Cell and nuclear recognition mechanisms mediated by mating type in filamentous ascomycetes

Patrick KT Shiu* and N Louise Glass†

Sexual development in filamentous ascomycetes requires mating-type genes to mediate recognition of compatible cell and nuclear types. Characterization of mating-type genes from various fungi shows that they primarily encode transcriptional regulators. Recent studies on mating-type-specific pheromones and internuclear recognition have shed light on how mating-type genes specify mating and nuclear identity in filamentous ascomycetes.

Addresses
*Department of Botany and The Biotechnology Laboratory, University of British Columbia, Vancouver, BC V6T 1Z3, Canada; e-mail: ktshiu@interchange.ubc.ca
*†Department of Plant and Microbial Biology, University of California, Berkeley, CA 94720-3102, USA
†e-mail: lglass@nature.berkeley.edu

Current Opinion in Microbiology 2000, **3**:183–188

1369-5274/00/$ – see front matter

Abbreviations
HMG high mobility group
MAP mitogen-activated protein

Introduction

A common feature of sexual morphology unites the diverse members of the Ascomycotina: their sexual progeny (ascospores) are enclosed in a sac (ascus). Different species within the ascomycetes can exhibit heterothallic, homothallic or pseudohomothallic breeding systems. In the 1920s, it was determined that mating type was conferred by alternative alleles present at the mating type locus (*mat*) in several heterothallic species of *Neurospora* and *Ascobolus* [1,2]. The allele type at the *mat* locus determines sexual identity (and compatibility) of an individual. Most heterothallic species of ascomycetes contain a single mating-type locus with two alternative alleles; multiple mating types have been reported only in one species [3].

In heterothallic and some pseudohomothallic species, fusion of opposite mating-type reproductive structures initiates sexual reproduction (Figure 1). Nuclei of the opposite mating type subsequently proliferate within the developing fruit body (perithecium) [4]. Nuclear fusion occurs in the ascus mother cell and only between nuclei of opposite mating-type. Meiosis and ascosporogenesis immediately follow karyogamy. Thus, nuclear fusion is temporally and spatially separated from mating. This aspect is in contrast to *Saccharomyces cerevisiae*, where mating is immediately followed by karyogamy to give stable diploids. How the synchronous proliferation of opposite mating-type nuclei is regulated and the basis of the internuclear recognition system that pair opposite mating-type nuclei prior to karyogamy are two enigmas regarding sexual reproduction in filamentous ascomycetes and are discussed in this review.

Mating-type genes

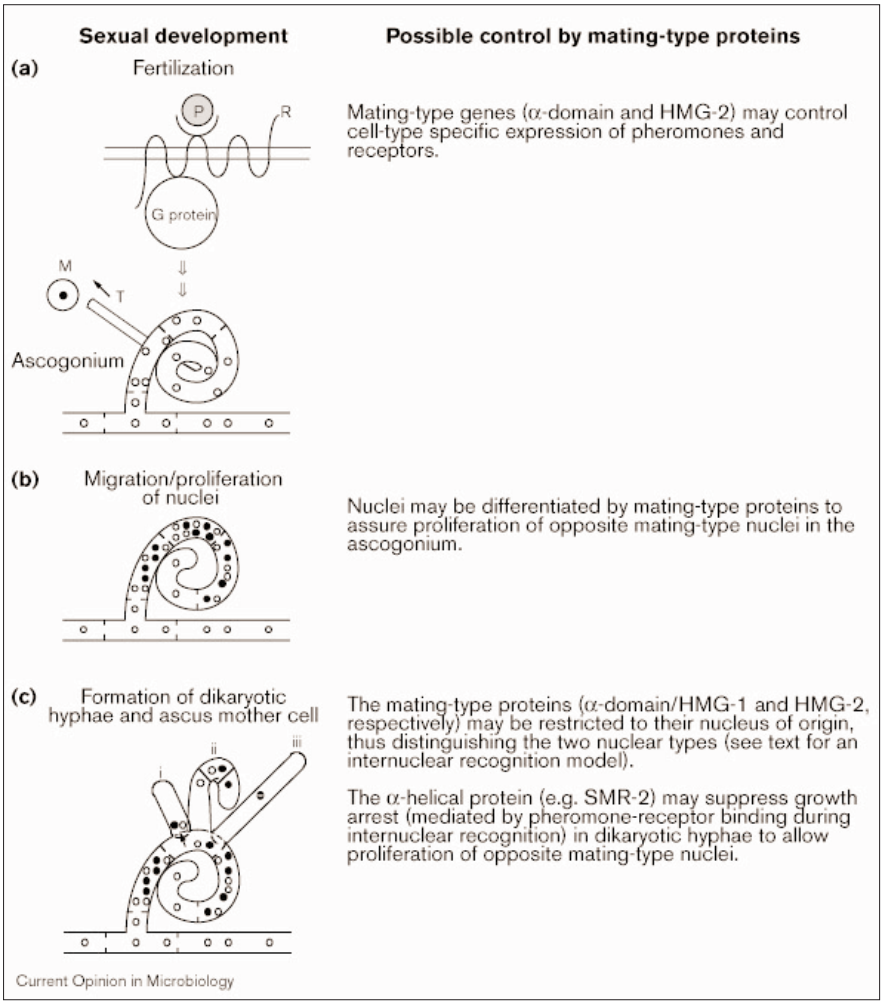
Common mating-type genes

The *mat* locus has been characterized from a number of heterothallic filamentous ascomycetes, including *N. crassa* [5–7], *Podospora anserina* [8,9], *Cochliobolus heterostrophus* [10], *Pyrenopeziza brassicae* [11], *Magnaporthe grisea* [12] and *Mycosphaerella graminicola* (C Waalwijk, personal communication). In all cases, opposite mating-type function is conferred by dissimilar sequences, known as idiomorphs, that occupy the *mat* locus in different mating-type strains [13]. Each idiomorph encodes one or more proteins that have similarity to transcriptional regulators [14].

In *S. cerevisiae*, the *MAT* ***a*** locus encodes a homeodomain protein (Mat**a**1p) and the *MAT* α locus encodes a transcriptional regulator (Matα1p) and a second homeodomain protein (Matα2p) [15,16]. The *mat* encoded proteins regulate haploid-specific genes required for cell–cell recognition and fusion (including cell-type-specific pheromones and receptors) and diploid-specific genes required for meiosis and sporulation [16,17]. In heterothallic filamentous ascomycetes (such as *N. crassa* and *P. anserina*), the *mat A* (or *mat–*) idiomorph encodes three proteins [14] (see Table 1). The first (MAT A-1; FMR1) displays a region of similarity to Matα1p of *S. cerevisiae* (α-domain protein), the second contains an acidic amphipathic α-helix and appears to be unique in filamentous ascomycetes (MAT A-2, SMR1; hereafter referred to as α-helical proteins) and the third is an HMG (high mobility group) protein (MAT A-3, SMR2, hereafter referred to as HMG-1). The *mat a* (or *mat+*) idiomorph also encodes an HMG protein (MAT a-1, FPR1; hereafter referred to as HMG-2). In other filamentous ascomycetes such as *C. heterostrophus*, the *mat* idiomorphs encode only one gene product each: the *MAT-1* idiomorph encodes an α-domain protein, while *MAT-2* encodes an HMG-2 protein [10].

The α-domain genes of *N. crassa*, *P. anserina* and *C. heterostrophus* have been shown to be both necessary and sufficient to confer mating specificity [5,8,10]. The mechanism of α-domain protein function is conserved and interchangeable among different ascomycete species [14,18,19]. The α-helical genes and HMG-1 genes of *N. crassa* and *P. anserina* are not required for mating, but are required for sexual development and apparently are not interchangeable among species [18,19]. The HMG-2 genes confer mating specificity for the alternative mating type [8,10,20] and are also interchangeable among

Figure 1



Sexual development and its regulation by mating-type genes in filamentous ascomycetes. Figures of sexual development are shown on the left and control by mating-type proteins is described on the right. **(a)** Fertilization. Pheromone (P) binding to receptor (R) initiates a signal, leading to growth of trichogyne (T) towards a male cell (M) and cell fusion. **(b)** Migration/proliferation of nuclei. The male nucleus migrates into the ascogonium and proliferates in conjunction with the nuclei donated by the female parent. **(c)** Formation of dikaryotic hyphae and ascus mother cell. (i) Opposite mating-type nuclei pair and migrate into dikaryotic hyphae. (ii) Opposite mating-type nuclei undergo a nuclear division and two nuclei are compartmentalized. (iii) Karyogamy occurs between opposite mating-type nuclei in ascus mother cell. Meiosis immediately follows karyogamy.

different species [18,14,19]. *N. crassa* MAT a-1 has been shown to bind DNA *in vitro* to a sequence in common with binding sites of HMG proteins from non-fungal species [21].

In the *mat A*-type idiomorph from *Pyrenopeziza brassicae*, a metallothionein-like protein is encoded by the mating-type locus in addition to an α-domain and a HMG-1 protein [11]; an α-helical protein homolog was not found (see Table 1). It is not clear how a metal-sequestering protein may be involved in mating, but it was suggested that the metallothionein could be an environmental sensor for the concentration of plant metal ions and could subsequently trigger sexual morphogenesis.

Mating-type genes in homothallic and asexual species

Homologs of mating-type genes from heterothallic species have been found in both homothallic and asexual species of filamentous fungi [17,22]. The mating-type locus from the homothallic species, *Sordaria macrospora*, is similar to that of *N. crassa* and *P. anserina*, except that the *mat A* and *mat a* sequences are linked [19] (see Table 1). Conservation of *S. macrospora* mating-type function was demonstrated by the fact that the *Smt* locus conferred self-mating when introduced into *P. anserina* [19].

Similarly, the conversion of a *C. heterostrophus MAT*-deletion strain into a self-fertile strain was obtained by the introduction of a naturally fused *MAT-1/MAT-2* (α-domain /HMG-2) gene from the homothallic species *C. luttrellii* [23••]. The analysis of recombination points in the sequences of the *MAT-1/MAT-2* fusion indicated that a homothallic species might arise from an uneven crossover event around the *mat* locus, resulting in either fusion or linkage of the mating-type idiomorphs. These data give support to the speculation that heterothallic fungi are ancestral to homothallic species and that a single recombination event between the two mating-type idiomorphs can lead to a transition in reproductive behavior [23••]. The above results with *S. macrospora* and *C. luttrellii* suggest that functional *mat* sequences are required for sexual reproduction in homothallic species, even though a mating event may not occur. Apparently, nuclei in reproductive hyphae are differentially recognized even in homothallic

Table 1

Mating-type proteins encoded by filamentous ascomycetes.

Ascomycetes	Mating-type locus	Type of proteins encoded by the *mat* locus				
		α-domain*	α-helical	HMG-1	HMG-2	Other
N. crassa	*mat A*	MAT A-1	MAT A-2	MAT A-3	–	–
	mat a	–	–	–	MAT a-1	–
P. anserina	*mat–*	FMR1	SMR1	SMR2	–	–
	mat+	–	–	–	FPR1	–
C. heterostrophus	*MAT-1*	MAT-1	–	–	–	–
	MAT-2	–	–	–	MAT-2	–
P. brassicae	*MAT 1-2*	PAD1	–	PHB2	–	PMT1†
	MAT 1-1	–	–	–	PHB1	–
S. macrospora (homothallic)	*Smt*	SMTA-1	SMTA-2	SMTA-3‡	SMTa-1	–

*Shows a region of similarity to Matα1p of *S. cerevisiae*. †PMT1 is a metallothionein-like protein. ‡*smtA-3* is a chimeric composed of *mat A* and *mat a*-like sequences. SMTA-3 has amino-terminal similarity with MAT A-3 but lacks a HMG domain.

species; *mat* function may be required for this process [24]. It is not clear how nuclear differentiation can be accomplished in a population of genetically identical nuclei, but mechanisms involving differential expression of mating-type genes and/or imprinting through male/female origin have been suggested [14].

Sexual reproduction is absent or infrequent in a large number of ascomycetes species. Although the transformation of an asexual species into a sexual one has not been achieved, *MAT-2*-like (HMG-2) genes have been isolated from several asexual *Cochliobolus* spp. (and related loculoascomycete genera) [25–27]. The introduction of *C. heterostrophus MAT* genes into the asexual species, *Bipolaris sacchari*, did not convert it to a sexual species, but such transformants initiated sexual development in crosses with *C. heterostrophus*. The asexual nature of *B. sacchari* is, therefore, presumably the result of mutations in genes other than those in the *mat* idiomorphs [27]. The presence of a mating-type locus similar to that of *S. cerevisiae* has also been reported in an asexual fungus that is a human pathogen, *Candida albicans* [28•].

Unlike yeast [29], mating type in filamentous ascomycetes is believed to be stable. However, evidence for the unidirectional switching of mating type has been reported in a few filamentous ascomycetes [30–32]. For example, in asci of *Chromocrea spinulosa*, four progeny are self-fertile and four are self-sterile. The self-fertile isolates always produce four self-sterile and four self-fertile progeny; the self-sterile isolates will cross with self-fertile isolates. The self-fertile progeny contain sequences for *MAT-1* (α-domain) and *MAT-2* (HMG-2) homologs, but the self-sterile progeny contain sequences only for MAT-1 protein (G Turgeon, personal communication). How a single culture produces progeny with different *mat* gene organization is unclear, but a programmed genomic rearrangement comparable to mating-type switching in yeast is possible.

Mating recognition and conjugation

The mating identity of *S. cerevisiae* cells is determined by a pheromone and receptor system; a cell of a particular mating-type expresses only one pheromone and a receptor for the pheromone produced by the opposite mating-type [33]. Binding of the pheromone to its cognate receptor facilitates mating by inducing a signal transduction event that leads to the transient arrest of the cell cycle and the induction of conjugation-specific genes. In filamentous ascomycetes, the attraction of female trichogynes toward male spermatia hinted at the existence of diffusible pheromones [34,35]. Pheromone precursor genes have been subsequently isolated from *Cryphonectria parasitica* [36,37•], *M. grisea* [38] and *N. crassa* (D Ebbole and D Bell-Pedersen, personal communication). The putative pheromones MF1/1 (of *C. parasitica*), MF2-1 (of *M. grisea*) and MFA (of *N. crassa*) contain features similar to *S. cerevisiae* α-factor, such as a kex-2 cleavage site [39]. The MF2/1, MF2/2 (of *C. parasitica*), MF1-1 (of *M. grisea*) and MFa (of *N. crassa*) putative pheromones have a CAAX prenylation motif found in many other fungal lipopeptide sex pheromones, such as **a**-factor from *S. cerevisiae* [39]. The pheromone precursor genes in these three species are present in all cell types but are expressed in a mating-type-specific manner. The *N. crassa* pheromone precursor genes are regulated by mating type, nutrition, macroconidiation and the circadian clock (D Ebbole and D Bell-Pedersen, personal communication).

In *S. cerevisiae*, pheromone binding allows the receptor to associate with a heterotrimeric G protein and subsequently release the Gβγ subunit [33]. The Gβγ subunit, through Ste20p (a serine/threonine kinase) and Ste5p (a scaffold protein), activates a cascade of phosphorylation by mitogen-activated protein (MAP) kinases: Ste11p→Ste7p→Fus3p/Kss1p [33]. Fus3p and Kss1p contribute to the activation of transcriptional factor Ste12p, which, in phosphorylated form, binds and activates the transcription

of many conjugation-specific genes (for the pheromone pathway and cell/nuclear fusion) [33]. Although G proteins and some components of the MAP kinase signal transduction pathway have been isolated in filamentous ascomycetes [17,40], it is still unclear if (and how) the pheromone signal is linked to a G protein/MAP kinase pathway that may potentially mediate mating and sexual development. Although the pheromone signaling system of filamentous ascomycetes may mimic those of yeast [17,40], outputs from the signaling pathway may mediate different processes, such as the migration of male nucleus into the ascogonium, proliferation of opposite mating-type nuclei and development of the fruiting body (see Figure 1).

Pheromones and receptors are not the only genes regulated by mating type during vegetative growth. In *N. crassa*, the expression of at least two sexual developmental (*sdv*) genes [41,42] depends upon functional *mat A-1* [41,42,43•]. The size and expression pattern of transcripts adjacent to the *mat* locus was also found to be mating-type specific [44].

Nuclear recognition and proliferation

After cell fusion in *S. cerevisiae*, a Mat**a**1p/Matα2p heterodimer is required for the repression of haploid mating-specific genes and de-repression of meiotic genes [16,17]. In filamentous fungi, *mat* genes are also required for post-fertilization functions, presumably to mediate proliferation and internuclear recognition in the ascogonium. The enigma of internuclear recognition during sexual reproduction has been investigated in *P. anserina*. Internuclear complementation tests suggest that FMR1 (α-domain) and SMR2 (HMG-1) are limited to the *mat*– nucleus, while FPR1 (HMG-2) is limited to the *mat*+ nucleus [45]. Thus, nuclear identity is mediated by the restriction of the *mat* products to the nucleus of origin (Figure 1c). Mutations in mating-type genes affect nuclear identity and lead to the formation of monokaryotic progeny and uniparental dikaryotic progeny (from karyogamy between nuclei of identical mating type) [45,46]. Internuclear recognition has been proposed to be mediated by the nucleus-limited expression of mating-type-specific pheromone and receptors, which are restricted to the plasma membrane region nearest to the nucleus of origin [47]. Spatial cues are generated when nuclei of opposite mating type are close enough to superimpose their domains and allow the binding of pheromones to their cognate receptors. This cue would trigger the migration of the nuclei of opposite mating-type into the dikaryotic hyphal cell, perhaps by reorganization of cytoskeleton and secretory apparatus [48,49•,50].

SMR1 (α-helical) is not a true mating type protein, since *SMR1* expression is not nucleus limited and can function in a *mat*–, *mat*+ or even both nuclei [45]. Mutations in *SMR1* lead to barren fruiting bodies [45]. Ascospore progeny containing both *mat*+ and constitutively transcribed *FMR1* and *SMR2* are unable to germinate; ascospore lethality can be suppressed by the introduction of a constitutively expressed *SMR1* gene (E Coppin and R Debuchy, personal communication). These data suggest that SMR1 may suppress growth arrest in biparental dikaryotic hyphae to allow proliferation of *mat*+ and *mat*– nuclei (Figure 1c).

Special features of the mating-type locus

In addition to mating type, various phenotypes are linked to the *mat* locus in filamentous fungi. These include senescence, premature-death, and ascospore size dimorphism [14]. However, the association of these phenotypes to the *mat* locus either has been shown to be due to a linked gene or has not been determined [14]. One non-mating function that has been assigned unambiguously to the *mat* locus is vegetative incompatibility. Vegetative incompatibility is a mechanism that prevents the formation of vigorous heterokaryons between genetically dissimilar individuals and is believed to be a ubiquitous phenomenon among ascomycetes [51–53]. In *N. crassa* (but not in all filamentous ascomycetes), the *mat* locus also functions as a vegetative incompatibility (*het*) locus. The fusion of *mat A* and *mat a* hyphae during vegetative growth results in growth inhibition, hyphal compartmentation and death [51]. Incompatibility is due to the molecular actions of MAT A-1 (α-domain) and MAT a-1 (HMG-2) [5,7]. Mutants of *mat A-1* and *mat a-1* that separate mating and vegetative incompatibility have been obtained, indicating that the two functions lie in separable functional domains and are not mutually inclusive [7,21,54,55]. Initial yeast two-hybrid data indicates that MAT A-1 and MAT a-1 physically interact (C Staben, personal communication). However, a mutation in *mat a-1*, which abolishes mating-type incompatibility but does not affect mating function, eliminated physical interaction between MAT A-1 and MAT a-1.

A recessive mutation unlinked to the mating-type locus, *tol*, suppresses mating-type associated vegetative incompatibility such that *tol A* and *tol a* strains form a vigorous heterokaryon [56•]. TOL apparently is not a downstream effector of *mat A-1*/*mat a-1* interaction, but may rather interact with MAT A-1 and MAT a-1 to form a complex that triggers vegetative incompatibility [56•]. Why MAT A-1 and MAT a-1 exhibit such diametrically opposed functions in the sexual and vegetative phases in *N. crassa* and their relationship to each other is still an unsolved enigma of mating-type function.

Recombination must be suppressed around the *mat* locus in heterothallic species to maintain heterozygousity of the *mat* idiomorphs. In the pseudohomothallic species, *N. tetrasperma*, recombination suppression around the *mat* locus assures segregation of *mat* idiomorphs in the first-meiotic division, which in turn allows packaging of both mating-type nuclei in the same ascospore [57]. In the case of *N. tetrasperma*, the non-recombining region extends to 50–60% of the mating-type chromosome (10% of the genome), thus making it heterozygous for many loci between sibling *A* and *a* nuclei [58,59•]. Cytological

evidence shows that recombination block in the mating-type chromosome correlates with an extensive unpaired region during meiosis [59•].

Future prospects

Although advances in cloning of *mat* loci has provided us with insight into the nature of fungal mating identity, much is still unclear about how mating-type polypeptides control complex programs of recognition, cellular specialization, structural formation and cell-type determination. For example, physical evidence for the direct regulation of target genes (either positive or negative) by the mating-type polypeptides is still missing. The components and the regulation of pheromone signal transduction pathway remain to be determined. Little is known about the molecular and cellular mechanism of internuclear recognition, proliferation and migration of nuclei of opposite mating type in ascogenous hyphae. The relationship between vegetative incompatibility and mating-type function is unclear. These areas remain to be explored and defined before we can truly understand the complex programs of mating and sexual development in filamentous ascomycetes.

Note added in proof

Phylogenetic study of *mat A-1* and *mat a-1* genes from several members of *Neurospora* and *Sordaria* genera demonstrated a strict separation between homothallic and heterothallic species, suggesting the change from one reproductive strategy to another may result from a single event [60]. PCR and hybridization data shows intra-specific conservation of mating-type genes (including the metallothionein gene) between *P. brassicae* and *Tapesia yallundae* [61].

Acknowledgements

We appreciate the communication of unpublished results from C Waalwijk, G Turgeon, D Ebbole, D Bell-Pedersen, E Coppin, R Debuchy, and C Staben. We thank R Debuchy for critical reviewing of the manuscript. PKT Shiu is a recipient of the Natural Sciences and Engineering Research Council of Canada (NSERC) postgraduate fellowship.

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