Rev Iberoam Micol. 2014;31(1):30–34

Revista Iberoamericana de Micología

www.elsevier.es/reviberoammicol

Mycologic Forum

The mating type-like loci of *Candida glabrata*

Patricia Yáñez-Carrillo, Karina A. Robledo-Márquez, Candy Y. Ramírez-Zavaleta [1], Alejandro De Las Peñas, Irene Castaño *

División de Biología Molecular, Instituto Potosino de Investigación Científica y Tecnológica (IPICYT), San Luis Potosí, San Luis Potosí, Mexico

ARTICLE INFO

Article history:
Received 16 August 2013
Accepted 27 September 2013
Available online 16 November 2013

Keywords:
Candida glabrata
Mating type-like loci
Subtelomeric silencing
Cell type identity

ABSTRACT

Candida glabrata, a haploid and opportunistic fungal pathogen that has not known sexual cycle, has conserved the majority of the genes required for mating and cell type identity. The *C. glabrata* genome contains three mating-type-like loci called *MTL1*, *MTL2* and *MTL3*. The three loci encode putative transcription factors, **a1**, α1 and α2 that regulate cell type identity and sexual reproduction in other fungi like the closely related *Saccharomyces cerevisiae*. *MTL1* can contain either **a** or α information. *MTL2*, which contains **a** information and *MTL3* with α information, are relatively close to two telomeres. *MTL1* and *MTL2* are transcriptionally active, while *MTL3* is subject to an incomplete silencing nucleated at the telomere that depends on the silencing proteins Sir2, Sir3, Sir4, yKu70/80, Rif1, Rap1 and Sum1. *C. glabrata* does not seem to maintain cell type identity, as cell type-specific genes are expressed regardless of the type (or even absence) of mating information. These data highlight important differences in the control of mating and cell type identity between the non-pathogenic yeast *S. cerevisiae* and *C. glabrata*, which might explain the absence of a sexual cycle in *C. glabrata*. The fact that *C. glabrata* has conserved the vast majority of the genes involved in mating might suggest that some of these genes perhaps have been rewired to control other processes important for the survival inside the host as a commensal or as a human pathogen.

This manuscript is part of the series of works presented at the "V International Workshop: Molecular genetic approaches to the study of human pathogenic fungi" (Oaxaca, Mexico, 2012).

Los loci de apareamiento de *Candida glabrata*

Palabras clave:
Candida glabrata
Loci similares a los de apareamiento
Silenciamiento subtelomérico
Identidad del tipo celular

RESUMEN

Candida glabrata, una levadura patógena haploide y oportunista, que carece de ciclo sexual conocido (asexual), conserva la mayoría de genes ortólogos requeridos en los procesos de apareamiento, esporulación y la identidad del tipo celular. El genoma de *C. glabrata* contiene 3 *loci* de apareamiento llamados *MTL1*, *MTL2* y *MTL3* que codifican los presuntos factores de transcripción **a1**, α1 y α2 que controlan la reproducción sexual e identidad celular en otros hongos, como *Saccharomyces cerevisiae* con el cual tiene una estrecha relación filogenética. *MTL1* puede contener información **a** o α; *MTL2* contiene información **a**, y *MTL3* que contiene información α1 y α2 son *loci* próximos a 2 telómeros. *MTL1* y *MTL2* son activos transcripcionalmente mientras que *MTL3* está sujeto a un silenciamiento que no es completo, que proviene del telómero y depende de las proteínas Sir2, Sir3, Sir4, yKu70/80, Rif1, Rap1 y Sum1. *C. glabrata* parece no mantener identidad de tipo celular ya que varios genes específicos de un tipo celular se expresan en todas las células con independencia del tipo de información de apareamiento en los loci *MTL*, o incluso, en su ausencia. Estos datos ilustran varias diferencias importantes entre la levadura no patógena *S. cerevisiae* y *C. glabrata* que podrían explicar la característica asexual en esta última. El hecho de que en *C. glabrata* se hayan conservado los genes necesarios para el apareamiento podría indicar que es posible que algunos de estos genes se hayan «reorganizado» para controlar otros procesos importantes en la supervivencia de *C. glabrata* en su huésped, como comensal o como patógeno.

Este artículo forma parte de una serie de estudios presentados en el «V International Workshop: Molecular genetic approaches to the study of human pathogenic fungi» (Oaxaca, México, 2012).

* Corresponding author.
E-mail address: icastano@ipicyt.edu.mx (I. Castaño).
[1] Current address: Department of Biomolecular Chemistry, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, USA.

1130-1406/$ – see front matter
http://dx.doi.org/10.1016/j.riam.2013.09.016

Sexual reproduction is thought to be advantageous in spite of the high cost in energy associated with it. Sex is thought to provide a means to eliminate deleterious mutations and promote genetic recombination, which in turn might produce progeny with a combination of beneficial traits that may be better adapted to changing environmental conditions.[26] Indeed, recent experiments in the model yeast *Saccharomyces cerevisiae* support this idea. The data indicate that under stressful conditions, sexual cells have an advantage over the obligate asexual congenic strain that only differed in their respective ability to mate. Instead, when these strains were grown under mild non-stressful conditions, there was no advantage for the obligate sexual strain.[13] Sexual reproduction is widely spread among eukaryotic organisms, even in many microbes that can reproduce asexually. However, there are some eukaryotes, including some fungi that appear to lack a sexual cycle. Only a few of the known species of fungi are associated with human disease, and many of the human pathogens have long since been thought to be asexual since no sexual reproduction has been observed. It is thought that sex in these pathogens might lead to loss of particular combinations of genes required to survive within the host.

Examples of asexual fungal pathogens are *Sporothrix schenckii*,[29] *Coccidioides immitis*, *Coccidioides posadasii*,[11] *Candida parapsilosis*,[40] *Candida glabrata* and others. However, in recent years there has been a surge in genomic studies that show that several of the human fungal pathogens contain the genes required for sexual reproduction, suggesting that they may have a cryptic sexual cycle, one that is controlled by very specific conditions, reviewed in some bibliographic references in this article.[21,24,32,33] This is the case of *C. immitis*, *C. posadasii*,[11] *Candida tropicalis*,[40] *Aspergillus fumigatus*,[37] *Candida albicans*[17] and *C. glabrata*.[9,44] For some of these fungal pathogens, a cryptic sexual or parasexual cycle was later discovered, like the case of *C. albicans*,[18] *C. tropicalis*,[38] *A. fumigatus*[34] and *Paracoccidiodes brasiliensis*.[42] These pathogens reproduce sexually under very particular conditions. In the case of *C. albicans* and *C. tropicalis*, in order to mate cells first have to undergo a morphological switch, which is the mating-competent stage.[30] For *A. fumigatus*, the sexual cycle can be observed in the laboratory after prolonged incubation (over 6 months) in the dark.[34] In *Cryptococcus neoformans* even though a sexual cycle has been documented in the laboratory for a long time,[22] mating is limited by the almost unisexual geographic distribution of only the α mating type.[25] In this way, these pathogens have retained the ability to generate genetic variation through controlled sexual or parasexual cycles in response to specific or changing conditions.[2,33]

For sexual reproduction to occur, two cells of opposite mating type must recognize each other through mating-specific pheromone and receptor signals. This is followed by cell–cell fusion, nuclear fusion and in many fungi by meiosis, although in some fungi like *C. albicans*, no meiosis has been observed, instead mating products undergo gradual chromosome loss until haploid chromosome content is achieved.[1]

In this review we will focus on the common opportunistic pathogen *C. glabrata*, an asexual haploid yeast, that shares a closer phylogenetic relationship with *S. cerevisiae* than to other *Candida* species.[5,14] *C. glabrata* is a commensal in healthy individuals but can become a successful pathogen associated with high mortality rates in immunocompromised patients.[36]

Control of sexual reproduction and cell type identity

Sexual reproduction and cell-type identity in most fungi are controlled by the genes encoded in the mating type locus called *MAT* (or *MTL* in some fungi). This locus encodes transcription factors that regulate the expression of genes that determine cell type identity and the signaling cascades that enable the cell to respond to the pheromone secreted by cells of the opposite mating type. These transcription factors are usually proteins containing a homeodomain or other types of regulatory domains like a α-domain or HMG (high mobility group) domain. Early studies in the non-pathogenic yeast *S. cerevisiae* have led to a detailed molecular mechanism for cell type identity control and mating. This organism, which can reproduce both sexually and asexually, contains three mating type loci (*MAT*, *HML* and *HMR*) of which only *MAT* is transcriptionally active and the other two loci are maintained repressed by a mechanism known as silencing.[15] Information present at the *MAT* locus can be either **a-type** or α-type while *HML* and *HMR* contain α and **a** information respectively, in over 97% of the strains studied. Control of cell type and mating involves a regulatory circuit determined by the **a1** protein and the α1 and α2 proteins encoded in the *MAT***a** and *MAT*α loci, respectively. The **a1** and α2 genes encode homeodomain-containing transcription factors while the α1 gene encodes a protein containing a α domain. In *MAT***a** haploids only **a**-specific genes (**a**sg) are expressed whereas in *MAT*α haploids only α-specific genes (αsg) are expressed. In both types of haploids a set of genes specific for haploid cells (hsg) is also expressed. After mating, the resultant diploid (**a**/α) forms a heterodimer with the proteins **a1** and α2 that represses α1, the hsg and some other genes involved with certain types of stress.[12,15,19] This regulatory circuit with some modifications also controls cell type identity in *C. albicans*, a diploid opportunistic human pathogen. Notably, a heterodimer composed of **a1**/α2 proteins is also formed in this organism and negatively regulates the phenotypic switch required for mating, therefore, indirectly controlling mating.[30]

Structure of the *C. glabrata* mating type-like loci *MTL1*, *MTL2*, and *MTL3*

Early studies reported that *C. glabrata* contains three mating type-like loci (*MTL*), in a similar configuration to that of the *MAT*, *HML* and *HMR* loci in *S. cerevisiae*.[41] *MTL1* corresponds to *MAT* while *MTL2* and *MTL3* to *HMR* and *HML*, respectively. In *C. glabrata*, *MTL1* and *MTL3* are in chromosome B, and *MTL2* is in chromosome E, whereas in *S. cerevisiae* the three loci are in chromosome III. It was initially proposed that *MTL1* is the expression locus and that *MTL2* and *MTL3* are transcriptionally silent, analogous to the situation in *S. cerevisiae*.[41] In the vast majority of *C. glabrata* isolates (approximately 97%), the information at *MTL2* is **a**, and α in *MTL3*. In contrast, the information in *MTL1* can be of either type, for example in the sequenced strain CBS138 (http://www.genolevures.org/cagl.html#), *MTL1* contains α whereas the BG14 strain[7] contains **a** information in this locus.[39] It has been reported that there is a bias toward **a**-type of information at *MTL1* in a collection of 190 *C. glabrata* clinical isolates from Africa, Europe, North America and South America where it was found that approximately 80% of the isolates contain **a** information and only 20% are α at this locus.[4] However, in our collection of 79 clinical isolates from three hospitals in Mexico, the α containing isolates are more frequent, since 64% of isolates contain α information at *MTL1* and 36% contain **a** information[23] (and Robledo-Márquez and Castaño, unpublished data). Therefore, it seems that the distribution of mating types varies depending on the geographical sites where the *C. glabrata* isolates are collected. It is not known whether there is a correlation between the information at *MTL1* and the pathogenicity in *C. glabrata* as there seems to be in *C. neoformans* where the α strains are more virulent than the very uncommon **a** strains.[10,25]