

- Definition and Mutant Phenotype
- The Perception and Transmission of the Mating Factor Signal
- Activation of Downstream Effectors
- Cell Cycle Arrest
- Induction of Mating Genes
- Mating Type Switching
- Regulation
- Mechanism
- Summary

Yeast Mating Type

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Yeast mating type is determined by alleles of a single genetic locus that encodes regulatory proteins governing genes encoding mating pheromones, pheromone receptors and downstream effectors regulating cell type. Some yeast are capable of switching mating type, a process involving gene replacement by information from silenced copies of the mating type locus found elsewhere in the genome.

Definition and Mutant Phenotype

Saccharomyces cerevisiae, baker's yeast, can exist in either a haploid ($1n$) or a diploid ($2n$) state. Haploids express one of two mating types, **a** or α (alpha). Haploids of either mating type are capable of mating with haploids of the opposite mating type in response to the action of mating pheromones. Mating results in fusion of haploid cells, forming an **a**/ α diploid, which is no longer capable of mating. Genetic analysis in the early days of yeast research showed that mating type was controlled by alleles of a single genetic locus, referred to as *MAT* (mating type). Haploid strains possess either the *MATa* or *MAT α* allele; **a**/ α diploids are heterozygous at this locus, carrying both alleles. Both haploids and diploids can undergo vegetative growth (mitotic cell cycles); **a**/ α diploids are also capable of undergoing meiosis to produce four haploid nuclei, which are then packaged into ascospores. The four products of a single meiosis are held together in a sac called an ascus. The alleles of the mating type locus segregate during meiosis, producing two mating type **a** spores and two mating type α spores in each ascus. Spores return to a vegetative growth pattern under appropriate nutritional conditions.

The genetic analysis of yeast mating type began with the isolation of sterile (*ste*) mutants unable to mate (MacKay and Manney, 1974a). They screened among a mutagenized population of α cells that carried a recessive drug resistance marker to find isolates that grew on selective medium containing the drug even when mixed with a large excess of **a** mating type cells bearing the dominant sensitivity allele. Some of these sterile mutants had defects at the mating type locus itself, while others mapped to different locations in the genome. These workers carried out additional studies to obtain sterile mutations in an **a** background. Subsequent analysis indicated that the sterile mutants not mapping to the mating type locus fell into one of three categories: those that caused sterility only in an **a** background, those that caused sterility only in an α background, and the majority class that were not specific and resulted in sterility in the presence of either allele at the mating type locus (MacKay and Manney, 1974b).

Sterile mutants mapping to the mating type locus provided important information about its structure and

function. Two complementation groups of sterile mutants at *MAT α* were found, thus identifying two different genes at this locus. Interestingly, mutants of these two genes had different phenotypes: *mat α 1* mutants showed reduced mating with both **a** and α and failed to produce α -factor or agglutinate with **a** cells; rare *MATa*/*mat α 1* diploids could be constructed and these could sporulate. On the other hand, *mat α 2* mutants were specifically defective in mating with **a** cells and showed two **a**-like phenotypes: they responded to α -factor and, at low efficiency, mated as **a** cells. When *MATa*/*mat α 2* diploids were constructed, they were found to be unable to sporulate. No mutations of *MATa* were found among the original sterile mutants; as it happens, these do not affect mating ability. They were found later through their effects on diploids (*MATa1*/*MAT α* cells mate as α and do not sporulate).

The properties of these mutations at the mating type locus led to the proposal of the ' α 1- α 2 model' for control of cell type (reviewed in Herskowitz and Oshima, 1981). This hypothesis stated: (1) that the *MAT α 1* gene product acts as a positive regulator of α -specific functions presumed to be encoded by α -specific genes; (2) that the *MAT α 2* gene product is a negative regulator of **a**-specific functions presumed to be encoded by **a**-specific genes; and (3) that sporulation requires both **a** and α information, presumably the products of the *MATa1* and *MAT α 2* genes. This model made several specific predictions, which were subsequently tested and confirmed.

Molecular analysis of the mating type locus revealed the basis of the action of its gene products. The products of *MATa1*, *MAT α 1* and *MAT α 2* are transcriptional regulators that function in various combinations to regulate expression of genes that give **a** and α haploids and **a**/ α diploids their unique properties, as shown in **Figure 1**. In α cells, *Mat α 1p* associates with the product of the *MCM1* gene to form an activator of α -specific genes. *Mat α 2p* also associates with *Mcm1p* to repress **a**-specific genes. In **a** cells, neither *Mat α 1p* nor *Mat α 2p* is present, and thus **a**-specific genes are expressed (through the action of

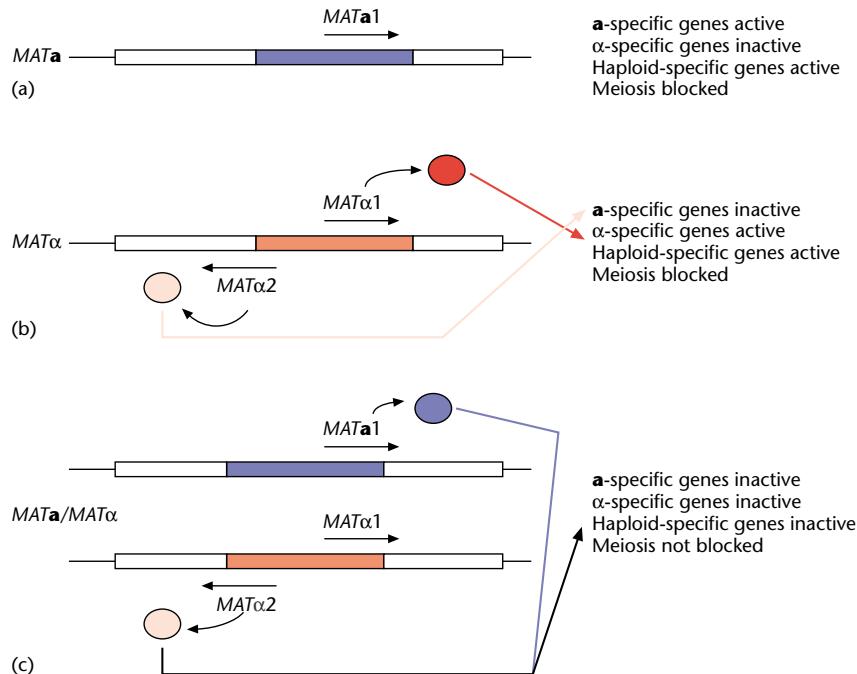


Figure 1 Genes active at the mating type locus in *a* or α haploids, or in *a*/ α diploids. The different colours indicate that there is a portion of this locus that is not the same in the two mating types. (a) In mating type *a* cells, the *MATa1* gene is expressed. *a*-specific genes are expressed by a default pathway; α -specific genes are not expressed; haploid-specific genes are expressed by default pathways; and one of the haploid-specific genes is a repressor of meiosis. (b) In mating type α cells, the *MAT α 1* and *MAT α 2* genes are both expressed. The former is an activator of α -specific genes and the latter a repressor of *a*-specific genes. Haploid-specific genes are expressed, including the repressor of meiosis. (c) When both alleles are present in an *a*/ α diploid, *MAT α 2* protein continues to repress *a*-specific genes as in (b), and interacts with the product of *MATa1* to repress the haploid-specific genes and allow meiosis and sporulation.

Mcm1p). The α - and *a*-specific genes include the loci encoding the mating factors and their receptors. Haploid-specific genes are expressed in both types of haploid. These encode components of mating factor signalling pathways, proteins required for cell fusion, the *HO* gene encoding the endonuclease needed for mating type switching, as discussed below, etc. In *a*/ α diploids, both mating-type alleles are present and expressed, and the *Mata1p*–*Mat α 2p* dimer is formed. This represses haploid-specific genes, including *RME1*, a repressor of meiosis. Thus diploids do not mate as either haploid and are capable of entering meiosis (Figure 1).

The Perception and Transmission of the Mating Factor Signal

To investigate the biochemical and physiological basis of the sterile phenotype of their mutants, MacKay and Manney (1974a) developed methods for measuring both the production of and the response to the appropriate mating pheromones. Normal *a* cells produce a peptide hormone called *a*-factor; normal α cells produce a similar α -factor peptide; both types of cell respond to the presence

of the opposite mating type pheromone by a morphological change described as ‘shmoo’ formation. Shmoos appear as elongated, pear-shaped cells growing in the direction of cells or purified mating pheromone of the opposite mating type.

Application of these tests by MacKay and Manney indicated that many of the sterile mutants failed to produce mating pheromone, thus demonstrating the importance of the mating pheromones in conjugation. On the other hand, mutants of *STE2* and *STE3* could produce the appropriate mating pheromone, but failed to respond to the opposite pheromone, suggesting that these genes encoded factors involved in the perception of or response to the mating factor signal. Still other mutants, identifying the genes *STE4* and *STE5*, among others, were nonspecific, defective in mating in both *a* and α backgrounds, and involved in the production of and response to both types of mating pheromone. The large number of mutants falling into the latter category suggested that many genes were required for pheromone production, pheromone response, and coordination of each with the cell cycle to result in mating.

It has subsequently been recognized, through the efforts of many laboratories, that these processes do, indeed, involve many gene products. The mating pheromones are produced by several steps, including transcription, transla-

tion, post-translational modification and/or processing, to yield active product, which is secreted into the environment. **Figure 2** illustrates the steps of this process. Pheromones are recognized and bound by the extracellular portion of the appropriate receptor molecule: *STE2* encodes the α -factor receptor, while *STE3* encodes the a-factor receptor. The receptors belong to the large class of seven-transmembrane-segment G protein-coupled receptors, which includes many that have been studied extensively in animal cells (Sprague and Thorner, 1992). Binding of pheromone to receptor produces a conformational change in the associated G protein, a heterotrimer comprised of the products of the *GPA1*, *STE4* and *STE18* genes (Kurjan, 1993). The $G\alpha$ subunit alternatively binds guanosine nucleoside diphosphate (GDP) or guanosine nucleoside triphosphate (GTP). In the absence of pheromone binding, $G\alpha$ is bound to GDP and to the $G\beta$ and $G\gamma$ subunits. When pheromone binds the receptor, the resulting conformational change causes conversion of $G\alpha$ -GDP to $G\alpha$ -GTP, which causes dissociation of $G\beta$ - $G\gamma$. The freed $G\beta$ - $G\gamma$ complex triggers a cascade of protein kinases (three of which form a typical mitogen-activated protein (MAP) kinase cascade), the products of the *STE20*, *STE11*, *STE7* and *FUS3* genes, in that order of action. An immediate downstream target of the final kinase (Fus3 protein) is the product of the *STE12* gene, a

transcription factor. Thus, the mating pheromone receptors and the G-protein complex function together as a molecular switch that is turned on or off by the binding of the pheromone (**Figure 2**).

Activation of Downstream Effectors

Mating pheromone binding to its receptor results in a cascade of phosphorylation events, culminating in phosphorylation of the product of the *STE12* gene, causing its activation. Phosphorylated Ste12 protein functions as an activator of transcription by binding to specific deoxyribonucleic acid (DNA) sequences called pheromone response elements in the promoters of genes under pheromone regulation. Such genes include many required for the production of and response to mating pheromones, as well as functions involved in arresting the cell cycle, promoting cell pairing and fusion, promoting nuclear fusion, and facilitating recovery from mating events. Some of these genes were specifically identified by searching for genes whose transcription was stimulated by mating factor treatment, whereas others had been identified on the basis of other properties and were later shown to be under pheromone regulation (Sprague and Thorner, 1992). More recently, genome-wide surveys have been performed to detect all genes upregulated by mating factor treatment, and have revealed additional downstream targets of this pathway (Roberts *et al.*, 2000).

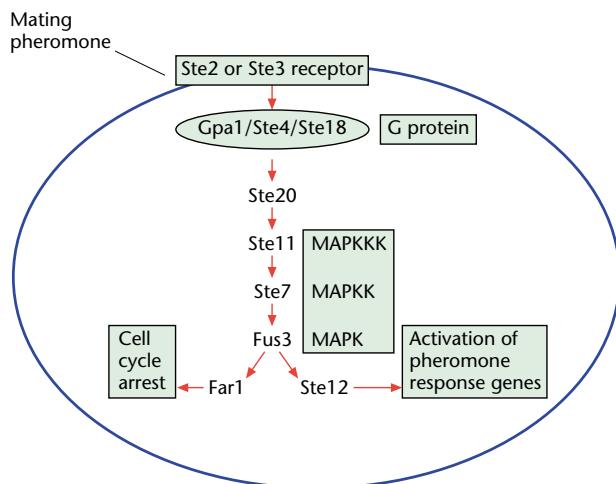


Figure 2 Signal transduction pathway for response to mating pheromone. Mating pheromone is an extracellular peptide that interacts with the extracellular portion of the appropriate transmembrane receptor (Ste2 or Ste3 protein). Binding of pheromone to receptor causes a conformational change in the associated G protein, which consists of three subunits ($G\alpha$, product of the *GPA1* gene, $G\beta$, product of *STE4* and $G\gamma$, product of *STE18*). This conformational change results in dissociation of the $G\beta$ and $G\gamma$ subunits, which activates Ste20 protein, a protein kinase. Ste20p phosphorylates the mitogen-activated protein (MAP) kinase kinase kinase (MAPKKK), Ste11p. This in turn phosphorylates the MAP kinase kinase (MAPKK) Ste7p, which phosphorylates the MAP kinase (Fus3p). Fus3p phosphorylates target proteins that regulate the cell cycle or activate transcription of genes required for mating.

Cell Cycle Arrest

One of the effects of mating pheromone on cells of the opposite mating type is blocking of the cell cycle late in the G1 phase. This step is prior to bud emergence and initiation of DNA replication for a new cell division cycle, and is also the point at which the *cdc* (cell division cycle) mutant with the earliest known cell cycle blockage point arrests. This point has been referred to as ‘START’ by Hartwell and colleagues (Pringle and Hartwell, 1981). In fact, so efficient and complete is the block imposed by α -factor on a cells, that purified α -factor has been widely used as a means of synchronizing a culture of yeast cells to pass simultaneously through cell cycle landmarks.

Cell cycle arrest is important in mating to ensure that both partners have only 1n haploid content of DNA at the time of nuclear fusion. If one cell had previously replicated its DNA at the time of fusion, the resulting zygote would be triploid rather than diploid. START not only represents a block to allow mating, but is also a point beyond which mating cannot occur, as was shown by use of temperature-sensitive *cdc* mutants that blocked the cell cycle at points later than START. Thus there is tight regulation between the cell cycle and mating, as described below.

The primary controller of entry into a new cell cycle at START is the cyclin-dependent kinase (CDK) encoded by the *CDC28* gene, homologues of which exist in all eukaryotic cells. Cdc28 protein associates with one of three G1 cyclins (products of the *CLN1*, *CLN2* or *CLN3* genes) to promote transcription of S phase-required genes and to degrade an inhibitor preventing entry into S phase. Mating pheromone prevents transition of the START point by means of the product of the *FAR1* gene, which is a phosphorylation target of the MAP kinase Fus3 protein. Phosphorylated Far1 protein is a CDK inhibitor that prevents the Cdc28p–cyclin complex from allowing the cell to pass START.

Not only do the mating pheromones regulate the cell cycle, but the converse is also true. Several of the genes involved in mating, such as those encoding the MAP kinase cascade or involved in mating type switching (e.g. *HO*), are transcribed in a cell cycle-dependent manner. There is a great deal of complex regulatory circuitry governing these phenomena.

Induction of Mating Genes

In addition to arresting the cell cycle, functions needed for mating alter cell polarity and cell morphology in preparation for joining with the mating partner. Many of these functions are transcriptionally regulated by Ste12p in response to mating factor binding and signal transduction. *FUS1* encodes an integral membrane protein needed for cell fusion. It is strongly upregulated in response to mating factor, and its product is localized to the tip of the shmoo; its precise role is not yet known.

Once the mating cells have fused, karyogamy, or nuclear fusion, must occur. Genes involved in this process are also under Ste12p regulation. One such is *KAR3*, whose transcription is increased 20-fold by pheromone treatment. The Kar3 protein is a kinesin-like motor protein required for nuclear fusion.

Mating Type Switching

The earliest studies of yeast life cycle and genetics by Winge and Lindgren and their respective colleagues made it clear that two different types of life cycle existed in yeast: homothallism and heterothallism. Homothallic yeasts produced diploid colonies from cultures grown up from a single yeast spore; these could sporulate but not mate, and all four spores from a single ascus showed the same behaviour. On the other hand, heterothallic yeasts gave rise to haploid cultures that could mate but not sporulate. Each ascus of a heterothallic yeast contained two spores of mating type **a** and two of mating type α . Crosses between spores of homothallic strains and haploid heterothallic

strains showed that homothallism and heterothallism were the result of alleles of a single locus, *D* (for diploidization; subsequently called *HO*, for homothallism), unlinked to the mating type locus *MAT*. The dominant *D* or *HO* allele results in homothallism by causing diploidization early in the vegetative growth of a spore; *d*- or *ho*-containing strains cannot diploidize and are heterothallic.

A series of experiments by Oshima and colleagues, and others, revealed that the mechanism of homothallic diploidization was the fusion of **a** and α cells, just as in diploidization of heterothallic yeast (Herskowitz and Oshima, 1981). This comes about as a result of some cells changing mating type during the growth of a homothallic strain. The first studies made use of spore-to-cell matings of ascospores of a homothallic strain with **a** or α cells of a heterothallic strain, and showed that even in homothallic strains the mating type locus segregates with the normal 2**a**:2 α ratio. Subsequently, naturally occurring variant yeast strains were identified with partial homothallic behaviour: sporulation of these strains produced asci containing two haploid mating-competent spores and two homothallic spores that would produce diploid colonies. The homothallic segregants continued to give rise to both heterothallic and homothallic spores in each generation. Strains that produced two homothallic and two **a** heterothallic spores were referred to as Hq strains; Hp strains gave rise to two homothallic and two α spores in each ascus. The interpretation of these results was that Hq strains lacked a function needed by *MATa* cells to diploidize, and that Hp strains were defective in a function needed for *MAT α* cells to diploidize. These functions are encoded by two genes originally identified as *HMa* and *HM α* , where *HMa* is required for diploidization of **a** cells and *HM α* is needed for diploidization of α cells. Mapping studies showed that the *HMa* (now referred to as *HML*) and *HM α* (now *HMR*) loci are located on opposite ends of the same chromosome as *MAT*, the mating type locus, which is near the centromere of this chromosome (III). Thus the functions of three genes, *HO*, *HML* and *HMR*, are needed for homothallic diploidization.

The standard chromosome III configuration of most laboratory yeast strains is *HML α MAT (a or α) HMRa*. If such a strain also carries the *HO* allele, both **a** and α spores will undergo diploidization. Hp strains are *HML α hma α (HMR α)* and cannot diploidize α spores. Hq strains are *hma (HMLa) HMRa* and cannot diploidize **a** spores. An *hma hma α* strain that carries the opposite mating type allele information at both *HM* loci (genotype *HMLa HMR α*), however, is capable of diploidization of both **a** and α spores. Thus the *hm* alleles are not defective, loss-of-function alleles; rather, they simply carry the opposite mating type information, such that '*hma α* ' is equivalent to *HMa*, and '*hma*' is equivalent to *HM α* . These observations suggested that mating type information at the *HM* loci is involved in homothallic diploidization. A second line of evidence supporting this hypothesis was that loss-of-

function, nonmating alleles of the *MAT* locus can be 'healed' in homothallic strains, giving rise to normal, mating-competent progeny.

These observations led to the development of the 'cassette model' for mating type switching (Herskowitz and Oshima, 1981). This model proposed that the *HM* loci contain silent, or unexpressed, copies of the mating type information that is also present in expressed form at *MAT*, the mating type locus. In homothallic strains, the information is copied from one of *HM* 'storage' loci into the *MAT* 'playback' locus. If α information is substituted for *a* information (or vice versa), the cell's mating type is switched and it can mate with an unswitched cell derived from the same homothallic spore. This results in formation of an *a*/ α diploid that does not undergo further switching or mating.

Regulation

The rules of switching were worked out by following pedigrees of isolated spores. A homothallic spore germinates and undergoes one cell cycle, to produce a mother cell and a newly created daughter cell by budding. The mother cell now becomes competent to switch and does so in the next cell cycle, in such a way that both the mother and its next daughter become the opposite mating type. These two rules of switching – that only mothers can switch, and mothers and daughters switch in pairs – can be explained by regulation of the *HO* gene, a required function for mating type switching (Haber, 1998). *HO* is turned on only in mothers and in the G1 phase of the cell cycle. Specific regulation of mating type switching requires the products of the *SWI* genes, originally identified by the isolation of switching-defective mutants. One of these, *SWI5*, encodes a transcription factor needed for *HO* expression. *SWI5* expression is itself restricted to mother cells by an interesting mechanism that involves asymmetrical messenger ribonucleic acid localization, a phenomenon that is not found elsewhere in yeast but is important in the regulation of development in mammalian embryos.

As discussed below, the *HO* gene encodes a site-specific endonuclease that initiates mating type switching by making a unique double-stranded cut in the DNA at *MAT*. When the mating type locus and silent *HM* loci were molecularly characterized, it was found that not only do complete copies of mating type information exist at the silent loci as well as at *MAT*, but so also does the *HO* cleavage site. What then keeps the information at the silent loci from being expressed and prevents *HO* endonuclease cleavage at these locations? Genetic analysis again provided the first clues: mutations that allow mating even in the presence of defective alleles at the mating type locus identified several *SIR* genes (silent information regulator) whose products are required for silencing the *HM* loci.

Such *sir* mutants suppress mating and sporulation defects of various mutations at *MAT* and allowed sporulation of *MATa*/*MATa* and *MAT α* /*MAT α* strains. They also permit cleavage at the *HM* loci by the *HO* endonuclease. Studies of the structure of yeast chromosome III at the *HM* loci show a different configuration of the genetic material at those locations than exists at *MAT*. The Sir proteins are required to create and maintain the special 'silenced' chromosome structure at the *HM* loci. Specific silencer sequences are found at the *HM* loci that are required for this unique chromosome structure. The mechanism of silencing is still an active area of research that has broader relevance for mechanisms of regulation of eukaryotic gene expression in general. In addition to the silent mating type loci, the telomere regions of yeast chromosomes are also silent, as are many loci in cells of higher eukaryotes.

Mechanism

The cassette model of mating type switching has subsequently been shown to be correct in its essential features (Herskowitz *et al.*, 1992; Haber, 1998). Switching comes about through a genetic recombination event initiated by specific DNA cleavage by the *HO* endonuclease at the *MAT* locus. Purified *HO* protein cleaves a 24-base pair (bp) recognition site, leaving 4-bp, 3' overhanging ends. Its mechanism of action is much like that of bacterial restriction endonucleases. Mutations in the *HO* recognition site prevent cleavage and mating type switching. Just as the ability of the mating pheromones to synchronize cells of the opposite mating type in their progression through the cell cycle has become a widely used tool of yeast biology, so too has the ability of *HO* endonuclease to make a specific, unique, double-stranded break in chromosomal DNA been exploited extensively to study the mechanisms of recombination both at the mating type locus and elsewhere in the yeast genome.

The cell's normal homologous recombination machinery repairs the cut by using one of the silent copies of the mating type information resident at the *HM* loci to replace the information at the active *MAT* locus. Specifically, the 3' overhanging ends left at *MAT* following *HO* endonuclease cleavage are processed by 5' to 3'-acting exonucleases, probably the products of the *RAD50*, *MRE11* and *XRS2* genes, to produce long, single-stranded 3' tails. The 3' tails can interact with the recombination-promoting *RAD51* gene product (a homologue of the bacterial *recA* gene) to create a nucleoprotein complex that searches for homologous DNA sequences, which exist at the *HM* loci. The free ends invade the homologous double-stranded region at *HML* or *HMR* and initiate a recombination event that results in the mating type information resident at the silent locus being copied to the *MAT* locus. This genetic exchange is almost always unidirectional, silent locus to

MAT, and does not involve recombination of outside genetic markers. Mating type switching is an example of general homologous recombination, however, because it requires many of the functions needed in recombinational repair of X-ray damage and in meiotic recombination.

Summary

Study of the seemingly arcane phenomena of mating type and mating type switching in the simple single-celled fungus *S. cerevisiae* has revealed unexpected complexity in the regulation of these processes that has shed light on basic mechanisms of eukaryotic cell biology.

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