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Editorial Open Access

Recent Advances in Understanding Yeast Genetics of Sex Determination

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Editorial

Sex determination is among the most fascinating areas of study in modern genetics and encompasses many topics, such as developmental mechanisms, behaviour, sex chromosome biology, population evolution and diversity. Yeasts from the subphylum Saccharomycotina are of great importance to humans, not only as pathogens but for numerous essential ecosystem services and serve as model to study evolution in action. The recent advent of inexpensive sequence information and other new tools has led to notable advances in our understanding of reproductive mechanisms over a broad range of species, revealing that genetic sex determination occurs in different ways with a myriad of outcomes in yeast.

Virtually all yeast species in the Hemiascomycetes lineage exist in three cell types: the mating competent a and α haploid cells and the product of their mating, the meiosis competent a/α cell diploid [1]. Sexual reproduction among yeasts can involve a single partner (homothallism) or two compatible partners (heterothallism) via three events: i) mating of unrelated haploids derived from diploid unrelated cells (amphimixis or outcrossing); ii) mating between spores from the same tetrad (automixis); iii) and mother daughter mating upon mating-type switching (haplo-selfing) [2]. In *Saccharomyces cerevisiae*, the mating-type a or α is determined by a single locus (*MAT*), which contains a (*MAT*a) or α (*MAT*α) genes and is located in the middle of the right arm of the chromosome III. The a-cells express a-specific genes (asgs), which are required for a-cells to mate with α-cells. Likewise, α-cells express the α-specific genes (αsgs). The third cell type, a/α, does not mate, because the asgs and αsgs are turned off. The asgs are on by default, and are repressed in α- and a/α-cells by a homeodomain protein (α2) that is encoded by *MAT*α. *MAT*α locus also encodes α1 transcriptional factor, which positively regulates the αsgs in α-cells.

S. cerevisiae has two additional copies of mating-type genes, *HML*α and *HMR*a, at distant locations on chromosome III. These genes are silenced and serve as donors during the recombination process that allows a *MAT*a cell to switch to *MAT*α or vice versa. In *S. cerevisiae* haplo-selfing is related to the presence of the endonuclease HO (Homothallism), which catalyzes the first step of *MAT* conversion that switch genetic material from one of two silent mating-type loci (*HMR* and *HML*) to the active *MAT* locus.

From mortimer's "genome renewal" to the "lonely spore" scenario

Mating-type switching is a highly regulated and complex process, so it must confer a benefit to yeast or it would not have been maintained by natural selection. The "Genome Renewal" hypothesis was firstly postulated by Robert Mortimer [3] and later revisited by Magwene [4] to explain high level of heterozygosity in wild populations of diploid and homothallic *S. cerevisiae*. Mortimer [4] posited that *S. cerevisiae* propagates vegetatively as diploid, increasing level of heteroygosity over generations. Rare sexual cycles involving meiosis followed by mating-type switching and haplo-selfing would facilitate the loss of deleterious alleles and fix beneficial ones in a homozygous diploid, thus leading to "Genome Renewal". Magwene argued that high levels of heterozygosity in *S. cerevisiae*, coupled with selfing during rare sexual cycles, can facilitate rapid adaptation to novel environments [4]. Indeed, for highly heterozygous homothallic strains, the adaptive evolutionary landscape has a high degree of "accessibility" because large regions of genotypic and phenotypic space can be sampled and tested in offsprings by local selection, getting the most favourable allele combinations to be fixed. This process occurs even more rapidly when a population is founded by clonal reproduction of a single or a few related individuals.

Another benefit gained by switching is under the name of "lonely spore" scenario [5,6]. Gordon et al. [6] proposed that the goal of switching is to maximize the ability of a young haploid colony to make new spore if nutrient level falls. Yeasts are dispersed to new habitats when they are eaten and excreted by insects [7]. Although ascospores (sets of four haploid spores formed by meiosis of a diploid) are structures that assist yeast cells to survive passage through the insect digestive tract, digestion by the insect may remove the ascus wall and causes some spores to become isolated [8]. If an isolated spore germinates, it has no way of making new spores unless it finds a mating partner of the opposite mating-type. Switching provides a partner, allowing cells to become diploid and able to make new spores.

How mating system has evolved?

Phylogenomics revealed that in subphylum Saccharomycotina mating system has evolved from an obligate heterothallic system (as seen in *Yarrowia lipolytica*), to heterothallism with low- switching frequency (as seen in *Kluyveromyces lactis*) and finally to a *HO*-catalyzed homothallic switching (as seen in *S. cerevisiae*), via a three-step events [9]. The first step was the origin of the HML and HMR cassettes (three-cassette system), which occurred in Saccharomycetaceae family after it had diverged from the GTG clade (including Debaryomycetaceae and the *Candida albicans* clade) and the methylotrophic yeasts *Hansenula polymorpha* and *Pichia pastoris*. These last yeasts are homothallic, but lack of *HO* and possess two *MAT* loci, which are switched by reversible inversion of a chromosomal section with *MAT*a genes at one end and a *MAT*α gene at the other end [10]. This inversion (or flip-flop)-based recombination mechanism moves genes between expressed and non-expressed sites. Hanson and co-workers [10] recently proposed that the three-cassette system evolved from a two-cassette flip-flop model.

The second step occurred independently in different species having silent cassettes, and consists in the acquisition of specialized machinery

for increasing the rate and/or accuracy of switching by directing a DSB to the *MAT* locus. In the *Saccharomyces* and their closest relatives *Zygosaccharomyces* species [11], the DSB is catalysed by the HO endonuclease. Rajaei et al. demonstrated that in *K. lactis* the DBS is made by the trasposase Kat1 [12].

The third event is the loss of an additional HMG domain gene (*MAT*a2), which codes for an HMG DNA-binding protein in the *MAT*à idiomorphs of several species, including *C. albicans*, *S. kluyveri* and *Z. rouxii*. In this vein, Tsong et al. [13] proposed an evolutionary model of transition from positive to negative regulation of asgs. In *C. albicans* persists the ancestral network where asgs are activated in cells by the a2-Mcm1 heterodimer, whereas in *K. lactis* an additional asgs repressor Mcm1-α2 appeared in α cells. *S. cerevisiae* lineage recently lost the *MAT*a2 gene, acquiring a α2-repressing mode of asgs by α2-Mcm1-α2 complex in α cells.

Focus on the *Zygosaccharomyces rouxii* complex

Zygosaccharomyces rouxii complex consists of salt-tolerant food yeasts which diverged from the *Saccharomyces* lineage after gaining the *HO* gene, but before the occurrence of a whole genome duplication (WGD) event in the ancestor of *Saccharomyces* clade [14].Three major groups were delineated, such as the haploid and mating-competent *Z. rouxii*, the diploid species *Z. sapae* (which rarely undergoes meiosis), and a subgroup of allodiploid and sterile strains with uncertain taxonomical position [15,16]. Beyond the phenotypic diversity [17], these yeasts exhibit abnormal chromosome variability, frequent gene duplication, marked ploidy variation, and unusual rDNA heterogeneity [15,18,19]. Watanabe et al. [20] and Solieri et al. [11] postulated that mating-type switching contributes to this genetic variation, which, in turn, favors phenotypic diversity and adaptation to hostile environments, such as salty food. Differently from *S. cerevisiae*, in *Zygosaccharomyces* yeasts the *HMR* locus and the *MAT-HML* linkage are located on distinct chromosomes. This means that *MAT*-like (*MTL*) loci are susceptible to ectopic and inter-chromosomal recombination events between two non-homologous chromosomes in haploids and two pairs of non-homologous chromosomes in diploids. Furthermore, as being an error prone mechanism, switching contributes to strong variability in organization and structure of sex chromosomes at many levels. Watanabe et al. [20] demonstrated that reciprocal translocation at the *MTL* loci was responsible of genomic instability in CBS 732^T stock of the type strain of the *Z. rouxii* species. Furthermore, translocation events make the *MTL* flanking regions variable in strains of the same species. Finally in the *Z. sapae* type strain $ABT301^T$, with aαaα genotype, an unusual cassette configuration without a *HMR* silent cassette [11], makes difficult the α-a switching and dys-regulates cell-type identity [21].

Applied perspectives

Sexual reproduction plays a central role in eukaryotic evolution by increasing genetic diversity and eliminating deleterious mutations. Therefore, meiosis and mating between members of genetically distinct populations have been exploited from old times to produce hybrid individuals with phenotypic novelty and heterosis, which can be selected for biotechnological purposes [22]. Strain improvement of food yeast mainly relies on classical breeding of strains followed by screening of progeny with enhanced properties of interest [23]. Tetrad analysis supplies comprehensive information about segregation pattern, gene linkage and recombination, which is needed as a basis for fundamental research and biotechnology. The knowledge of functional mating system and the way to restore it when impaired in sterile hybrids will thus reduce the amount of efforts required for breeding process and assist the study of genetic determinants of important industrial traits.

A proper regulation of the expression, activation, and interaction of *MAT* locus genes is also or essential for growth and differentiation in yeasts, since they are master regulators of cell-type identity. For instance, in *C. albicans* sexual reproduction governs the switching between morphological forms and it is correlated to the shift from opportunistic to pathogenic status [24]. Furthermore, reproductive gene isolation and incompatibilities among *MAT*-related genes are invoked as sources of reproductive isolation during fungi speciation, together with cito-nuclear incompatibilities [25]. Therefore, the understanding of the mating system may provide proper disease management strategies and can elucidate the speciation and evolution of life history in ascomycetes.

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