2 Nuclear Dynamics and Cell Growth in Fungi

Samantha E. Roberts[1], Amy S. Gladfelter[1]

CONTENTS

I. Introduction

Nuclei are the repositories of genetic information in eukaryotic cells. These organelles are highly dynamic in terms of both physical movement and genetic change from the level of gene expression to large-scale genome alterations. Fungal systems provide an especially excellent model for understanding the fundamentals of nuclear behavior in all cells and display a range of strategies for manipulating both the position and content of genetic information to adapt to the external environment as well as the constantly changing cellular context during growth. From the first characterizations of nuclear motility within **basidiomycete** mycelia to the present day, fungal cells have provided researchers with countless complex problems, many still awaiting inquiry. Investigations into fundamental activities within fungi have yielded insights into processes such as the mechanical dynamics of **growth**, **evolution**, and mechanisms of **pathogenesis** that have furthered our understanding of eukaryotic cell biology as a whole. While there are numerous excellent reviews on various aspects of nuclear mobility, exchange of genetic material, the interplay between nuclear behavior and cell growth, and principles of evolution in the fungal kingdom, we seek in this chapter to communicate a more integrative view of these processes to illustrate the remarkable adaptability and dynamic behaviors of nuclei.

II. Physical Nuclear Mobility

Throughout the entire spectrum of morphologies exhibited by fungi from **uninucleate** baker's yeast only microns in diameter to **multinucleate mycelia** of mushroom species that can cover multiple square miles, nuclei are strategically and actively positioned to facilitate their interactions with other cellular components and contribute to successful growth and reproduction of the organism. Nuclei are transported throughout the cell for a variety of purposes by a combination of precise active and bulk passive mechanisms.

A. Mechanics of Nuclear Movement

The **microtubule cytoskeleton** is essential for nuclear positioning in fungi. One of the most

[1]Department of Biological Sciences, Dartmouth College, Hanover, NH, 03755, USA; e-mail: Amy.Gladfelter@dartmouth.edu

Growth, Differentiation and Sexuality, 3rd Edition
The Mycota I
J. Wendland (Ed.)
© Springer International Publishing Switzerland 2016

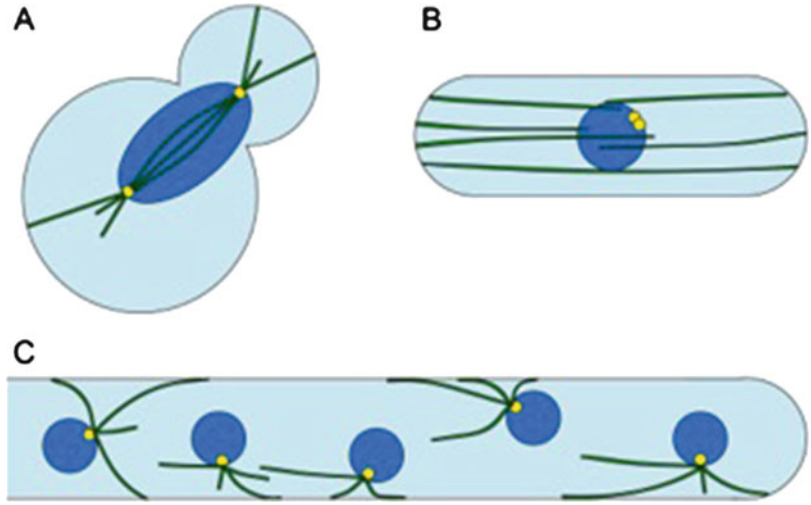

Fig. 2.1 Overview of the microtubule cytoskeleton in different species. (**a**) *S. cerevisiae* microtubules emanate from the spindle pole bodies and interact with the cell cortex to orient the nucleus during mitosis. (**b**) *S. pombe* microtubules associate with the nuclear envelope and push against the cell cortex to center the nucleus within the cell. (**c**) Microtubules emanating from SPBs in filamentous fungi interact with the cell cortex and dynamically position nuclei within a constantly flowing cytoplasm

extensively studied microtubule-dependent nuclear processes is **migration during mitosis** in *Saccharomyces cerevisiae*. Astral microtubules emanating from the **spindle pole body** (SPB, the microtubule-organizing center of fungal cells) embedded within the nuclear envelope are captured by cortical dynein and used to orient the nucleus so that the daughter nucleus will traverse the bud neck during spindle elongation (Fig. 2.1a). **Microtubule defects** or **dynein mutations** cause misalignment of the spindle and generation of a binucleate mother and an anucleate daughter cell. The details of this process can be found in many excellent review articles on the subject, but here it is essential to note that conserved functions of microtubules, associated motors, and accessory proteins primarily coordinate these nuclear movements (ten Hoopen et al. 2012; Ananthanarayanan et al. 2013).

In the antithesis to mitosis, **karyogamy**, two haploid nuclei must be brought together for fusion prior to **meiosis**. Genetic and molecular analyses of the *S. cerevisiae kar* mutants have revealed that this process also depends upon microtubules and microtubule-associated motors (Rose and Fink 1987; Meluh and Rose 1990; Endow et al. 1994; Miller and Rose 1998). The kinesin Kar3 associates with the SPB of each nucleus and captures microtubules emanating from the SPB of the partner nucleus. The force generated by these motors brings the two nuclei together prior to fusion (Melloy et al. 2007; Gibeaux et al. 2013). The process of nuclear envelope fusion begins with fusion of the separate SPBs so that after completion of karyogamy, the diploid nucleus contains one SPB with a half-bridge (the construction site of a new SPB). In this way, the number of microtubule nucleation sites is regulated to successfully segregate chromosomes during meiosis (Byers and Goetsch 1975; Gibeaux et al. 2013; Gibeaux and Knop 2014).

In contrast to budding yeast, which have the hourglass of the mother-bud neck as a cellular landmark, nuclei in fission yeast cells must achieve proper positioning through alternative mechanisms. In *Schizosaccharomyces pombe*, **dynamically unstable microtubules** associated with the nuclear envelope generate pushing forces against the plasma membrane and keep the nucleus centered within the cell (Fig. 2.1b) (Tran et al. 2001). In the case of a nucleus that has been displaced from the center

(e.g., by centrifugation), microtubules on one side must grow much longer than those on the alternate side to reach the cortex. This increases the chance of shorter microtubules reaching the cortex on the closer end of the cell, and these stiffer, shorter microtubules exert more force on the closer cell end. These interactions are sufficient to return the nucleus to the center of the cell (Daga et al. 2006). However, microtubule motors are important for nuclear positioning during other processes in *S. pombe*. During meiosis, **nuclear oscillations** within the cell promote chromosome pairing and recombination. These oscillations are generated by changes in **dynein localization** that exert forces on the nucleus from different directions through time (Vogel et al. 2009).

It is clear that the **cell shape** can influence nuclear positioning, and therefore **dimorphic** fungi encounter unique challenges with respect to nuclear mobility. For example, in the **yeast form** of *Candida albicans*, the nucleus must be positioned properly during mitosis to produce uninucleate progeny. It has been shown that, as in *S. cerevisiae*, dynein-dependent nuclear oscillations coordinate nuclear positioning in the yeast form during mitosis (Finley and Berman 2005; Finley et al. 2008). Indeed, the velocity of nuclear movement in both yeast and hyphae is reduced in dynein mutants (Finley et al. 2008). Often, dynein mutants in the yeast form are able to successfully segregate nuclei during mitosis because although nuclear division may proceed in the mother cell, a spindle checkpoint prevents cytokinesis before a nucleus eventually moves into the bud (Finley and Berman 2005). However, nuclei must also undergo long-range transport after transition to the **hyphal** growth form. In *C. albicans*, microtubule-dependent nuclear migration within hyphae is important for ensuring appropriate timing of **septum** formation relative to mitosis, and this process is not successful in dynein mutants (Finley and Berman 2005). Similarly, in the corn pathogen *Ustilago maydis*, microtubules are not essential during initial **germ tube** formation, but are required for hyphal growth after **infection** initiation (Fuchs et al. 2005). Dimorphic species are able to adapt the same machinery to transport nuclei within very different spatial contexts. Investigation into the different behavior of microtubules and microtubule-associated motors between these two growth strategies can provide insight into adaptations during the evolution of multinucleated cells and other cells with complex geometries.

Microtubule-dependent nuclear transport in **multinucleate** fungi serves to properly distribute nuclei throughout the mycelium. Compromised microtubules, dynein, or dynein activators in the filamentous fungi *Neurospora crassa*, *Aspergillus nidulans*, *Ashbya gossypii*, and *Nectria haematococca* result in a disruption of normal nuclear spatial distribution (Oakley and Morris 1980; Plamann et al. 1994; Tinsley et al. 1996; Inoue et al. 1998; Grava et al. 2011). In these organisms, SPB-associated microtubules interact with dynein at the cortex to generate force required for nuclear movement (Fig. 2.1c). In the yeast *S. cerevisiae*, the protein Num1 localizes to the cortex and interacts with cytoplasmic microtubules and dynein to facilitate nuclear positioning during mitosis (Farkasovsky and Küntzel 1995, 2001). Homologues of this protein in *A. gossypii* (Num1) and *A. nidulans* (ApsA) are also required for normal nuclear positioning, suggesting a conserved role for cortical dynein anchoring in nuclear positioning (Fischer and Timberlake 1995; Grava et al. 2011). In *A. gossypii*, it has been demonstrated that microtubules are required for active redistribution of nuclei and maintenance of consistent internuclear distance, though the precise nature of microtubule interactions remains unclear and involves the activity of kinesins as well as dynein (Anderson et al. 2013). There is also evidence for the involvement of kinesins in nuclear positioning from studies in *A. nidulans*, but further investigation is required to understand their involvement in these processes (Requena et al. 2001; Zhang et al. 2003).

Nuclear movement and division must be coupled to **cell growth**. In some species both nuclear movement and polarized secretion require microtubules, providing a strategy for linking these processes. For example, in addition to nuclear distribution, polarized growth becomes compromised when microtubules are disrupted in *N. crassa*, *A. nidulans*, or

N. haematococca (Plamann et al. 1994; Inoue et al. 1998; Horio and Oakley 2005). However, in *A. gossypii*, microtubule-based nuclear transport and actin-based polarized growth are sufficiently uncoupled to allow continuation of growth despite aberrantly positioned nuclei in mutant strains or pharmacologic disruption of microtubules (Gladfelter et al. 2006; Grava et al. 2011). This may be because *A. gossypii* is more closely related to the yeast *S. cerevisiae*, in which nuclear movements and polarized growth are also relatively distinct processes (Dietrich et al. 2004). It may be that the more divergent filamentous fungi from *S. cerevisiae* have adapted to more closely coordinate nuclear dynamics with polarized growth by using the same cytoskeleton for both. Interestingly, the **rates of polarized growth** differ in all of these species from 0.1 to 0.5 μm/min in *A. nidulans*, 1–2 μm/min in *A. gossypii*, 3 μm/min in *N. haematococca*, and 1.3–12.9 μm/min of individual *N. crassa* hyphae, though mature mycelium in race tubes has been measured at up to 80 μm/min (Ryan et al. 1943; Wu et al. 1998; Horio and Oakley 2005; Araujo-Palomares et al. 2007; Kohli et al. 2008). The mechanistic differences behind this variation are currently unclear, though they likely depend upon differential allocation of resources for growth, vesicle production and fusion rates, cytoskeletal dynamics, and differences between cytoskeletal motors in each species. In the species for which it has been measured (*A. nidulans*, *N. crassa*, and *A. gossypii*), the growth rate is highly dependent upon the age of the cell, probably due to increased capacity for transport of components required for growth, such as vesicles, to hyphal tips (Horio and Oakley 2005; Araujo-Palomares et al. 2007; Kohli et al. 2008).

An additional transportive force upon nuclei in filamentous fungal cells is that produced by **cytoplasmic streaming**. The cytoplasm of these cells continually moves toward the growing tips indiscriminately carrying cytosolic components and organelles (Ramos-Garcia et al. 2009; Lang et al. 2010; Abadeh and Lew 2013). This promotes transport of necessary components to growth sites and guides nuclei, cytosol, and other organelles into new hyphae upon symmetry breaking and polarity establishment. Investigations of **nutrient transport** on the millimeter and centimeter scale have indicated that osmotic and pump-driven water uptake during growth induces mass flow throughout the mycelial network, contributing to nutrient dispersal throughout the organism (Heaton et al. 2010). The pressure generated by this flow is thought to promote apical growth (Lew 2005). Many species are capable of vegetative and/or sexual **hyphal fusion**, generating even more complex networks and fluid flows. During vegetative fusion in *N. crassa*, nuclei from each partner move into the other, rapidly redistributing the genotypes throughout the fused network (Fig. 2.2a). It has been demonstrated that the combination of complex network geometry and bulk cytoplasmic flow strongly influences this nuclear mixing (Roper et al. 2013). It remains to be thoroughly investigated how large-scale fluid movements throughout mycelial networks relate to dynamic flow within individual hyphae. The activity of the same cytoskeletal motors that actively transport nuclei throughout the mycelium has been shown to generate **complex fluid flows** on the order of microns that promote nutrient uptake and mixing throughout the cells of some plant species. For example, in cells of the algal weed *Chara corallina*, cytoplasmic streaming has been described as "barber pole flow," because two bands of flow with opposite polarity spiral along the length of the cell (Goldstein et al. 2008). Additionally, it has been demonstrated using various experimental and modeling techniques that the activity of motors within eukaryotic cells contributes significantly to patterns and rates of diffusion within the cytoplasm (Brangwynne et al. 2008). It is likely that similar processes contribute to dynamic cytoplasmic flow over micron-scale regions of mycelial networks, and the role these play in nuclear distribution throughout large networks is an area open for investigation.

The placement of **septal pores** along hyphae provides another mechanism for the cell to regulate fluid flow between compartments. In species such as *N. crassa*, pores in healthy cells are left open allowing for cytoplasmic flow and

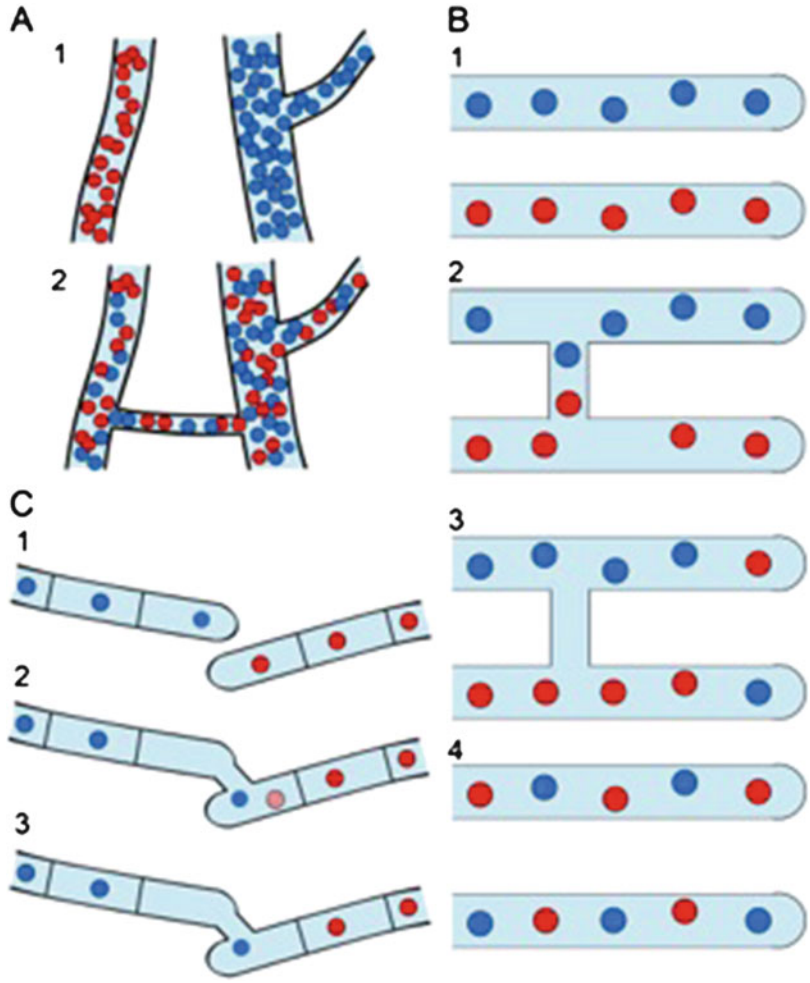

Fig. 2.2 Nuclear interactions during vegetative fusion of fungal cells. (**a**) Upon fusion of compatible *N. crassa* hyphae, the two nuclear genotypes (*denoted in red and blue*) rapidly intermix within the fused mycelium. (**b**) During formation of a dikaryon in basidiomycetes, a nucleus from each fusion partner moves into the other fusion partner (2). These nuclei move to the growing tips of the cell (3). Subsequent mitotic events result in alternation of genotypes in these hyphae (4). (**c**) After migration of a donor nucleus into a compartment of a host cell of *F. oxysporum* (2), the host cell nucleus is degraded (3)

nuclear movement between compartments (Shatkin and Tatum 1959). Upon damage to a portion of the cell, or signaling during the **heterokaryon incompatibility response**, a specialized proteinaceous plug termed the **Woronin body** blocks septal pores to prevent damage to and loss of cytoplasm from other regions (Jedd and Chua 2000; Tenney et al. 2000). However, not all cells utilize this type of flow for nuclear transport. Some cells lay down complete septa between compartments, such as *Fusarium oxysporum* (Ruiz-Roldan et al. 2010). In these cells, cytoplasmic components do not move between different parts of the mycelium, even in healthy cells, and nuclei in different hyphal compartments cannot intermix.

B. Functions of Movement in Reproduction

One of the most universal roles of nuclear mobility is **segregation of sister chromosomes** into separate cells during mitosis. Many fungal cells undergo completely **closed mitosis**, in

which the nuclear envelope does not degrade (Heath 1980). The SPB's location within the nuclear envelope allows nuclear transportation via force generation by cytoskeletal motors on associated microtubules. This motor activity is coordinated with **cell cycle checkpoints** and the **cytokinetic machinery** to ensure daughter cells do not separate until each contains a nucleus. Failure to properly position the nucleus throughout this process results in the production of multinucleate and anucleate cells (Morris et al. 1995). In uninucleate species, the resulting **ploidy** changes can lead to **genome instability** and **cell death**. In some cell types, nuclear placement itself helps specify the plane of division. The position of the nucleus coordinates the placement of the actomyosin ring during *S. pombe* cytokinesis, promoting creation of equally sized daughter cells (Paoletti and Chang 2000). Nuclear positioning in this species, therefore, is essential to normal partitioning of resources during cytokinesis.

Not all fungi undergo closed mitosis, however. Some partially degrade the nuclear envelope during mitosis, such as the disassembly of portions of the **nuclear pore complex** (NPC) in *A. nidulans* (Osmani et al. 2006). Others such as *S. pombe* open a **fenestra** in the nuclear envelope during mitosis for transient SPB insertion (Ding et al. 1997). In *U. maydis*, extranuclear microtubule-organizing centers (MTOCs) orchestrate mitosis along with SPBs. To allow cytoplasmic microtubules access to kinetochores, the nuclear envelope is torn open in this species during prophase by dynein-generated forces (Straube et al. 2005). The differences among fungal mitotic strategies and comparisons with other eukaryotes have furthered our understanding of the evolution of mitosis.

Sexual reproduction involves the recombination of genetic material from two individuals. This requires bringing nuclei from two parents into physical proximity for nuclear fusion to occur. Though mating increases the genetic diversity essential for the survival of the species, it involves certain risks on the part of the individual. Fusion of separate individuals in order to bring different nuclei together can entail mixing of cytoplasm and potential transmission of deleterious elements such as **viruses**, **prions**, or **parasitic mitochondrial DNA genotypes**. Uninucleate cells must accept the consequences of taking these risks and will often only initiate sexual reproduction in the event of environmental adversity. This has the twofold benefit in many species of increasing genetic variation, which will hopefully help the next generation survive the stress and generation of environmentally resistant spores.

Many multinucleate ascomycetes permit nuclear encounters only in specialized **mating structures**. It has been hypothesized that this, in combination with **mating type** and **heterokaryon incompatibility** mechanisms, serves to protect the rest of the organism from parasitic elements (Buss 1982, 1987; Debets and Griffiths 1998). Nuclei enter the mating structure to form a dikaryon and subsequently undergo karyogamy (nuclear fusion) and meiosis to produce sexual spores. In basidiomycetes, donor nuclei move into a host cell upon fusion (**anastomosis**) of two compatible mates and rapidly migrate to hyphal tips, 2–3 mm per hour in *Schizophyllum commune* (Niederpruem 1980) and an astonishing 4 cm per hour in *Coprinellus congregatus* (Ross 1976). Both host and donor genotypes then exist together and replicate in a stable dikaryotic mycelium. Through formation of specialized "clamp cells" in some species and regulation of nuclear positioning and mitotic spindle length, the nuclei with different genotypes in these regions alternate positions along the hypha (Fig. 2.2b). Each hyphal compartment contains one nucleus of each type, and upon reception of environmental cues, genetically different nuclei will pair up, fuse, and undergo meiosis to generate sexual spores (Brown and Casselton 2001). Donor nuclei do not necessarily propagate throughout the entire mycelium, which serves a similar function to specialized sexual structures in ascomycetes. In *Termitomyces* species, a dikaryotic mycelium is only generated at the interface between mating monokaryons (Nobre et al. 2014). Subapical regions retain their monokaryon identity, and in the event that fusion is detrimental to the survival of the genotype, these regions of the mycelium are free to make contacts with other mating partners.

Exchange of nuclei between **basidiomycete monokaryons** is often reciprocal, with hyphae of both individuals acting as both a nuclear donor and recipient. Fusion with a compatible mating partner induces nuclear migration into the partner cell. If incompatible hyphae fuse with each other, nuclear migration does not occur. It is likely that products of the mating-type loci interact with dynein and the microtubule cytoskeleton to regulate nuclear transport during these events. Interestingly, during fusion between a dikaryon and a monokaryon, the dikaryon will donate a nucleus to the monokaryon generating a new dikaryon. However, the individual that was already a dikaryon does not accept additional nuclei from the monokaryon (Swiezynski and Day 1960). Furthermore, under these conditions, the monokaryon preferentially accepts nuclei from the dikaryon that are more different from itself (Ellingboe and Raper 1962; Raper 1966). In another example of how nuclear identity influences events after cell fusion, hyphal fusion in the basidiomycete *F. oxysporum* can be followed by **degradation** of the nucleus from the host compartment (Fig. 2.2c) (Ruiz-Roldan et al. 2010). Interestingly, although nuclear genetic material is shared during dikaryotization, the host cell generally retains its **mitochondrial genome** and other **cytoplasmic elements** through unknown processes (Lee and Taylor 1993; Marcinko-Kuehn et al. 1994). The mechanisms by which cells identify the genotypes present within them, limit this number to a maximum of two, and ensure proper pairing upon the decision to undertake karyogamy and spore production are unknown.

Generation and release of **spores** or **conidia** is a highly regulated process, but control mechanisms vary between species. Uninucleate *S. cerevisiae* and *S. pombe* produce a set of four haploid spores within an ascus membrane. Many fungal species produce uninucleate spores, but *Aspergillus* species contain two and some mycorrhizal fungal spores contain 2000–20,000 nuclei with multiple different genotypes (Burggraaf and Beringer 1989; Becard and Pfeffer 1993; Hijri et al. 1999). During either sexual or asexual production of spores or conidia, the appropriate number of nuclei must be moved and packaged into specialized compartments and sometimes into specialized structures prior to release into the environment. This transport is dependent upon the microtubule cytoskeleton. Multinucleate *A. gossypii* designates specialized spore producing hyphal compartments that fill up with spores prior to bursting to release them into the environment (Wendland and Walther 2005; Kemper et al. 2011). *Aspergillus* and *Neurospora* species produce elegant structures upon which conidia are poised for maximum dispersal, though these are dwarfed by the elaborate fruiting bodies common among the basidiomycetes (mushrooms). Dynein mutants of *Aspergillus oryzae* form abnormally shaped anucleate and multinucleate conidia (Maruyama et al. 2003). *A. nidulans* mutants with abnormal nuclear distribution likewise create malformed metulae and phialides (parts of the **conidiophore**) and anucleate or multinucleate conidia (de Queiroz and de Azevedo 1998; Castiglioni Pascon et al. 2001) or anucleate sterigmata (also part of the conidiophore), resulting in the arrest of further conidial development (Fischer and Timberlake 1995). In all of these cases, the meiosis must be coordinated with a specific developmental program to trigger the morphological changes necessary to produce the environmentally resistant spore and (if applicable) its dispersion structure, further indicating the coupling of nuclear mobility and growth programs in multinucleate fungi.

Chytrid fungi, recently appreciated as major **amphibian pathogens**, create **flagellated spores** that are capable of active movement through their environment (Letcher et al. 2008; Letcher and Powell 2014). These motile sexual structures find each other for mating. *Rhizophydiales* produce multinucleate sporangia that undergo multiple cytokinetic events during maturation to release uninucleate zoospores (Berger et al. 2005; Letcher et al. 2008). It has been demonstrated that subgroups of chytrids exhibit differences in nuclear positioning and microtubule cytoskeleton organization, but further research is required to determine the mechanisms of nuclear positioning in this poorly understood fungal lineage (Letcher and Powell 2014). Examinations of these fungi in

the early 1900s yielded many qualitative observations about their vegetative, sexual, and parasitic interactions. From these, it is clear that there are many types of interesting nuclear interactions in these species that have not been investigated in more recent years, but merit further research. For example, during *Olpidiopsis* sexual reproduction, one **multinucleate thallus** donates all of its cytoplasm to another to create the resting zoospore. The two sets of nuclei then undergo karyogamy, meiosis, and the cytokinetic events necessary to produce uninucleate zoospores (Sparrow 1935). The process by which nuclei of opposite mating types find each other in this large multinucleate cytoplasm and how cytokinesis is linked to the events following meiosis remain completely mysterious, but will likely provide insight into similar processes observed in the basidiomycetes.

The first chytrid **genome sequencing project** was undertaken for the important amphibian pathogen *Batrachochytrium dendrobatidis*. Most of the *B. dendrobatidis* genome was sequenced and assembled by the Broad Institute Fungal Genome Initiative. More recently, the genomes of two other chytrids are being sequenced as part of the Broad Institute Origins of Multicellularity Project: *Spizellomyces punctatus* and *Allomyces macrogynus* (Ruiz-Trillo et al. 2007). This genomic information will allow more research into chytrid pathogenicity and control strategies, as well as general chytrid and fungal biology.

C. Functions of Nuclear Movement During Vegetative Growth

In addition to the necessity of nuclear movement during reproduction, cells require regulated and dynamic nuclear positioning during **vegetative growth**. As previously discussed, dynein activity is required in the filamentous fungi *N. crassa*, *A. nidulans*, *A. gossypii*, and *N. haematococca* to maintain regular internuclear spacing. In cells with compromised microtubules, dynein, or dynein activators, nuclei form large clusters, precluding effective regulation of nuclear activity, mitosis, and polarized growth. Although these cells all actively move nuclei within the cytoplasm, the average distance differs between different species, and internuclear spacing is dynamic within a single cell (Suelmann et al. 1997; Grava et al. 2011; Anderson et al. 2013). This suggests that different cells have adapted nuclear mobility and mitosis in different ways to optimize the fitness of the organism.

In *A. gossypii*, nuclei actively repulse their neighbors via SPB-associated microtubules to maintain regular internuclear spacing and a consistent **nuclear-cytoplasmic ratio** (Gladfelter et al. 2006; Anderson et al. 2013). This poses a conundrum when it comes to mitotic strategies within multinucleate cells. If nuclei duplicate either **synchronously** (e.g., *Physarum polycephalum*) or in **waves of synchrony** that progress at a different rate than apical growth (e.g., *A. nidulans*), the cell experiences rapid changes of nuclear-cytoplasmic ratio and gene dosage (Nygaard et al. 1960; Clutterbuck 1970). This is in stark contrast with studies of the tightly regulated nuclear-cytoplasmic ratio in *S. pombe* (Neumann and Nurse 2007). Obviously these organisms have developed ways to tolerate these fluctuations, but other species employ various strategies to avoid these problems. *N. crassa* and *A. gossypii* exhibit **asynchronous** mitosis within the common mycelium. Mitotic events happen only frequently enough to maintain the nuclear-cytoplasmic ratio, and nuclei continually bypass each other and mix within these hyphae (Grava and Philippsen 2010; Roper et al. 2013). In other species, such as *Alternaria solani*, only nuclei within the most apical compartment undergo mitosis (King and Alexander 1969). In *N. crassa*, *A. gossypii*, and *A. solani*, nuclei maintain constant internuclear distances while producing sufficient nuclei to populate new growth regions. The optimal internuclear distance in a given species can even change in response to its environment, similar to how cell size can be nutrient controlled in single-celled yeasts (Unger and Hartwell 1976; Johnston et al. 1977; Fantes and Nurse 1977). In *A. gossypii*, starvation prolongs the G2 phase of the cell cycle, leading to increased average internuclear spacing (Helfer and Gladfelter 2006).

Internuclear distance in *S. commune* varies depending on the growth substrate, and cell secretes different types of **hydrophobins** to aid in surface attachment (Schuurs et al. 1998). It is tempting to speculate that the altered internuclear distance contributes to the regulation of the production of these proteins, though further investigation is required. Interactions between environment, gene expression, and nuclear spacing are fascinating areas for future research. It is clear that nuclear division is linked with cellular growth and nutrient availability, but recently it has been shown that other external signals also regulate mitosis. In the **circadian** model organism *N. crassa*, asynchronously dividing nuclei can be synchronized using periodic light exposure (Hong et al. 2014). The intersection between the highly studied circadian rhythm regulation and cell cycle control is only beginning to be understood (Zamborszky et al. 2014).

Nuclear positioning can also influence the organization of the surrounding cytosol. Recent studies have shown that organization of cytoplasmic factors and regular internuclear spacing are both important in the generation of nuclear asynchrony in *A. gossypii* (Lee et al. 2013; Anderson et al. 2013). Transcripts encoding the G1 cyclin protein, Cln3, are concentrated in the vicinity of nuclei via an aggregation-prone RNA-binding protein. It is hypothesized that by forming RNA-protein complexes, transcript diffusivity is limited and neighboring nuclei are prevented from sharing gene products (Lee et al. 2013). It is intriguing to speculate that the assembly of **RNA-protein aggregates** of different sizes and degrees of diffusivity is tuned to match the spacing between nuclei. The mechanisms by which these **membrane-free domains** are created and associated with a specific nucleus are areas of active study but are known to involve the formation of higher-order assemblies between RNAs and polyQ tracts in RNA-binding proteins (Lee et al. 2013). Furthermore, it raises the possibility that fungi have mechanisms to restrict cooperation between genetically distinct nuclei in a common cytoplasm.

Multinucleate cells have the opportunity to contain nuclei with different genotypes. This **heterokaryon** state has been hypothesized to confer fitness advantages, as the rest of the population can dilute deleterious alleles. Indeed, it has been demonstrated in several species that heterokaryons grow more rapidly than their homokaryon counterparts (Jinks 1952; James et al. 2008; Samils et al. 2014; Nobre et al. 2014). A prime example of nuclear cooperation in a heterokaryon is that of mating-type loci within *S. commune*. In this organism, nuclei with nonfunctional genes at the B mating locus have a growth advantage in the homokaryon state, but these genes contribute to hook cell fusion and nuclear migration during mating, meaning these homokaryons are at a disadvantage for sexual reproduction (Raper 1985). In heterokaryons with nuclei containing functional and nonfunctional alleles of these mating genes, nuclei with the functional alleles are overrepresented, but the mycelium grows better than the homokaryon. This suggests that dilution of the functional B alleles can be advantageous to an individual. In *N. crassa*, nuclei from different parents rapidly disseminate throughout the mycelium after fusion (Fig. 2.2a) (Roper et al. 2013). The benefits of this are surely to share beneficial and dilute deleterious alleles throughout the whole cell, but the mechanisms for this active redistribution are unknown.

In general, **heterokaryosis** seems to provide a cell with the advantage of as many potentially beneficial alleles as possible, without having to "decide" on any specific genotype. In a system with multiple genotypes contained in a single nucleus, all of these must be inherited together, given the physical limitations of mitosis. When multiple nuclei coexist within the cell, there is the potential for selection at the level of each nucleus to optimize the balance of genotypes that will benefit the organism. Sister nuclei sharing the cytoplasm provide buffering capacity for mutational exploration, but only the fittest genotypes will be able to generate new individuals after sexual or asexual spore production.

III. Genome Content Dynamics

In any discussion about the genetics of multinucleate fungi, we must constantly bear in mind the varying levels of **selection** at play.

Each nucleus is a potential unit of selection, and yet different genotypes may come together in one cell to increase the fitness of the organism as a whole. In multinucleate as well as uninucleate cells, the genetic identity of a nucleus and each cell is constantly in flux due to mutation, random drift, and active response to environmental cues.

A. Inter-organism Interactions

Fungi must react rapidly and appropriately to interactions with each other and with the environment in order to survive. Different species have developed elaborate **mating** and **vegetative fusion** strategies in order to maximize the benefits of interacting with other individuals. In order to discern the suitability of a potential mate, fungi have developed various **mating-type** structures. Most ascomycetes utilize a system with only two mating types, while many basidiomycetes have four, and some even have thousands (Raper 1985; Glass and Kuldau 1992; Casselton and Challen 2006). More mating types in the population means that an encounter between two individuals is more likely to result in successful mating. Often karyogamy, meiosis, and sexual spore production are heavily dependent upon environmental cues such as nutrient starvation. In these scenarios, generation of genetic variability by mating combined with the production of environmentally resistant spores improves the chances of survival in the next generation. In some cases, mating-type mechanisms have been co-opted by **fungal parasites** (Burgeff 1924). *Parasitella parasitica* parasitizes zygomycetous fungi and uses the regulatory pathways involved in sexual fusion to initiate infection (Schultze et al. 2005). Interestingly, this means that the "mating type" of a *P. parasitica* individual must be the opposite of its intended target. The infection process involves transfer of *P. parasitica* cytoplasm to the host cell, and parasite-host gene transfer has been observed during infection of *Absidia glauca* (Kellner et al. 1993). Although "mating type" appropriately evokes specific connotations, these parasitic interactions highlight the most basic role of these loci: self- and nonself-recognition.

Another process that involves distinguishing between self and nonself is the fusion of hyphae during vegetative growth. In contrast with fusion of cells for sexual reproduction, many fungi can also fuse to form a hybrid mycelium, or heterokaryon, with different genotypes. In contrast with the mating types that encourage reproduction between genetically different parents, **vegetative fusion** is unsuccessful if the partners are not genetically similar, termed **vegetative** or **heterokaryon incompatibility** (Glass and Kaneko 2003). Cells have the potential to benefit from mycelial fusion by sharing of nutrients, increasing the genetic diversity of the individual, enabling an individual to cover more area in the search for nutrients, and having a better chance of outcompeting rival mycelia (Aanen et al. 2009; Richard et al. 2012). This is especially true of newly germinated cells. A new colony can more rapidly establish if spores germinate and fuse with related cells to share resources and spread, as has been shown for *N. crassa* and *F. oxysporum* (Roca et al. 2010; Ruiz-Roldan et al. 2010). Additionally, hyphae from the same cell can fuse with each other, facilitating rapid movement of nuclei and nutrients throughout the cell. This is especially important in the case of heterokaryons, where nuclei containing different genetic materials are actively distributed throughout a hybrid mycelium to allow sharing of gene products between different genotypes (Pitchaimani and Maheshwari 2003; Roper et al. 2013).

Despite the potential benefits, many different loci participate in the heterokaryon incompatibility response, making it highly unlikely that two cells that find each other in the wild will be compatible. In the event that two incompatible cells fuse, the heterokaryon incompatibility response is triggered, nearby septal pores close, and the fusion compartment undergoes **programmed cell death** (Glass and Kaneko 2003). Vegetative incompatibility is thought to prevent parasitism by selfish genotypes such as the spore killer variants in *N. crassa*, *Fusarium moniliforme*, and *Podospora anserina*, which prevent formation of spores without the spore killer gene (Padieu and Bernet 1967; Kathariou and Spieth 1982; Turner and Perkins 1991;

Hammond et al. 2012). In other examples, certain genotypes may "cheat" and use common resources to produce extra spores at the expense of their heterokaryon partners. Additionally, nonnuclear elements such as viruses or parasitic mtDNA can have negative consequences for fusion partners (Caten 1972; Anagnostakis 1982; Debets et al. 1994; Cortesi and Milgroom 2001). Heterokaryon incompatibility seeks to prevent these scenarios by ensuring that only closely related mycelia can fuse into a single cell (Debets and Griffiths 1998). In most species, the incidence of **selfish genotypes** such as spore killer are low in wild populations, despite the potential for competition between nuclei in a common cell, especially during spore production and dissemination into new environments. Various modeling studies have sought to investigate why these genotypes are not more prevalent. These have shown that the threat of negative fusion consequences can result in the rapid development of many heterokaryon incompatibility loci (Muirhead et al. 2002; Czaran et al. 2014). This suggests that in the presence of heterokaryon incompatibility responses, selfish nuclei do not have the opportunity to compete with nuclei of differing genotypes. In this situation, selfish genotypes and nuclei are unable to become prevalent in the population. Multinucleate fungal cells, therefore, have evolved elaborate mechanisms to limit competition between syncytial nuclei.

B. Intra-organism Interactions

Within a single multinucleate cell, different genotypes are potentially in competition with each other, while the combination of different alleles can confer an advantage to the cell as a whole. The individual must maintain a delicate balance between nuclear **competition** and **cooperation** in order to grow, reproduce, and be competitive in the environment (Fig. 2.3). Despite the evolution of heterokaryon incompatibility loci discussed above, cells containing nuclei with variable genotypes are common. For example, in one study, 26 % of wild *F. moniliforme* isolates contained multiple genetically distinct nuclear populations (SIDHU 1983). One possible reason

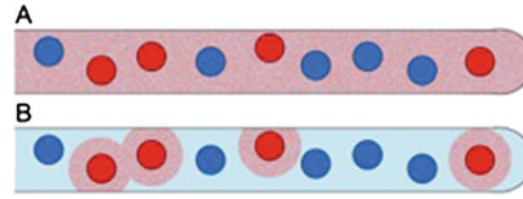

Fig. 2.3 Nuclear competition and cooperation in a syncytium. (**a**) Cooperation—A subset of nuclei that have a different genotype or level of activity (*red*) may share their gene products with all other nuclei in the cytoplasm. (**b**) Competition and autonomy—A subset of genetically different or differentially active nuclei may sequester gene products and limit dissemination to other nuclei in the same cytoplasm

for the prevalence of heterokaryosis is the potential for complementation of different genotypes and the ability to rapidly adapt to different environmental conditions. In the case of the *senescent Neurospora* gene, the wild-type gene product promotes stabilization of the mitochondrial genome. Homokaryons harboring the mutation undergo rapid changes in their mitochondrial genome and do not survive (Navaraj 2000). This phenotype is masked by coexistence with wild-type nuclei in a heterokaryon and therefore is able to persist in wild populations (Fig. 2.3a). Similar senescent phenotypes, some also the result of mitochondrial dysfunction, have been identified in wild isolates of other species as well, indicating that masked deleterious alleles may be a common feature of heterokaryotic fungi (D'Souza et al. 2005). Mutations or ploidy changes during vegetative growth can result in heterokaryosis. Alternatively, it can arise from fusion of cells with matching heterokaryon incompatibility loci but differences elsewhere in the genome. While much of the research on heterokaryons has been completed using auxotrophic markers and was limited to identifying two separate genotypes, it has been demonstrated that *Heterobasidion parviporum* cells can stably contain at least three distinct genotypes, and more examples of such "polykaryotic" cells are sure to follow (James et al. 2008).

The ratio of different genotypes within an individual has been shown to change over time in response to different environmental conditions or developmental stage. These changes offer the potential to rapidly produce a specific

response in the organism, without having to wait for mutation and evolutionary change (Jinks 1952; James et al. 2008). Consistent with these observations, heterokaryosis has been proposed as a mechanism to promote variability and adaptability of fungi in different environmental conditions and stresses.

An additional mechanism for rapid adaptation fungal cells is exemplified in the response of the dimorphic opportunistic pathogen *C. albicans* to clinical treatment using the antifungal **fluconazole**. This organism undergoes changes in **ploidy** resulting in severe genome instability to rapidly generate genome changes in its search for a way to overcome this stressor (Selmecki et al. 2009). Other human pathogens including *Cryptococcus neoformans* and *Candida glabrata* have also been found to rapidly rearrange the genome in response to host immune system stress (Fries and Casadevall 1998; Shin et al. 2007). Though these ploidy alterations have been examined in the context of **pathogenesis**, large-scale genome rearrangements are likely involved in environmental response and evolution in additional fungal species. For example, many industrial *Saccharomyces* strains are polyploid, despite experiments showing that under both stressed and unstressed conditions laboratory strains converge on diploidy (Gerstein et al. 2006; Querol and Bond 2009). Ploidy variation has also been detected in wild isolates of the plant pathogen *Botrytis cinerea*, supporting the hypothesis that this is a widespread fungal adaptation strategy (Büttner et al. 1994).

One of the most rapid strategies for responding to different environmental and developmental needs is alteration of **gene expression**. Large, multinucleate cells are uniquely adapted to exquisitely fine-tune the expression of genes over varying spatial scales. In *N. crassa*, for example, an mRNA profiling study demonstrated considerable differences in the transcripts present in different regions of the same colony, particularly between regions of differing ages (Kasuga and Glass 2008). These transcriptional changes likely promote and respond to functional and physical differences between different areas, as, for example, newer portions of the cell scavenge for nutrients and some older regions develop conidia. In the examination of laboratory-created *N. crassa* strains containing a subset of *his*-nuclei, the amount of enzyme produced was unrelated to the proportion of nuclei within the mycelium, indicating advanced mechanisms for regulating gene expression (Pitchaimani and Maheshwari 2003). Splice variants may also play an important role in gene expression changes and may be more common in fungi than previously appreciated (Grutzmann et al. 2014).

In one example on a smaller spatial scale, only a subset (~12 %) of *A. gossypii* nuclei transcribe the G1 cyclin *CLN3* at any given time, based on a single molecule (sm)FISH study (Lee et al. 2013). This behavior, coupled with membrane-free cytoplasmic compartmentalization strategies, promotes the asynchronous mitotic events characteristic of this fungus (Lee et al. 2013). Mechanisms for generating nuclear transcriptional autonomy in this species when neighboring nuclei are typically only ~5 μm apart remain unclear (Grava et al. 2011).

Another potential method of controlling the expression of different genotypes is **degradation** of a subset of nuclei. In a number of multinucleate species, nuclear degradation has been observed. All nuclei within the fusion compartment during the heterokaryon incompatibility response are degraded, along with everything else within this compartment, to protect the remainder of the cell from potential parasitic elements (Marek et al. 2003). In other species vegetative fusion and nuclear migration can result in degradation of a nucleus in the recipient cell. This was first observed in several basidiomycetes including *S. commune* (Todd and Caylmore 1985), *Coriolus versicolor* (Aylmore and Todd 1984), *Coprinus cinereus* (Bensaude 1918), and *Typhula trifolii* (Noble 1937). Only recently, however, has similar behavior been observed in an ascomycete *F. oxysporum* (Ruiz-Roldan et al. 2010). In contrast to the heterokaryon incompatibility response, this nuclear degradation can occur even between compatible mating partners, and the mechanisms by which nuclei are identified for degradation require further investigation (Ruiz-Roldan et al. 2010).

Nuclei may also be disassembled in order to recycle components. It has been proposed that

an advantage of multinucleate cells is that nuclei can serve as nitrogen and phosphorus storage for later use. During **starvation** in *S. cerevisiae*, nuclear material may be scavenged by a process termed piecemeal microautophagy of the nucleus (Krick et al. 2009). In older regions of *Neurospora* cells, nuclei appear to dissolve, staining poorly with DNA dyes, but evidence for similar degradation of nuclei in subapical hyphal compartments is lacking in other species (Maheshwari 2005). In *P. anserina*, perithecia (fruiting bodies) can only be produced using nutrients scavenged from hyphae, which are degraded upon nutrient exhaustion in order to produce spores (Bernet 1992). In the case of **appressorium** development in *Magnaporthe oryzae*, degradation of nuclei by a separate macroautophagy pathway in the germ tube is required for pathogenesis (Veneault-Fourrey 2006; He et al. 2012). It is thought that the resources in the germ tube are necessary for establishing infection (Solomon et al. 2003). Interestingly, this is not true for all appressorium-forming plant pathogens, as *Colletotrichum gloeosporioides* germ tubes do not undergo autophagy and remain viable after establishment of infection (Nesher et al. 2008). Why cellular degradation is necessary for cellular processes such as perithecium or appressorium formation in some species and not others remains to be investigated.

IV. Open Questions

Though the behavior of nuclei in single cells and the exchange of genetic material between individuals have fascinated mycologists for a century and considerable advances have been made in our understanding of these complex organisms, there still remains a substantial amount of work to do in understanding the biology of these systems. A few topics of current and future interest are presented here, but this is by no means an exhaustive list.

A. Nucleus-Cytoplasm Communication

Many questions still remain in the field with respect to how nuclei organize the cytoplasm around them. Asynchronous nuclear division despite continuous cytoplasm in some species presents fertile ground for the research of membrane-free **cytoplasmic compartmentalization** as well as nuclear intrinsic behaviors. It is likely that an elaborate combination of cytoplasmic organization, genetic differences, epigenetic modification, nuclear import disparities, and other factors is required to produce functionally different regions of complex fungal cells over a vast range of scales from microns to meters and even kilometers in some cases. Nuclei in different areas of the cell must respond to nutrients, light sources, other fungi, and many more stimuli in their local environment while sharing resources and contributing to the success of an extremely large organism. How various conditions are transmitted to specific nuclei, and how those nuclei produce a coordinated or autonomous response, is a very open question.

In some cases, it has been demonstrated that nucleocytoplasmic transport is dependent upon the same processes responsible for large-scale nuclear mobility. For example, in *U. maydis* NPC positioning in the nuclear envelope is mediated by microtubules (Steinberg et al. 2012). It is possible that this increases nuclear sampling of different environments and limits activity of less functional nuclei. Different species employ variable mechanisms for nuclear-cytoplasmic communication. For example, while many multinucleate fungi undergo a completely closed mitosis, *A. nidulans* partially disassembles NPCs during nuclear division (Osmani et al. 2006). This disassembly surely facilitates communication of **mitotic signals** in the parasynchronous mitotic waves observed in this species. Evidence from *A. gossypii* indicates that heterogeneous localization of proteins containing disordered regions is important for generating nuclear asynchrony (Lee et al. 2013). Similar mechanisms have been proposed in various systems for segregating **age-dependent damage**, and uncontrolled aggregation of proteins is linked to a variety of neurodegenerative diseases. The normal functions of aggregation-prone proteins in mammalian neurons have proven difficult to dissect, though oil-and-water-like phase separations of such proteins have been proposed as an organizing principle of cells (Weber and Brangwynne 2012)

{Li:2013fx} {Banjade:2014cz}. The large hyphal networks of filamentous fungal cells require highly advanced cytoplasmic organization and offer an excellent model system in which to study these processes.

Effective cytoplasmic organization likely depends upon regulation of the **nucleocytoplasmic ratio**. The ratio of nuclear to cytoplasmic volume has been demonstrated to be tightly controlled in the size control model *S. pombe* (Schmidt and Schibler 1995; Jovtchev et al. 2006; Jorgensen et al. 2007; Neumann and Nurse 2007). In multinucleate *A. gossypii* cells, mitosis can be inhibited by microtubule-destabilizing drugs, but actin-dependent polarized growth continues. Under these conditions, the nuclear density decreases, and upon release nuclei will progress through the cell cycle more rapidly until they achieve a wild-type nuclear density (Gladfelter et al. 2006). Achievement of an optimal nucleocytoplasmic ratio is an interesting challenge all cells face, and how this ratio is sensed and can regulate cell cycle progression is an area of active research.

In addition to communication with the cytoplasm, nuclei must coordinate their activity with organelles. The endoplasmic reticulum is likely an important hub for cytoplasmic organization; being contiguous with the nuclear envelope, it is in perfect position to mediate interactions between the nucleus and the cytoplasm. Its well-documented interactions with mitochondria in different cell types also render it a prime candidate for a mediator of nucleocytoplasmic and **intra-organelle communication**. Mitochondrial behavior has been shown in *S. cerevisiae* to regulate nuclear activity (Rodley et al. 2012). These interactions are almost certainly essential for adaptation to different metabolic states. Precisely how these communications are mediated and how these signals are coordinated in large cells with multiple nuclei, complex geometries, as they simultaneously experience different environmental conditions are all topics requiring further investigation.

B. Nucleus-Nucleus Communication

In multinucleate cells, nuclei with deleterious alleles must rely on their neighbors for gene products and expression must be regulated so that the appropriate gene dosage is achieved. Changes in expression in response to different environmental cues and developmental needs must be coordinated across nuclei over very different spatial scales. Within syncytia, the mechanisms by which genes are regulated in a **nuclear autonomous** manner and the decision made to share or sequester specific gene products remain unclear (Fig. 2.3). Nuclei within the same cell cooperate to contribute to the maintenance of the larger organism, but are potential units of selection and therefore potentially are in conflict with each other, not unlike how single cells become cancerous in our own bodies. How cells navigate the delicate balance between benefits of **heterokaryosis** and detriments of **nuclear competition** is a fascinating topic, and further research may help us understand this potential driving force of fungal evolution.

Monitoring of the genetic identity of nuclei has most clearly been observed in **dikaryons** of *Basidiomycota*. Limitation of each cell to only two genotypes requires poorly understood monitoring of the state of each nucleus, though there is evidence from *P. anserina* that mating-type-specific presentation of nuclear envelope proteins helps ensure hyphal compartments contain nuclei of different mating types (Zickler et al. 1995). This may be controlled by gene dosage sensing mechanisms related to the mating-type loci, but many questions remain: How is nuclear migration in dikaryon-monokaryon matings inhibited? How is the more genetically different nucleus of the heterokaryon selected to fertilize the monokaryon? After hyphal fusion in *U. maydis*, the host nucleus may be degraded, but how is the "host cell" nucleus specified, and what keeps the donor cell nucleus safe from degradation machinery?

An obvious benefit to the multinucleate strategy is the ability to share resources and products between different nuclei. Though autonomous mitotic and transcriptional behavior in some fungi indicates differences in local concentrations of protein or susceptibility of nuclei to these signals, it is clear that in some situations gene products can be shared between different parts of the cell and different nuclei. In

A. gossypii, when the mitotic cyclin *CLB1/2* was deleted and reintroduced on a plasmid, all nuclei were able to accumulate the protein even if they did not harbor the plasmid (Gladfelter et al. 2006). Using smFISH it was demonstrated that only a subset of nuclei are transcriptionally active for the G1 cyclin *CLN3* in these cells, but sharing of these gene products (at least at the transcript level) increased synchronous mitosis between neighboring nuclei (Lee et al. 2013). Similar phenomena in other filamentous fungi, especially those that undergo asynchronous mitosis, are likely waiting to be observed. The mechanisms controlling nuclear activity to ensure proper stoichiometry of products within the cell, the decision to limit the range of activity of specific gene products to one or only a subset of nuclei, and the maintenance of nuclear activity "identity" as nuclei continuously move throughout these cells are all open questions that apply to many different fungal species and cells in general.

C. Coupling of Cell Growth, Size Control, and Nuclear Division

Though the microtubule cytoskeleton is essential for proper nuclear transport in all fungal systems examined thus far, it is of variable importance in **polarized growth**. In the yeast *S. cerevisiae* and the closely related filamentous *A. gossypii*, microtubules are dispensable for polarized growth, which is instead completely dependent upon actin-dependent transport (Gladfelter et al. 2006). In both *A. nidulans* and *N. crassa*, however, evidence suggests both actin and microtubules are important for regulating polarized growth (Riquelme et al. 2002; Zhang et al. 2011). In *U. maydis*, microtubules are not involved in the growth of the yeast form or germ tube and initiation of pathogenesis, but later stages of invasive hyphal growth require them (Fuchs et al. 2005). This spectrum of microtubule involvement in polarized growth may reflect the development of systems in hyphal cells to link nuclear dynamics with cell growth, but further investigation into the coupling of these systems is needed.

In uninucleate cells, nuclear division is elegantly coordinated with the cytokinetic machinery during cell cycle progression. In multinucleate cells, however, these processes have been uncoupled and alternate mechanisms exist to specify sites for formation of open septal pores, and subsequent signals can trigger complete separation of hyphal compartments, e.g., during heterokaryon incompatibility or environmental stress. Some organisms even are capable of both coupled and uncoupled nucleokinesis and cytokinesis. During germ tube formation in *M. oryzae*, mitosis is linked to septation, but these processes become uncoupled during appressorium formation and subsequent infection (Saunders et al. 2010).

V. Concluding Remarks

Fungal systems have provided excellent models over the past century for understanding the fundamentals of nuclear behavior in all cells. These studies have demonstrated that nuclei are not passive DNA repositories, but highly dynamic organelles that have sophisticated interactions with growth, reproduction, and a variety of other cellular processes. In multinucleate cells, nuclei maintain a delicate balance between competition and cooperation to create elaborate, sometimes gigantic, cellular structures that allow them to survive and thrive in their various environments. Understanding the mechanisms underlying nuclear movement and genetic dynamics within fungal cells has provided insight into analogous processes in our own cells. Studies of mitosis in *S. cerevisiae* paved the way for similar investigations in mammalian cells, and the delicate balance between nuclear competition and cooperation in multinucleate cells can help us understand challenges in the analogous state of multicellularity. Despite the rich history of research into fungal nuclear dynamics, it is clear that we still have much to learn and there are numerous avenues of investigation that have yet to be thoroughly explored.

References

Aanen DK, de Fine Licht HH, Debets AJM et al (2009) High symbiont relatedness stabilizes mutualistic cooperation in fungus-growing termites. Science 326:1103–1106. doi:10.1126/science.1173462

Abadeh A, Lew RR (2013) Mass flow and velocity profiles in *Neurospora* hyphae: partial plug flow dominates intra-hyphal transport. Microbiology 159:2386–2394. doi:10.1099/mic.0.071191-0

Anagnostakis SL (1982) Biological control of chestnut blight. Science 215:466–471

Ananthanarayanan V, Schattat M, Vogel SK et al (2013) Dynein motion switches from diffusive to directed upon cortical anchoring. Cell 153:1526–1536. doi:10.1016/j.cell.2013.05.020

Anderson CA, Eser U, Korndorf T et al (2013) Nuclear repulsion enables division autonomy in a single cytoplasm. Curr Biol 23:1999–2010. doi:10.1016/j.cub.2013.07.076

Araujo-Palomares CL, Castro-Longoria E, Riquelme M (2007) Ontogeny of the Spitzenkörper in germlings of *Neurospora crassa*. Fungal Genet Biol 44:492–503. doi:10.1016/j.fgb.2006.10.004

Aylmore RC, Todd NK (1984) Hyphal fusion in *Coriolus versicolor*. In: Jennings DH, Rayner ADM (eds) The ecology and physiology of the fungal mycelium. Cambridge University Press, Cambridge

Becard G, Pfeffer PE (1993) Status of nuclear division in arbuscular mycorrhizal fungi during in vitro development. Protoplasma 174:62–68

Bensaude M (1918) Recherches sur le cycle évolutif et la sexualité chez les Basidiomycètes. (PhD Thesis). Imprimerie Nemourienne, Nemours, France, Advisor: Henri Bouloy

Berger L, Hyatt AD, Speare R, Longcore JE (2005) Life cycle stages of the amphibian chytrid *Batrachochytrium dendrobatidis*. Dis Aquat Org 68:51–63. doi:10.3354/dao068051

Bernet J (1992) In *Podospora anserina*, protoplasmic incompatibility genes are involved in cell-death control via multiple gene interactions. Heredity 68:79–87

Brangwynne CP, Koenderink GH, MacKintosh FC, Weitz DA (2008) Cytoplasmic diffusion: molecular motors mix it up. J Cell Biol 183:583–587. doi:10.1083/jcb.200806149

Brown AJ, Casselton LA (2001) Mating in mushrooms: increasing the chances but prolonging the affair. Trends Genet 17:393–400

Burgeff H (1924) Untersuchungen über Sexualitat und Parasitismus bei Mucorineen. In: Goebel K (ed) Botanische Abhandlungen. Fischer, Jena, Germany, pp 1–135

Burggraaf JP, Beringer JE (1989) Absence of nuclear DNA synthesis in vesicular-arbuscular mycorrhizal fungi during in vitro development. New Phytol 1:25–33

Buss LW (1982) Somatic cell parasitism and the evolution of somatic tissue compatibility. Proc Natl Acad Sci USA 79:5337–5341

Buss L (1987) The evolution of individuality. Princeton University Press, Princeton, NJ

Büttner P, Koch F, Voigt K et al (1994) Variations in ploidy among isolates of *Botrytis cinerea*: implications for genetic and molecular analyses. Curr Genet 25:445–450

Byers B, Goetsch L (1975) Behavior of spindles and spindle plaques in the cell cycle and conjugation of *Saccharomyces cerevisiae*. J Bacteriol 124:511–523

Casselton LA, Challen MP (2006) The mating type genes of the basidiomycetes. In: Kües U, Fischer R (eds) The mycota. Springer, Berlin, pp 357–374

Castiglioni Pascon R, Pizzirani-Kleiner AA, Miller BL (2001) The *Aspergillus nidulans bncA1* mutation causes defects in the cell division cycle, nuclear movement and developmental morphogenesis. Mol Gen Genet 264:546–554

Caten CE (1972) Vegetative incompatibility and cytoplasmic infection in fungi. J Gen Microbiol 72:221–229

Clutterbuck AJ (1970) Synchronous nuclear division and septation in *Aspergillus nidulans*. J Gen Microbiol 60:133–135

Cortesi P, Milgroom MG (2001) Outcrossing and diversity of vegetative compatibility types in populations of *Eutypa lata* from grapevines. J Plant Pathol 83:79–86

Czaran T, Hoekstra RF, Aanen DK (2014) Selection against somatic parasitism can maintain allorecognition in fungi. Fungal Genet Biol 73:128–137. doi:10.1016/j.fgb.2014.09.010

D'Souza AD, Sultana S, Maheshwari R (2005) Characterization and prevalence of a circular mitochondrial plasmid in senescence-prone isolates of *Neurospora intermedia*. Curr Genet 47:182–193. doi:10.1007/s00294-004-0558-9

Daga RR, Yonetani A, Chang F (2006) Asymmetric microtubule pushing forces in nuclear centering. Curr Biol 16:1544–1550. doi:10.1016/j.cub.2006.06.026

de Queiroz MV, de Azevedo JL (1998) Characterization of an *Aspergillus nidulans* mutant with abnormal distribution of nuclei in hyphae, metulae, phialides and conidia. FEMS Microbiol Lett 166:49–55

Debets A, Griffiths A (1998) Polymorphism of hetgenes prevents resource plundering in *Neurospora crassa*. Mycol Res 102:1343–1349

Debets F, Yang X, Griffiths AJF (1994) Vegetative incompatibility in *Neurospora*: its effect on horizontal transfer of mitochondrial plasmids and senescence in natural populations. Curr Genet 26:113–119. doi:10.1007/BF00313797

Dietrich FS, Voegeli S, Brachat S et al (2004) The *Ashbya gossypii* genome as a tool for mapping the ancient *Saccharomyces cerevisiae* genome. Science 304:304–307. doi:10.1126/science.1095781

Ding R, West RR, Morphew DM et al (1997) The spindle pole body of *Schizosaccharomyces pombe* enters and leaves the nuclear envelope as the cell cycle proceeds. Mol Biol Cell 8:1461–1479

Ellingboe AH, Raper JR (1962) The Buller phenomenon in *Schizophyllum commune*: nuclear selection in fully compatible dikaryotic-homokaryotic matings. Am J Bot 49:454–459

Endow SA, Kang SJ, Satterwhite LL et al (1994) Yeast Kar3 is a minus-end microtubule motor protein that destabilizes microtubules preferentially at the minus ends. EMBO J 13:2708–2713

Fantes P, Nurse P (1977) Control of cell size at division in fission yeast by a growth-modulated size control over nuclear division. Exp Cell Res 107:377–386

Farkasovsky M, Küntzel H (1995) Yeast Num1p associates with the mother cell cortex during S/G2 phase and affects microtubular functions. J Cell Biol 131:1003–1014

Farkasovsky M, Küntzel H (2001) Cortical Num1p interacts with the dynein intermediate chain pac11p and cytoplasmic microtubules in budding yeast. J Cell Biol 152:251–262. doi:10.1083/jcb.152.2.251

Finley KR, Berman J (2005) Microtubules in *Candida albicans* hyphae drive nuclear dynamics and connect cell cycle progression to morphogenesis. Eukaryot Cell 4:1697–1711. doi:10.1128/EC.4.10.1697-1711.2005

Finley KR, Bouchonville KJ, Quick A, Berman J (2008) Dynein-dependent nuclear dynamics affect morphogenesis in *Candida albicans* by means of the Bub2p spindle checkpoint. J Cell Sci 121:724–724. doi:10.1242/jcs.03498

Fischer R, Timberlake WE (1995) *Aspergillus nidulans* Apsa (Anucleate Primary Sterigmata) encodes a coiled-coil protein required for nuclear positioning and completion of asexual development. J Cell Biol 128:485–498

Fries BC, Casadevall A (1998) Serial isolates of *Cryptococcus neoformans* from patients with AIDS differ in virulence for mice. J Infect Dis 178:1761–1766

Fuchs U, Manns I, Steinberg G (2005) Microtubules are dispensable for the initial pathogenic development but required for long-distance hyphal growth in the corn smut fungus *Ustilago maydis*. Mol Biol Cell 16:2746–2758. doi:10.1091/mbc.E05-03-0176

Gerstein AC, Chun HE, Grant A, Otto SP (2006) Genomic convergence toward diploidy in *Saccharomyces cerevisiae*. PLoS Genet 2:1396–1401. doi:10.1371/journal

Gibeaux R, Knop M (2014) When yeast cells meet, karyogamy! Nucleus 4:182–188. doi:10.4161/nucl.25021

Gibeaux R, Politi AZ, Nedelec F et al (2013) Spindle pole body-anchored Kar3 drives the nucleus along microtubules from another nucleus in preparation for nuclear fusion during yeast karyogamy. Genes Dev 27:335–349. doi:10.1101/gad.206318.112

Gladfelter AS, Hungerbuehler AK, Philippsen P (2006) Asynchronous nuclear division cycles in multinucleated cells. J Cell Biol 172:347–362. doi:10.1083/jcb.2050703

Glass NL, Kaneko I (2003) Fatal attraction: nonself recognition and heterokaryon incompatibility in filamentous fungi. Eukaryot Cell 2:1–8. doi:10.1128/EC.2.1.1-8.2003

Glass NL, Kuldau GA (1992) Mating type and vegetative incompatibility in filamentous ascomycetes. Annu Rev Phytopathol 30:201–224. doi:10.1146/annurev.py.30.090192.001221

Goldstein RE, Tuval I, van de Meent J-W (2008) From the cover: microfluidics of cytoplasmic streaming and its implications for intracellular transport. Proc Natl Acad Sci USA 105:3663–3667. doi:10.1073/pnas.0707223105

Grava S, Philippsen P (2010) Dynamics of multiple nuclei in *Ashbya gossypii* hyphae depend on control of cytoplasmic microtubules length by Bik1, Kip2, Kip3, and not on a capture/shrinkage mechanism. Mol Biol Cell 21:3680–3692

Grava S, Keller M, Voegeli S et al (2011) Clustering of nuclei in multinucleated hyphae is prevented by dynein-driven bidirectional nuclear movements and microtubule growth control in *Ashbya gossypii*. Eukaryot Cell 10:902–915. doi:10.1128/EC.05095-11

Grutzmann K, Szafranski K, Pohl M et al (2014) Fungal alternative splicing is associated with multicellular complexity and virulence: a genome-wide multispecies study. DNA Res 21:27–39. doi:10.1093/dnares/dst038

Hammond TM, Rehard DG, Xiao H, Shiu PKT (2012) Molecular dissection of *Neurospora* Spore killer meiotic drive elements. Proc Natl Acad Sci USA 109:12093–12098. doi:10.1073/pnas.1203267109

He M, Kershaw MJ, Soanes DM et al (2012) Infection-associated nuclear degeneration in the rice blast fungus *Magnaporthe oryzae* requires non-selective macro-autophagy. PLoS ONE 7, e33270. doi:10.1371/journal.pone.0033270.s009

Heath IB (1980) Variant mitoses in lower eukaryotes: indicators of the evolution of mitosis. Int Rev Cytol 64:1–80

Heaton LLM, Lopez E, Maini PK et al (2010) Growth-induced mass flows in fungal networks. Proc R Soc B Biol Sci 277:3265–3274. doi:10.1093/jxb/38.5.889

Helfer H, Gladfelter AS (2006) AgSwe1p regulates mitosis in response to morphogenesis and nutrients in multinucleated *Ashbya gossypii* cells. Mol Biol Cell 17:4494–4512. doi:10.1091/mbc.E06

Hijri M, Hosny M, van Tuinen D, Dulieu H (1999) Intraspecific ITS polymorphism in *Scutellospora castanea* (Glomales, Zygomycota) is structured within multinucleate spores. Fungal Genet Biol 26:141–151

Hong CI, Zamborszky J, Baek M et al (2014) Circadian rhythms synchronize mitosis in *Neurospora*

crassa. Proc Natl Acad Sci USA 111:1397–1402. doi:10.1073/pnas.1319399111

Horio T, Oakley BR (2005) The role of microtubules in rapid hyphal tip growth of *Aspergillus nidulans*. Mol Biol Cell 16:918–926. doi:10.1091/mbc.E04-09-0798

Inoue S, Turgeon BG, Yoder OC, Aist JR (1998) Role of fungal dynein in hyphal growth, microtubule organization, spindle pole body motility and nuclear migration. J Cell Sci 111:1555–1566

James TY, Stenlid J, Olson Å, Johannesson H (2008) Evolutionary significance of imbalanced nuclear ratios within heterokaryons of the basidiomycete fungus *Heterobasidion parviporum*. Evolution 62:2279–2296. doi:10.1111/j.1558-5646.2008.00462.x

Jedd G, Chua NH (2000) A new self-assembled peroxisomal vesicle required for efficient resealing of the plasma membrane. Nat Cell Biol 2:226–231. doi:10.1038/35008652

Jinks JL (1952) Heterokaryosis - a system of adaptation in wild fungi. Proc R Soc Lond B Biol Sci 140:83–99

Johnston GC, Pringle JR, Hartwell LH (1977) Coordination of growth with cell division in the yeast *Saccharomyces cerevisiae*. Exp Cell Res 105:79–98

Jorgensen P, Edgington NP, Schneider BL et al (2007) The size of the nucleus increases as yeast cells grow. Mol Biol Cell 18:3523–3532. doi:10.1091/mbc.E06-10-0973

Jovtchev G, Schubert V, Meister A et al (2006) Nuclear DNA content and nuclear and cell volume are positively correlated in angiosperms. Cytogenet Genome Res 114:77–82. doi:10.1159/000091932

Kasuga T, Glass NL (2008) Dissecting colony development of *Neurospora crassa* using mRNA profiling and comparative genomics approaches. Eukaryot Cell 7:1549–1564. doi:10.1128/EC.00195-08

Kathariou S, Spieth PT (1982) Spore killer polymorphism in *Fusarium moniliforme*. Genetics 102:19–24

Kellner M, Burmester A, Wöstemeyer A, Wöstemeyer J (1993) Transfer of genetic information from the mycoparasite *Parasitella parasitica* to its host *Absidia glauca*. Curr Genet 23:334–337

Kemper M, Mohlzahn L, Lickfeld M et al (2011) A Bnr-like formin links actin to the spindle pole body during sporulation in the filamentous fungus *Ashbya gossypii*. Mol Microbiol 80:1276–1295. doi:10.1111/j.1365-2958.2011.07644.x

King SB, Alexander LJ (1969) Nuclear behavior septation and hyphal growth of *Alternaria solani*. Am J Bot 56:249–253

Kohli M, Galati V, Boudier K et al (2008) Growth-speed-correlated localization of exocyst and polarisome components in growth zones of *Ashbya gossypii* hyphal tips. J Cell Sci 121:3878–3889. doi:10.1242/jcs.033852

Krick R, Muhe Y, Prick T et al (2009) Piecemeal microautophagy of the nucleus: Genetic and morphological traits. Autophagy 5:270–272

Lang C, Grava S, van den Hoorn T et al (2010) Mobility, microtubule nucleation and structure of microtubule-organizing centers in multinucleated hyphae of *Ashbya gossypii*. Mol Biol Cell 21:18–28. doi:10.1091/mbc.E09-01-0063

Lee SB, Taylor JW (1993) Uniparental inheritance and replacement of mitochondrial DNA in *Neurospora tetrasperma*. Genetics 134:1063–1075

Lee C, Zhang H, Baker AE et al (2013) Protein aggregation behavior regulates cyclin transcript localization and cell-cycle control. Dev Cell 25:572–584. doi:10.1016/j.devcel.2013.05.007

Letcher PM, Powell MJ (2014) Hypothesized evolutionary trends in zoospore ultrastructural characters in Chytridiales (Chytridiomycota). Mycologia 106:379–396. doi:10.3852/13-219

Letcher PM, Vélez CG, Barrantes ME et al (2008) Ultrastructural and molecular analyses of Rhizophydiales (Chytridiomycota) isolates from North America and Argentina. Mycol Res 112:759–782. doi:10.1016/j.mycres.2008.01.025

Lew RR (2005) Mass flow and pressure-driven hyphal extension in *Neurospora crassa*. Microbiology 151:2685–2692. doi:10.1099/mic.0.27947-0

Maheshwari R (2005) Nuclear behavior in fungal hyphae. FEMS Microbiol Lett 249:7–14. doi:10.1016/j.femsle.2005.06.031

Marcinko-Kuehn MM, Yang XX, Debets FF et al (1994) A kalilo-like linear plasmid in Louisiana field isolates of the pseudohomothallic fungus *Neurospora tetrasperma*. Curr Genet 26:336–343. doi:10.1007/BF00310498

Marek SM, Wu J, Louise Glass N et al (2003) Nuclear DNA degradation during heterokaryon incompatibility in *Neurospora crassa*. Fungal Genet Biol 40:126–137. doi:10.1016/S1087-1845(03)00086-0

Maruyama J-I, Nakajima H, Kitamoto K (2003) Novel role of cytoplasmic dynein motor in maintenance of the nuclear number in conidia through organized conidiation in *Aspergillus oryzae*. Biochem Biophys Res Commun 307:900–906. doi:10.1016/S0006-291X(03)01267-1

Melloy P, Shen S, White E et al (2007) Nuclear fusion during yeast mating occurs by a three-step pathway. J Cell Biol 179:659–670. doi:10.1083/jcb.200706151

Meluh PB, Rose MD (1990) KAR3, a kinesin-related gene required for yeast nuclear fusion. Cell 60:1029–1041

Miller RK, Rose MD (1998) Kar9p is a novel cortical protein required for cytoplasmic microtubule orientation in yeast. J Cell Biol 140:377–390

Morris NR, Xiang X, Beckwith SM (1995) Nuclear migration advances in fungi. Trends Cell Biol 5:278–282

Muirhead CA, Glass NL, Slatkin M (2002) Multilocus self-recognition systems in fungi as a cause of trans-species polymorphism. Genetics 161:633–641

Navaraj A (2000) Senescent: a new *Neurospora crassa* nuclear gene mutant derived from nature exhibits mitochondrial abnormalities and a "death" phenotype. Fungal Genet Biol 29:165–173. doi:10.1006/fgbi.2000.1193

Nesher I, Barhoom S, Sharon A (2008) Cell cycle and cell death are not necessary for appressorium formation and plant infection in the fungal plant pathogen *Colletotrichum gloeosporioides*. BMC Biol 6:9. doi:10.1186/1741-7007-6-9

Neumann FR, Nurse P (2007) Nuclear size control in fission yeast. J Cell Biol 179:593–600. doi:10.1083/jcb.200708054

Niederpruem DJ (1980) Direct studies of dikaryotization in *Schizophyllum commune*. I. Live intercellular nuclear migration patterns. Arch Microbiol 128:162–171

Noble M (1937) The morphology and cytology of *Typhula trifolii* Rostr. Ann Bot 1:67–98

Nobre T, Koopmanschap B, Baars JJ et al (2014) The scope for nuclear selection within Termitomyces fungi associated with fungus-growing termites is limited. BMC Evol Biol 14:1–12. doi:10.1186/1471-2148-14-121

Nygaard OF, Güttes S, Rusch HP (1960) Nucleic acid metabolism in a slime mold with synchronous mitosis. Biochim Biophys Acta 38:298–306. doi:10.1016/0006-3002(60)91245-2

Oakley BR, Morris NR (1980) Nuclear movement is beta-tubulin-dependent in *Aspergillus nidulans*. Cell 19:255–262

Osmani AH, Davies J, Liu H-L et al (2006) Systematic deletion and mitotic localization of the nuclear pore complex proteins of *Aspergillus nidulans*. Mol Biol Cell 17:4946–4961. doi:10.1091/mbc.E06-07-0657

Padieu E, Bernet J (1967) Mode of action of the genes responsible for abortion of certain products of meiosis in the ascomycete, *Podospora anserina*. C R Acad Sci Hebd Seances Acad Sci D 264:2300–2303

Paoletti A, Chang F (2000) Analysis of Mid1p, a protein required for placement of the cell division site, reveals a link between the nucleus and the cell surface in fission yeast. Mol Biol Cell 11:2757–2773

Pitchaimani K, Maheshwari R (2003) Extreme nuclear disproportion and constancy of enzyme activity in a heterokaryon of *Neurospora crassa*. J Genet 82:1–6

Plamann M, Minke PF, Tinsley JH, Bruno KS (1994) Cytoplasmic dynein and actin-related protein Arp1 are required for normal nuclear distribution in filamentous fungi. J Cell Biol 127:139–149

Querol A, Bond U (2009) The complex and dynamic genomes of industrial yeasts. FEMS Microbiol Lett 293:1–10. doi:10.1111/j.1574-6968.2008.01480.x

Ramos-Garcia SL, Roberson RW, Freitag M et al (2009) Cytoplasmic bulk flow propels nuclei in mature hyphae of *Neurospora crassa*. Eukaryot Cell 8:1880–1890. doi:10.1128/EC.00062-09

Raper JR (1966) Genetics of sexuality in higher fungi. Ronald Press, New York, NY

Raper CA (1985) B-Mating-type genes influence survival of nuclei separated from heterokaryons of *Schizophyllum*. Exp Mycol 9:149–160

Requena N, Alberti-Segui C, Winzenburg E et al (2001) Genetic evidence for a microtubule-destabilizing effect of conventional kinesin and analysis of its consequences for the control of nuclear distribution in *Aspergillus nidulans*. Mol Microbiol 42:121–132

Richard F, Glass NL, Pringle A (2012) Cooperation among germinating spores facilitates the growth of the fungus, *Neurospora crassa*. Biol Lett 8:419–422. doi:10.1098/rsbl.2011.1141

Riquelme M, Roberson RW, McDaniel DP, Bartnicki-Garcia S (2002) The effects of ropy-1 mutation on cytoplasmic organization and intracellular motility in mature hyphae of *Neurospora crassa*. Fungal Genet Biol 37:171–179

Roca MG, Kuo H-C, Lichius A et al (2010) Nuclear dynamics, mitosis, and the cytoskeleton during the early stages of colony initiation in *Neurospora crassa*. Eukaryot Cell 9:1171–1183. doi:10.1128/EC.00329-09

Rodley CDM, Grand RS, Gehlen LR et al (2012) Mitochondrial-nuclear dna interactions contribute to the regulation of nuclear transcript levels as part of the inter-organelle communication system. PLoS ONE 7, e30943. doi:10.1371/journal.pone.0030943.s023

Roper M, Simonin A, Hickey PC et al (2013) Nuclear dynamics in a fungal chimera. Proc Natl Acad Sci USA 110:12875–12880. doi:10.1073/pnas.1220842110

Rose MD, Fink GR (1987) KAR1, a gene required for function of both intranuclear and extranuclear microtubules in yeast. Cell 48:1047–1060

Ross IK (1976) Nuclear migration rates in *Coprinus congregatus*: a new record? Mycologia 68:418–422

Ruiz-Roldan MC, Kohli M, Roncero MIG et al (2010) Nuclear dynamics during germination, conidiation, and hyphal fusion of *Fusarium oxysporum*. Eukaryot Cell 9:1216–1224. doi:10.1128/EC.00040-10

Ruiz-Trillo I, Burger G, Holland PWH et al (2007) The origins of multicellularity: a multi-taxon genome initiative. Trends Genet 23:113–118. doi:10.1016/j.tig.2007.01.005

Ryan FJ, Beadle GW, Tatum EL (1943) The tube method of measuring the growth rate of *Neurospora*. Am J Bot 30:784–799

Samils N, Oliva J, Johannesson H (2014) Nuclear interactions in a heterokaryon: insight from the model *Neurospora tetrasperma*. Proc R Soc B Biol Sci 281:20140084–20140084. doi:10.1371/journal.pgen.1002820

Saunders DG, Dagdas YF, Talbot NJ (2010) Spatial uncoupling of mitosis and cytokinesis during appressorium-mediated plant infection by the

rice blast fungus *Magnaporthe oryzae*. Plant Cell 22:2417–2428. doi:10.1105/tpc.110.074492

Schmidt EE, Schibler U (1995) Cell size regulation, a mechanism that controls cellular RNA accumulation: consequences on regulation of the ubiquitous transcription factors Oct1 and NF-Y and the liver-enriched transcription factor DBP. J Cell Biol 128:467–483

Schultze K, Schimek C, Wöstemeyer J, Burmester A (2005) Sexuality and parasitism share common regulatory pathways in the fungus *Parasitella parasitica*. Gene 348:33–44. doi:10.1016/j.gene.2005.01.007

Schuurs TA, Dalstra HJ, Scheer JM, Wessels JG (1998) Positioning of nuclei in the secondary mycelium of *Schizophyllum commune* in relation to differential gene expression. Fungal Genet Biol 23:150–161

Selmecki AM, Dulmage K, Cowen LE et al (2009) Acquisition of aneuploidy provides increased fitness during the evolution of antifungal drug resistance. PLoS Genet 5, e1000705. doi:10.1371/journal.pgen.1000705.s009

Shatkin AJ, Tatum EL (1959) Electron microscopy of *Neurospora crassa* mycelia. J Biophys Biochem Cytol 6:423–426

Shin JH, Chae MJ, Song JW et al (2007) Changes in karyotype and azole susceptibility of sequential bloodstream isolates from patients with *Candida glabrata* candidemia. J Clin Microbiol 45:2385–2391. doi:10.1128/JCM.00381-07

Sidhu GS (1983) Genetics of *Gibberella fujikuroi*.3. Significance of heterokaryosis in naturally-occurring corn isolates. Can J Bot-Rev Can Bot 61:3320–3325

Solomon PS, Tan K, Oliver RP (2003) The nutrient supply of pathogenic fungi; a fertile field for study. Mol Plant Pathol 4:203–210

Sparrow FK (1935) Recent contributions to our knowledge of the aquatic phycomycetes. Biol Rev 10:152–186

Steinberg G, Schuster M, Theisen U et al (2012) Motor-driven motility of fungal nuclear pores organizes chromosomes and fosters nucleocytoplasmic transport. J Cell Biol 198:343–355. doi:10.1083/jcb.201201087

Straube A, Weber I, Steinberg G (2005) A novel mechanism of nuclear envelope break-down in a fungus: nuclear migration strips off the envelope. EMBO J 24:1674–1685. doi:10.1038/sj.emboj.7600644

Suelmann R, Sievers N, Fischer R (1997) Nuclear traffic in fungal hyphae: in vivo study of nuclear migration and positioning in *Aspergillus nidulans*. Mol Microbiol 25:757–769

Swiezynski KM, Day PR (1960) Migration of nuclei in *Coprinus lagopus*. Genet Res 1:129–139

ten Hoopen R, Cepeda-Garcia C, Fernandez-Arruti R et al (2012) Mechanism for astral microtubule capture by cortical bud6p priming spindle polarity in *S. cerevisiae*. Curr Biol 22:1075–1083. doi:10.1016/j.cub.2012.04.059

Tenney K, Hunt I, Sweigard J et al (2000) hex-1, a gene unique to filamentous fungi, encodes the major protein of the Woronin body and functions as a plug for septal pores. Fungal Genet Biol 31:205–217. doi:10.1006/fgbi.2000.1230

Tinsley JH, Minke PF, Bruno KS, Plamann M (1996) p150 (Glued), the largest subunit of the dynactin complex, is nonessential in *Neurospora* but required for nuclear distribution. Mol Biol Cell 7:731–742

Todd NK, Caylmore RC (1985) Cytology of hyphal interactions and reactions in *Schizophyllum commune*. In: Developmental biology of higher fungi

Tran PT, Marsh L, Doye V et al (2001) A mechanism for nuclear positioning in fission yeast based on microtubule pushing. J Cell Biol 153:397–411

Turner BC, Perkins DD (1991) Meiotic drive in *Neurospora* and other fungi. Am Nat 137:416–429

Unger MW, Hartwell LH (1976) Control of cell division in *Saccharomyces cerevisiae* by methionyl-tRNA. Proc Natl Acad Sci USA 73:1664–1668

Veneault-Fourrey C (2006) Autophagic fungal cell death is necessary for infection by the rice blast fungus. Science 312:580–583. doi:10.1126/science.1124550

Vogel SK, Pavin N, Maghelli N et al (2009) Self-organization of dynein motors generates meiotic nuclear oscillations. PLoS Biol 7, e87. doi:10.1371/journal.pbio.1000087.sv007

Weber SC, Brangwynne CP (2012) Getting RNA and protein in phase. Cell 149:1188–1191. doi:10.1016/j.cell.2012.05.022

Wendland J, Walther A (2005) *Ashbya gossypii*: a model for fungal developmental biology. Nat Rev Microbiol 3:421–429. doi:10.1038/nrmicro1148

Wu Q, Sandrock TM, Turgeon BG et al (1998) A fungal kinesin required for organelle motility, hyphal growth, and morphogenesis. Mol Biol Cell 9:89–101

Zamborszky J, Csikász-Nagy A, Hong CI (2014) *Neurospora crassa* as a model organism to explore the interconnected network of the cell cycle and the circadian clock. Fungal Genet Biol 71:52–57. doi:10.1016/j.fgb.2014.08.014

Zhang J, Li S, Fischer R, Xiang X (2003) Accumulation of cytoplasmic dynein and dynactin at microtubule plus ends in *Aspergillus nidulans* is kinesin dependent. Mol Biol Cell 14:1479–1488. doi:10.1091/mbc.E02-08-0516

Zhang J, Tan K, Wu X et al (2011) *Aspergillus* myosin-V supports polarized growth in the absence of microtubule-based transport. PLoS ONE 6, e28575. doi:10.1371/journal.pone.0028575

Zickler D, Arnaise S, Coppin E et al (1995) Altered mating-type identity in the fungus *Podospora anserina* leads to selfish nuclei, uniparental progeny, and haploid meiosis. Genetics 140:493–502

http://www.springer.com/978-3-319-25842-3

Growth, Differentiation and Sexuality
Wendland, J. (Ed.)
2016, XIX, 521 p. 97 illus., 35 illus. in color., Hardcover
ISBN: 978-3-319-25842-3