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Fungal Meiosis and Parasexual Reproduction – Lessons from Pathogenic Yeast

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Summary

Meiosis is an integral part of sexual reproduction in eukaryotic species. It performs the dual functions of halving the genetic content in the cell, as well as increasing genetic diversity by promoting recombination between chromosome homologs. Despite extensive studies of meiosis in model yeast, it is now apparent that both the regulation of meiosis and the machinery mediating recombination has significantly diverged, even between closely related species. To highlight this, we discuss new studies on sex in *Candida* species, a diverse collection of hemiascomycetes that are related to *S. cerevisiae* and are important human pathogens. These provide new insights into the most conserved, as well as the most plastic, aspects of meiosis, meiotic recombination, and related parasexual processes.

Introduction

Sexual reproduction is a common attribute of eukaryotic species where it provides an adaptive advantage over species that are strictly asexual. During sex, fusion of gametes results in formation of cells with higher ploidy. Completion of sexual reproduction therefore requires a reductive DNA division, typically mediated by meiosis, in which diploid cells regenerate haploid gametes. Sexual reproduction evolved once very early in evolution in the eukaryotic lineage, and thus all asexual eukaryotes presumably derived from sexual ancestors [1].

Studies in yeast have played a central role in elucidating the regulation, machinery, and significance of sexual reproduction. In particular, experiments on the model ascomycetes, *Saccharomyces cerevisiae* and *Schizosaccharomyces pombe*, have detailed the molecular steps during mating and meiosis. However, despite the wealth of information obtained from these systems, it is now recognized that a surprising plasticity exists in sexual mechanisms from different species. We will review the meiotic programs of *S. cerevisiae* and *S. pombe*, and compare meiosis in these organisms with that recently described in *Candida* species. The latter are a diverse collection of hemiascomyces yeast related to *S. cerevisiae*, and are the most common cause of opportunistic fungal infections in humans. We emphasize differences in sexual differentiation between model and pathogenic yeast, and predict that additional surprises will emerge as genomic and functional studies are completed on these fungi that have important implications for human health.

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Regulation of Meiosis in Model Yeast

S. cerevisiae and *S. pombe* show distinct meiotic programs, both in terms of their regulation and the physical structures underpinning nuclear division and recombination. Several reviews have discussed the regulation of meiosis [2–6], the role of cohesins [7,8], and the mechanism of meiotic recombination [9–12], and we will therefore provide a simplified overview.

Meiotic Entry in Budding Yeast

Mating in *S. cerevisiae* occurs between haploid a and α cells producing a/α diploids. The latter are unable to mate, but are competent to undergo meiosis and sporulation in response to environmental cues. A key transcriptional regulator mediating this cell-type specificity is the a1/α2 heterodimer that represses expression of mating genes [13,14]. In addition, a1/α2 inhibits expression of *RME1*, which itself encodes a negative regulator of meiosis (Table 1). *RME1* plays an important role in preventing haploid a or α cells from initiating meiosis, a potentially catastrophic event [15]. The direct target of *RME1* is *IME1*, which encodes a transcription factor that, in concert with Ume6, regulates downstream meiotic genes [16] (Figure 1). Multiple pathways converge on *IME1* that are sensitive to cell type and nutritional signals. In particular, the *IME4* gene is induced under starvation conditions and encodes an N^6-methyladenosine activity that activates *IME1*, and potentially other targets, through modification of their mRNA [17,18]. More recently, it was shown that *IME4* expression is also cell type regulated by a mechanism of transcriptional interference. Thus, haploid a or α cells produce an antisense RNA against *IME4*, whereas in a/α diploids expression of the antisense RNA is blocked by a1/α2, thereby enhancing expression of the sense RNA [19]. This demonstrates a novel mechanism by which cell type specificity in yeast is mediated by a noncoding RNA. Immediately downstream of Ime1 is Ime2, a serine-threonine kinase that positively regulates subsequent events in meiosis [2,20]. Ime2 also negatively regulates Ime1, targeting it for degradation, thereby restricting Ime1 to a narrow window of activity [22]. Profiling of synchronous meioses have revealed a cascade of sequential gene expression involving more than 1000 genes divided between seven temporal groups [23].

Meiotic Entry in Fission Yeast

Mating in *S. pombe* occurs under conditions of nutritional stress and generates diploid h^+/h^- zygotes. Co-operation of h^+ and h^- mating-type proteins (M_c and P_m) induces expression of the *mei3* gene, initiating entry into meiosis [26]. M_c and P_m therefore provide cell-type specific regulation of meiosis analogous to that of a1/α2 in *S. cerevisiae* (Figure 1)[27]. Downstream of Mei3 there is a key interaction between Pat1, a serine/threonine kinase, and Mei2, an RNA-binding protein. Mei2 is a key factor for induction of meiosis, but is normally inhibited due to phosphorylation by Pat1 [28]. Inhibition is relieved upon expression of Mei3, which binds to Pat1 thereby inactivating it [29], although a Mei3-independent pathway may also exist for activation of meiosis [30]. Mei2 is essential for the initiation of meiosis and prevents the degradation of key meiosis-specific transcripts [31]. Transcriptional waves subsequently accompany progression through sporulation, and transcription factors have been identified that regulate specific stages including Rep1 (early genes), Mei4 (middle genes), and Atf21/Atf31 (late genes) [32,33]. Comparison of *S. pombe* and *S. cerevisiae* transcriptomes reveals relatively little overlap between species, although shared components include those of the anaphase-promoting complex and recombination/cohesin genes, such as *REC8* and *DMC1* [32].

Chromosome Pairing and Meiotic Recombination

The first DNA division in meiosis is reductional, with homologous chromosomes segregating from one another (meiosis I), while the second meiotic division is equational, with separation

of sister chromatids (meiosis II). A conserved complex of cohesins holds sister chromatids together during meiosis I, possibly via a ring structure that encircles the chromatids [34]. In many eukaryotes, including *S. cerevisiae* and *S. pombe*, Rec8 provides meiosis-specific cohesin activity, and cleavage of this protein is necessary prior to separation of sister chromatids during meiosis II [35,36].

Meiotic recombination also plays an active role in pairing homologous chromosomes in yeast. Central to meiotic recombination is the formation and repair of DNA double-strand breaks (DSBs) introduced by the highly conserved Spo11 protein (Table 2) [9]. DSBs are subsequently processed by the MRX complex (Mre11-Rad50-Xrs2) into single-stranded DNA regions in preparation for strand exchange by the RecA homologs, Rad51 and Dmc1 [9,37]. Dmc1, in particular, is a meiosis-specific activity important for homologous recombination in many, but not all, eukaryotes [38]. Accessory factors act to promote DSB formation and strand exchange, although these factors tend to be poorly conserved or even species-specific [9,39].

Higher order structures mediate meiotic chromosome segregation in both *S. cerevisiae* and *S. pombe*. In *S. cerevisiae*, as in most other eukaryotes, synaptonemal complexes (SC) are formed during meiosis and these proteinaceous structures facilitate pairing of homologous chromosomes [40]. A number of proteins are implicated in SC formation including the ZMM (Zip1-Zip4, Msh4/Msh5 and Mer3) family of proteins [11,40], which play a structural role in the SC (particularly Zip1) while also directing the program of genetic recombination. Thus, ZMM proteins promote the processing of meiotic DSBs into crossover events (where there is an exchange of flanking markers) rather than noncrossover events [41,42]. In contrast, meiosis in *S. pombe* does not involve SC formation, although minimal structures (linear elements) support pairing of homologous chromosomes. These structures share some components with the SC (Table 2), but are not essential for meiotic recombination [8,43].

Sex and Meiosis in *Candida* species

Species belonging to the *Candida* genus were historically classified as budding yeast that were asexual and formed either pseudohyphae or true hyphae [44]. Many of these species are human pathogens and cluster in a single clade within the hemiascomycetes (Figure 2)[45,46]. Sexual lifestyles have now been confirmed for several *Candida* species and these reveal a surprising diversity in their programs. Thus, *C. glabrata*, *C. parapsilosis*, and *C. tropicalis* have many of the genes necessary for mating and meiosis, and yet sex has never been observed in these species [45]. In contrast, *C. lusitaniae* and *C. guilliermondii* have established sexual cycles including sporulation and ascospore formation [44]. *C. albicans* is somewhere between these two extremes; efficient mating occurs but a conventional meiosis has yet to be demonstrated [47–50]. Molecular studies of sexual differentiation in *C. lusitaniae* and *C. albicans* have now been completed, and these will be contrasted with those in model yeast.

Sexual Reproduction in *Candida lusitaniae*

C. lusitaniae exhibits a surprisingly efficient program of meiosis and sporulation given that this species is lacking many ‘key’ meiotic components [51]. Missing factors include the recombinase Dmc1, synaptonemal complex proteins Zip1-Zip4, as well as activities that promote crossover formation (Msh4/Msh5 and Mer3). In fact, *C. lusitaniae* is missing most of the top candidate genes identified as hallmarks of meiosis and sexual reproduction in eukaryotic species (the ‘meiotic toolkit’ genes, Table 2)[52]. Despite the loss of these factors, *C. lusitaniae* undergoes Spo11-mediated meiotic recombination at frequencies similar to that of other sexual fungi [51]. The lack of conserved SC components suggests that meiosis may involve minimal structures for chromosome pairing similar to *S. pombe*. However, while a homolog of Rec8 is present in *C. lusitaniae*, other factors such as Hop1 and Mek1 that contribute to linear elements in *S. pombe* are missing [8,43,45]. It therefore appears that very

rudimentary structures mediate chromosome pairing and recombination during *C. lusitaniae* meiosis.

Sexual differentiation in *C. lusitaniae* is also unusual in that, unlike the related hemiascomycete *S. cerevisiae*, it is no longer under control of the a1/α2 complex. *C. lusitaniae* has retained the a1 gene, and this gene is necessary for meiosis and sporulation, but the α2 gene is missing from the sequenced *MTL*α locus (Figure 1) [45,51]. Presumably, another α-specific gene is required for determining cell type as only a/α (not a/a or α/α diploids sporulate. One candidate is the α1 gene, although how a1 cooperates with α1 to specify cell type and promote meiosis is an intriguing question for the future. Furthermore, while *C. lusitaniae* contains homologs of many regulatory factors involved in meiosis (including *IME2*, *IME4*, *RME1*, and *NDT80*) there is no homolog of *IME1*, the master regulator in *S. cerevisiae* (Table 2) [45,51]. The transcriptional circuitry regulating meiosis has therefore diverged since *S. cerevisiae* and *C. lusitaniae* last shared a common ancestor. Similar rewiring of the mating type circuitry has also occurred between *S. cerevisiae* and the *Candida* species [53–55], again illustrating the highly plastic nature of sexual processes.

Sexual reproduction *C. lusitaniae* involves a haploid-diploid-haploid cycle similar to that in model yeast. Surprisingly, however, while the products of meiosis are mainly haploid, about one-third of meiotic products are diploid or aneuploid [51]. The latter may be due to inefficient chromosome segregation and meiotic nondisjunction, particularly given the limited repertoire of meiotic components present in the *C. lusitaniae* genome. Interestingly, similar levels of aneuploidy (7–35%) also occur during human oogenesis and can lead to miscarriage and birth defects [56], although it is not clear what consequences aneuploidy may have for *C. lusitaniae* biology. In addition, *C. lusitaniae* asci typically contain two ascospores (dyads) rather than four ascospores (tetrads) as often formed during meiosis in *S. cerevisiae* and *S. pombe*. Chromosome missegregation during *C. lusitaniae* meiosis could generate many non-viable forms, and reducing the number of spores may help limit investment in dead-end products [51]. A parallel exists with *S. cerevisiae*, as meiosis performed in limiting acetate conditions produces dyads rather than tetrads, again preserving cell resources while allowing sporulation to proceed [57–59]. In this case, unpackaged nuclei get degraded during ascus maturation leaving two intact, haploid ascospores.

Parasexual Reproduction in *Candida albicans*

In contrast to *C. lusitaniae*, which is rarely encountered in the clinic, *C. albicans* is a prevalent human pathogen that causes both mucosal and systemic infections [60]. Despite its clinical importance, the sexual lifestyle of *C. albicans* has remained an enigma. Long thought to be an obligate asexual organism, mating of diploid strains has been demonstrated both *in vitro* and *in vivo*, and is regulated by a unique mechanism of phenotypic switching [48–50,61]. *MTL*a and *MTL*α cells can switch between white and opaque forms, but only cells in the opaque state are competent for mating [50]. The key regulator of the opaque state is Wor1, as high levels of this protein are sufficient to drive cells to the opaque form, although a complex network of positive and negative feedback loops regulates heritable Wor1 expression [61]. White-opaque switching is inhibited in a/α cells as the a1/α2 complex represses expression of the *WOR1* gene, locking cells in the white state (Figure 1)[50]. The white-opaque switch therefore adds an additional layer of sophistication to *C. albicans* mating, presumably to regulate sexual reproduction in response to environmental cues from the mammalian host or other, yet to be discovered, niches.

Despite efficient mating between opaque a and α cells, and the presence of many ‘meiosis-specific’ genes in the sequenced genome (Table 2), a conventional meiosis has yet to be uncovered in *C. albicans* [45,62]. In its place, a parasexual mechanism has been described

involving efficient and cooperative chromosome loss [63]. Thus, culture of tetraploids on certain laboratory media causes genomic instability and loss of chromosomes from the tetraploid, resulting in the formation of diploid (and numerous aneuploid) forms of *C. albicans* [63,64]. One potential advantage of the parasexual program over a traditional meiosis is that it does not culminate in the production of spores. This may be significant given that spores are often highly antigenic and could therefore minimize detection of mating products by the host immune system [65].

Despite the apparent absence of a conventional meiosis in *C. albicans*, several meiosis-specific genes have been shown to encode functional products. For example, a homolog of Dmc1 is present in *C. albicans* and can successfully substitute for *S. cerevisiae* Dmc1 function in meiosis [66]. In addition, Spo11 is required for the initiation of meiotic recombination in many eukaryotes, and was recently implicated in mediating recombination during the parasexual cycle of *C. albicans* [64]. It therefore remains to be seen whether other meiosis-specific genes have also been reprogrammed to function in the parasexual program. If so, the parasexual cycle may represent a *bona fide* alternative to a conventional meiosis. Alternatively, the parasexual cycle may simply signify a particularly inefficient meiosis, especially given the high rates of aneuploidy now reported during meiosis in *C. lusitaniae* [51]. Finally, an exciting possibility is that a cryptic meiosis still exists for *C. albicans*, and that the appropriate conditions have not been identified to initiate this program. In this regard, it is interesting to note that a novel mode of same-sex mating has recently been demonstrated for *C. albicans* [67]. While the products of same-sex mating can undergo the parasexual pathway, further experimentation will determine if a conventional meiosis/sporulation can be performed by these cells.

Conclusions

An emerging theme is that programs of sexual reproduction exhibit a remarkable degree of plasticity. This is particularly true of meiosis, where recent genomic and functional studies have revealed marked differences even between closely related species. Thus, while much has been learned about sexual reproduction from studies in model yeast, it is now apparent that differences between species are likely to be almost as striking as the similarities. A striking example of this sexual diversity is provided by *C. lusitaniae*, which is able to undergo efficient sporulation and homologous recombination yet is apparently lacking much of the molecular machinery associated with meiosis in other organisms. Additional studies will be necessary to reveal how this is achieved with such a limited repertoire of meiotic components.

Finally, while we have focused on recent experiments in *Candida*, exciting developments have been made concerning sex and meiosis in other pathogenic fungi. In particular, a complete sexual cycle has now been demonstrated for *Aspergillus neoformans* [68], the most prevalent airbourne fungal pathogen, and novel modes of same-sex mating and meiosis have been shown to occur during ‘haploid fruiting’ in *Cryptococcus neoformans* [69], a causative agent of meningoencephalitis. As additional genomes are sequenced, the ability to analyze the role of putative mating and meiosis genes will accelerate, and will undoubtedly lead to a clearer picture of the evolution and consequences of sex in fungi and higher eukaryotes.

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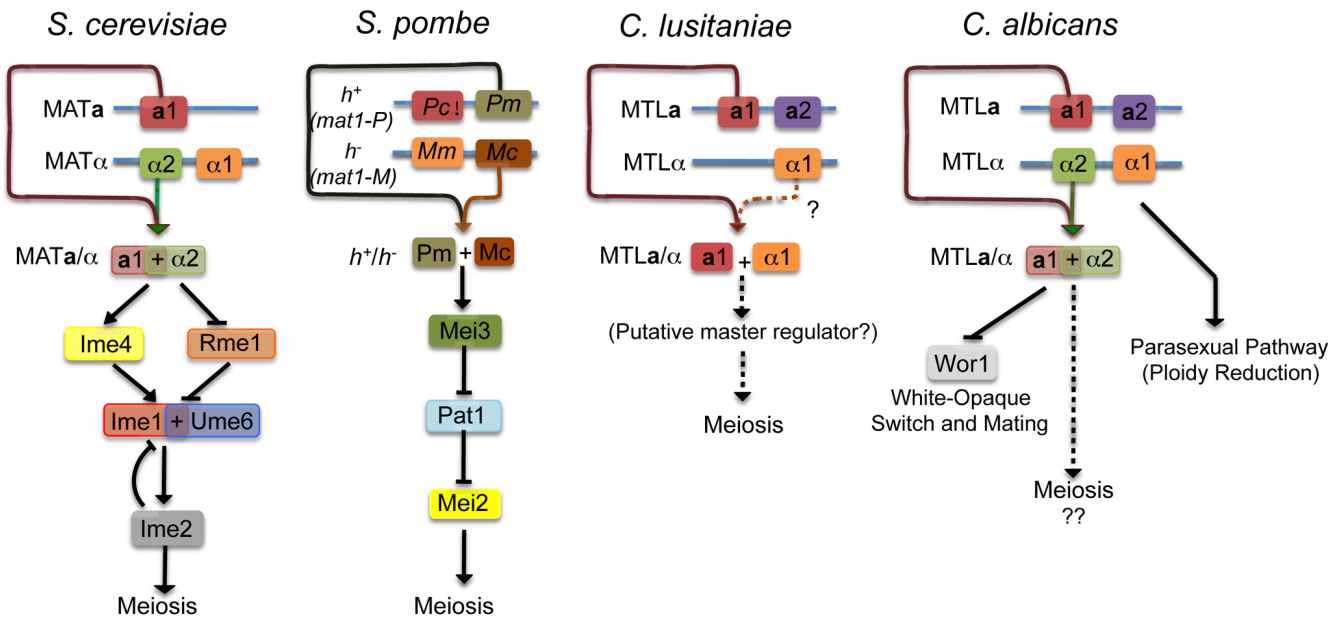

Figure 1. Regulation of Sexual Programs in Yeast

Meiotic entry is induced by nutritional starvation and the presence of mating type alleles from both sexes for *S. cerevisiae*, *S. pombe* and *C. lusitaniae*. Note that meiosis in *S. pombe* requires all four genes encoded at the mating locus; Pm and Mc subsequently activate expression of the meiotic regulator, Mei3. Meiosis has recently been investigated in *C. lusitaniae* and requires the presence of **a**1, possibly in combination with α1, but the downstream effectors of meiosis have not been identified. *C. albicans* does not undergo a conventional meiosis yet efficient mating of diploid **a** and α strains occurs and is regulated by Wor1 and the white-opaque phenotypic switch. Tetraploid cells can undergo a parasexual program of random and concerted chromosome loss to return to the diploid state.

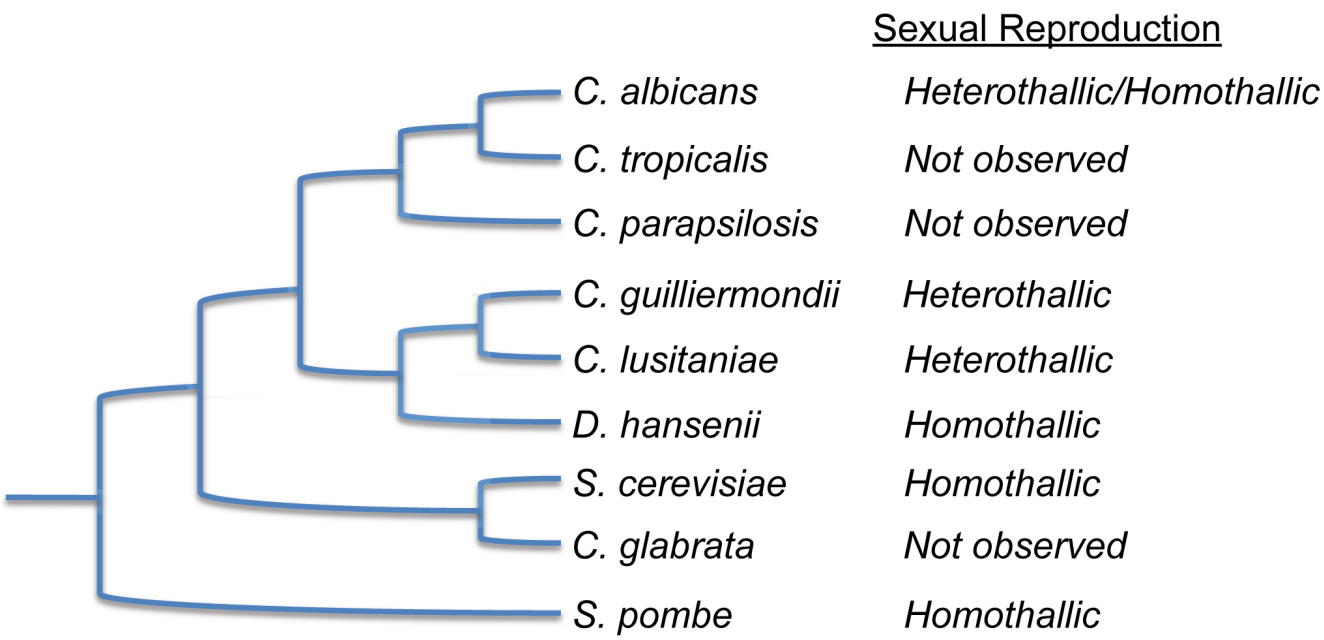

Figure 2. Phylogeny of Sequenced *Candida* Species

Phylogenetic tree of the hemiascomycetes (*S. cerevisiae* and sequenced *Candida* species) as well as the related ascomycete, *S. pombe*. Heterothallic organisms are out-crossing species, whereas homothallic organisms are self-fertile. Note that *C. albicans* exhibits both homothallic and heterothallic modes of reproduction, but undergoes a parasexual cycle rather than a conventional meiosis. Most natural isolates of *S. cerevisiae* are homothallic although heterothallic isolates have also been described. Figure adapted from the Broad Institute (www.broadinstitute.org).

Table 1
List of Genes Regulating Meiosis and Sporulation in *S. cerevisiae*

Genes involved in meiosis and sporulation in *S. cerevisiae* are listed, as well as homologous genes from *C. lusitaniae* and *C. albicans* genomes. Although a meiotic program has been identified in *C. lusitaniae*, functional tests of these putative meiosis genes have not been performed. In the case of *C. albicans*, a conventional meiosis has not been observed, and several genes that function in meiosis in *S. cerevisiae* have been shown to have an unrelated function in *C. albicans*. Homologous genes for *C. albicans* and *C. lusitaniae* were identified by the Broad Institute using reciprocal BLAST against *S. cerevisiae* meiotic and sporulation genes (www.broadinstitute.org). Absence of a homolog is designated as (−) in this table.

Genes Regulating Meiosis in *S. cerevisiae*				
Function of gene product in *S. cerevisiae*	***S. cerevisiae***	***C. lusitaniae***	***C. albicans***	**Function of gene product in *C. albicans***
Homeodomain protein that acts with *MAT*α2 to repress mating and permit meiotic induction in **a**/α diploids.	*MAT***a**1	*MTL***a**1	*MTL***a**1	Homeodomain protein that acts with *MTL*α2 to repress white-phenotypic switching and mating in **a**/α opaque cells.
Homeodomain protein, promotes α–specific gene expression pattern.	*MAT*α1	CLUG04923	*MTL*α1	Homeodomain protein, promotes α-specific gene expression patterns.
Homeodomain protein, promotes α-specific gene expression and acts with *MAT***a**1 to repress mating and permit meiotic induction in **a**/α diploids.	*MAT*α2	-	*MTL*α2	Homeodomain protein that acts with *MTL***a**1 to repress white-opaque phenotypic switching and mating in **a**/α cells.
Cell type dependent meiotic repressor.	*RME1*	CLUG05819	orf19.4438	White-phase specific gene expression. Upregulation correlates with clinical resistance to fluconazole, an antifungal.
Methlytransferase required for nutrient sensing and activation of *IME1*.	*IME4*	CLUG03093	orf19.1476	*No experimental data*
Meiotic kinase required for sporulation and activation of *IME1*.	*RIM11*	CLUG05114 CLUG01530	orf19.791	*No experimental data*
Glucose repressed kinase, positive regulator of *IME1*.	*RIM15*	CLUG04432	orf19.7044	*No experimental data*
Serine/threonine kinase important for meiotic entry and chromosome segregation.	*MCK1*	CLUG01530	orf19.3459	*No experimental data*
Master transcription factor required for induction of the meiotic pathway.	*IME1*	-	-	
Kinase required for activation of early meiosis genes.	*IME2*	CLUG00015	orf19.2395	Mutants are hyper-susceptible to the antifungal Amphotericin B.
Transcription factor required for induction of middle-meiosis genes.	*NDT80*	CLUG00404 CLUG05634	orf19.2119 (orf19.513)	Expression induced by antifungal treatment, required for basal level of antifungal drug tolerance in wild type cells.

Genes Involved in *S. cerevisiae* Sporulation				
Function in *S. cerevisiae*	***S. cerevisiae***	***C. lusitaniae***	***C. albicans***	**Function in *C. albicans.***
Serine/threonine kinase involved with spore wall formation, expressed at the end of meiosis	*SPS1*	CLUG04805	orf19.3049	*No experimental data*
Sporulation specific MAP kinase required for outer spore wall synthesis.	*SMK1*	CLUG04129	orf19.7208	Putative MAP kinase, mutant produces wrinkled colonies.
Sporulation specific enzyme required for dityrosine synthesis, a cell wall precursor.	*DIT1*	CLUG03886	orf19.1741	*No experimental data*
Sporulation specific enzyme required for dityrosine synthesis and cell wall maturation.	*DIT2*	CLUG02306	orf19.554	Involved with chlamydospore (asexual spore) formation and dityrosine synthesis.
Sporulation specific septin.	*SPR3*	CLUG04558	orf19.1524	Required for septin formation.
Non-essential protein expressed during sporulation.	*SPS4*	CLUG05767	orf19.7568	*No experimental data*

Table 2

Meiotic Genes Involved in Homologous Recombination and Synaptonemal Complex Formation

Homologs of *S. cerevisiae* genes required for homologous recombination and synaptonemal complex formation were compared across a subset of eukaryotic species. The presence of a gene homolog is designated by (+) and absence of a homolog by (−). Genes representing the best markers for predicting the presence of a meiotic pathway ("meiotic toolkit" genes, [52]) are also indicated (*). Note that *S. pombe* does not form synaptonemal complexes but uses linear elements that involve Rec8, Hop1, Hop2, Mek1, and Rec10 (homolog of *S. cerevisiae* Red1). *C. lusitaniae* demonstrates meiotic competence culminating in the formation of recombinant spores yet is lacking six of the eight meiotic toolkit genes, as well as homologs of most of the genes associated with synaptonemal complex/linear element formation.

Genes Involved in Homologous Recombination					
Function of gene product in *S. cerevisiae*	***S. cerevisiae***	***C. lusitaniae***	***C. albicans***	***S. pombe***	***M. musculus***
Meiosis specific gene, important for processing dsDNA breaks for repair during homologous recombination.	*DMC1**	−	+	+	+
Dmc1 cofactor; forms a complex with Sae3 for dsDNA break processing during homologous recombination.	*MEI5*	−	+	+	+
Meiosis specific helicase.	*MER3/HFM1*	−	+	−	+
Mismatch repair gene that is important for DNA crossover during meiosis.	*MLH1*	+	+	+	+
Endonuclease that complexes with *MUS81* to cleave branched DNA; involved in joint molecule formation/resolution during recombination.	*MMS4*	+	+	+	+
Forms a complex with *HOP1*, important for chromosome pairing and repair of dsDNA breaks.	*MND1**	−	+	+	+
Subunit of MRX complex, required for dsDNA break repair during homologous recombination.	*MRE11*	+	+	+	+
Forms a complex with *MSH5*, essential for regulating crossover events during meiosis.	*MSH4**	−	+	−	+
Forms a complex with *MSH4*, essential for regulating crossover events during meiosis.	*MSH5**	−	+	−	+
Endonuclease that complexes with *MMS4* to cleave branched DNA; involved in joint molecule formation/resolution during recombination.	*MUS81*	+	+	+	+
Subunit of MRX complex, required for dsDNA break repair during homologous recombination.	*RAD50*	+	+	+	+
Meiotic protein important for strand invasion and exchange during homologous recombination.	*RAD51*	+	+	+	+
Meiotic protein that stimulates strand exchange during homologous recombination.	*RAD52*	+	+	+	+
Dmc1 cofactor; forms a complex with Mei5 for dsDNA break processing during homologous recombination.	*SAE3*	−	+	+	+
Helicase, regulates meiotic crossover formation events.	*SGS1*	+	+	+	+
Meiosis specific protein that stimulates homologous recombination by catalyzing the formation of dsDNA breaks.	*SPO11**	+	+	+	+
Component of the MRX complex, important for dsDNA repair during homologous recombination.	*XRS2 (NBS1)*	−	−	+	+

Synaptonemal Complex Genes.					
Function of gene product in *S. cerevisiae*	***S. cerevisiae***	***C. lusitaniae***	***C. albicans***	***S. pombe***	***M. musculus***
Meiosis specific protein, localizes to axial elements of the synaptonemal complex. Required for homologous recombination.	*HOP1**	−	+	+	+

Synaptonemal Complex Genes.					
Function of gene product in *S. cerevisiae*	***S. cerevisiae***	***C. lusitaniae***	***C. albicans***	***S. pombe***	***M. musculus***
Meiosis protein that promotes recombination between homologous chromosomes and prevents recombination between non-homologous chromosomes.	*HOP2**	−	+	+	+
Meiosis specific serine/threonine kinase that promotes recombination between homologous chromosomes.	*MEK1*	−	+	+	+
Sister chromatid cohesin protein.	*REC8**	+	+	+	+
Protein component of axial element in the synaptonemal complex.	*RED1*	−	−	+	+
Structural component of synaptonemal complex, promotes recombination between homologs.	*ZIP1*	−	−	−	+
Meiosis specific protein important for synaptonemal complex formation.	*ZIP2*	−	+	−	+
Sumo E3 ligase, localizes to synapse initiation sites and is required for synaptonemal complex formation.	*ZIP3*	−	+	−	+
Meiosis specific gene essential for synapsis during homologous recombination.	*ZIP4*	−	−	−	−