for nuclear distribution [43]. The fact that the *nud* mutants can be partially suppressed by a low dose of a microtubule depolymerizing drug benomyl supports such a notion [44]. Work from *S. cerevisiae* on antagonizing motors involved in spindle positioning also supports such an idea [31].

In addition to the genes that encode proteins homologous to the known subunits of the cytoplasmic dynein and dynactin complexes, other genes have been identified that are required for nuclear migration in filamentous fungi. These include the *nudF* [45], *nudC* [46] and *nudE* (VP Efimov, NR Morris, unpublished data) genes in *A. nidulans*, and the *ro-2* [47], *ro-10* and *ro-11* [48••] genes in *N. crassa*. We suspect some of these represent *in vivo* regulators of cytoplasmic dynein. In *N. crassa*, a *ro*-10 mutant affects the stability of the p150 Glued protein in the dynactin complex [48••]. In *A. nidulans*, *nudF* functions in the cytoplasmic dynein pathway as evidenced by the *nudF7* and *nuclA* double mutant analysis [49]. More interestingly, the phenotype of the *nudF* deletion mutant can be suppressed by a mutation in the *nudA* gene that encodes cytoplasmic dynein heavy chain [49], which suggests that *nudF* could regulate some aspects of cytoplasmic dynein function. Two other genes, *apsA* [50] and *apsB* [51••], that affect nuclear migration, particularly during the development of conidia, have also been cloned in *A. nidulans*.

## The relationship between hyphal tip growth and nuclear migration

Hyphal growth is an asymmetric process with new synthesis occurring only at one end. Although nuclei do occasionally move in opposite directions in the cell, the main direction of nuclear migration is toward the growing tip [14••,27]. During hyphal elongation, tip growth may occur before nuclear migration, and such a notion is supported by the fact that initial germ tube elongation occurs without nuclear migration in the *nud* mutants [29]. The simplest explanation to account for the tip-ward nuclear migration is that nuclei are attached to the tip through astral microtubules from their associated MTOCs. It has been proposed that an interaction between microtubules and cytoplasmically anchored dynein could generate force and that this force might be proportional to microtubule length [43]. Thus, unbalanced astral microtubule lengths might generate independent nuclear movements and the longer astral microtubules that probe tips and branches could produce tip-ward nuclear movement. A dynein-dependent interaction between astral microtubules from adjacent nuclei has been proposed to account for separation and regular spacing of nuclei [30]. Laser tweezer experiments have directly demonstrated dynein-dependent nuclear anchoring in *Nectria haematococca* [14••], and dynein was also shown to be required for microtubule aster formation and the astral pulling force [52••].

Tip growth and/or its associated microtubule elongation may also activate cytoplasmic dynein, which in turn functions as either a minus end motor or part of the microtubule coupling and depolymerization machinery to pull the nuclei toward the tip (discussed in [44]). Immunocytochemical localization of cytoplasmic dynein

and dynactin at the hyphal tip in *A. nidulans* and *N. crassa* is consistent with the hypothesis that invokes attachment of nuclei via astral microtubules to dynein and dynactin at the tip [28,48••,53]. However, new observations in living cells of *A. nidulans* have suggested that GFP–dynein is most likely to be concentrated at microtubule ends near the tip, but not at the hyphal tips *per se* (X Xiang, DA Winklemann, NR Morris, unpublished data). It is possible that cytoplasmic dynein on the ends of microtubules can directly exert force on microtubules to facilitate the tip–microtubule interaction. Such a dynein-dependent interaction between microtubules and the cortex has been demonstrated in the budding yeast *S. cerevisiae* [54], where cytoplasmic dynein locates along the astral microtubules [55] and the Kar9p protein may function as a microtubule receptor at the bud tip [56].

In wild-type strains, once a growing tip is formed, it tends to grow in a straight line with branches. Nuclear migration defective mutants grow slowly with curled and hyperbranched hyphal morphology [30,45]. The slow tip growth could be caused by the nuclei being too far from the tip to supply materials required for tip growth or by a defective dynein-dependent retrograde transport for recycling tip transport materials [57]. The Spitzenkorper apparently regulates the direction of tip growth, which is also dependent upon the microtubules [9••]. The Spitzenkorper in wild-type cells is positioned in the center of the growing tip and is thought to act as a material distribution center for new wall synthesis. Interference with dynein, dynactin or microtubules causes eccentric wall deposition and consequently a meandering and hyperbranched mycelium, suggesting that the dynein/dynactin/microtubule system positions the Spitzenkorper. Whether the effect of dynein on the direction of hyphal tip growth is caused by a shift in position of the Spitzenkorper that results from the defective microtubule–tip interaction and/or by an alteration in microtubule dynamics caused by dynein deficiency, as in yeast [54], remains to be determined.

## Conclusions

The vegetative growth of filamentous fungi is highly polarized. Molecules required for the polarized tip growth are being identified, and their future characterization should lead to a better understanding of the process of hyphal tip growth. Molecular studies are also in progress on a related process, nuclear migration along the growing hyphae, which uses the cytoplasmic dynein/dynactin system. Future work should further establish regulatory pathways that control cytoplasmic dynein function. In addition, the role of dynein in the behavior of the Spitzenkorper and microtubules needs to be addressed.

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