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The oxidative stress response of the opportunistic fungal pathogen *Candida glabrata*

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ABSTRACT

Organisms have evolved different strategies to respond to oxidative stress generated as a by-product of aerobic respiration and thus maintain the redox homeostasis within the cell. In particular, fungal pathogens are exposed to reactive oxygen species (ROS) when they interact with the phagocytic cells of the host which are the first line of defense against fungal infections. These pathogens have co-opted the enzymatic (catalases, superoxide dismutases (SODs), and peroxidases) and non-enzymatic (glutathione) mechanisms used to maintain the redox homeostasis within the cell, to resist oxidative stress and ensure survival within the host. Several virulence factors have been related to the response to oxidative stress in pathogenic fungi. The opportunistic fungal pathogen *Candida glabrata* (*C. glabrata*) is the second most common cause of candidiasis after *Candida albicans* (*C. albicans*). *C. glabrata* has a well defined oxidative stress response (OSR), which include both enzymatic and non-enzymatic mechanisms. *C. glabrata* OSR is controlled by the well-conserved transcription factors Yap1, Skn7, Msn2 and Msn4. In this review, we describe the OSR of *C. glabrata*, what is known about its core elements, its regulation and how *C. glabrata* interacts with the host.

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).

Respuesta al estrés oxidante en el hongo patógeno oportunista *Candida glabrata*

Palabras clave:
Candida glabrata
Yap1
Cta1
Skn7
Glutatión
Especies reactivas del oxígeno

RESUMEN

Los microorganismos han establecido diferentes estrategias para controlar el estrés oxidante generado durante la respiración aeróbica y, por consiguiente, mantener la homeostasia redox en la célula. En particular, los hongos patógenos se exponen a especies reactivas del oxígeno cuando interactúan con las células fagocíticas del huésped que son la primera línea de defensa contra estos agentes infecciosos. Estos patógenos han reclutado sistemas enzimáticos (catalasas, superóxido dismutasas y peroxidasas) y no enzimáticos (glutatión) que normalmente utilizan para mantener la homeostasis redox en la célula, para resistir frente al estrés oxidante y garantizar la supervivencia dentro del huésped. Varios factores de virulencia se han relacionado con la respuesta al estrés oxidante de los hongos patógenos. El hongo patógeno oportunista *Candida glabrata* (*C. glabrata*) es la segunda causa más frecuente de candidiasis después de *Candida albicans* (*C. albicans*). *C. glabrata* tiene una respuesta bien definida al estrés oxidante, que incluye sistemas enzimáticos y no enzimáticos y está regulada por los factores de transcripción Yap1, Skn7, Msn2 y Msn4. En esta revisión, describimos los elementos de la respuesta de *C. glabrata* a dicho estrés, cómo se regula y cómo *C. glabrata* interacciona con el huésped.

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).

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Yeast cells growing in an aerobic environment are exposed to reactive oxygen species (ROS) such as the superoxide anion ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2) and hydroxyl radical ($OH^{\bullet}$). ROS are formed as by-products, during normal aerobic metabolism, and could damage all biomolecules and cause cell death.[14] However, in order to maintain the redox homeostasis in the cell, a variety of enzymatic (catalases, SODs, and peroxidases) and non-enzymatic (glutathione) defense mechanisms are induced. This response is tightly controlled and is known as oxidative stress response (OSR).

Phagocytes are the first line of host defense against fungal infections. Upon interaction with the pathogen, phagocytes rapidly produce ROS through the NADPH oxidase complex.[1] Deficiencies in the NADPH oxidase result in increased susceptibility to fungal and bacterial infections underlying the importance of the oxidative killing of microbes. These data show how the pathogens antioxidant systems are necessary to survive the oxidative stress generated by host phagocytes during infection.[22] Until recently, it was not well-known how *Candida glabrata* responds to host cell phagocytosis and how it can survive and persist inside the phagolysosome.

C. glabrata is a haploid yeast found as a commensal in healthy individuals, but causes serious infections in immune compromised humans. In the past three decades, *C. glabrata* has become the second most common cause of candidiasis after *Candida albicans* (*C. albicans*). *C. glabrata* infections are difficult to treat and often result in high mortality in immune compromised hospitalized patients.[2] In the past 10 years, the molecular mechanisms enabling *C. glabrata* to become a successful human pathogen have been described. *C. glabrata* OSR appears to play a central role in the survival inside macrophages: *C. glabrata* neutralizes the ROS generated by the macrophage[38] by inducing antioxidant defenses,[28,29] inhibits the maturation of the phagolysosome[32] and ultimately replicates inside phagosomes.[15] In this review, we will focus on the OSR of *C. glabrata*.

Enzymatic defenses

Catalases

In aerobic organisms, catalases are ubiquitous enzymes that decompose H_2O_2 to water and oxygen. They function as scavengers of H_2O_2 to maintain the redox balance in the cell. Given that H_2O_2 has been found to be a signaling molecule, catalases are also important for growth regulation and development.[25] *C. glabrata* has one catalase CgCta1[5] (Table 1), a mono-functional 57-kDa heme-containing protein, classified as a small subunit catalase and is 85% similar to the *Saccharomyces cerevisiae* peroxisomal catalase, ScCta1. Although CgCta1 does not have a canonical C-terminal peroxisomal targeting signal (PTS1),[5] it has been shown to localize in the cytosol and accumulates in peroxisomes during respiration and inside phagocytic cells.[28] Furthermore, the expression of Cg*CTA1* is induced in the presence of oxidative stress and in carbon source deprivation.[29] Interestingly, the Cg*CTA1* locus does not maintain genic order when compared to other sequenced hemiascomycete yeasts.[23] In particular, the upstream region of *CTA1* is approximately 4.5 kb, much longer than the average 454 bp intergenic regions of *C. glabrata*.[36]

The in vitro resistance of *C. glabrata* to H_2O_2 is very high, compared to *S. cerevisiae* or *C. albicans*[5] and this in vitro resistance is mediated by the CgCta1; however, in a murine model of systemic infection the *cta1*△ mutant was not affected in the colonization phenotype of target organs in vivo.[5] This suggested that other antioxidant molecules could be compensating for the absence of CgCta1. Analysis of the double mutants lacking glutathione or thioredoxin suggested that theses antioxidant molecules are not responsible for compensating in vivo the absence of CgCta1.[10] To date, the role of CgCta1 as a virulence factor has not been established as in other pathogenic fungi.[8]

Superoxide dismutases

SODs are metalloenzymes that catalyze the dismutation of $O_2^{\bullet-}$ into H_2O_2 and oxygen. These enzymes protect cells against oxidative damage and scavenge $O_2^{\bullet-}$ radicals generated during aerobic metabolism. Based on their metal cofactor, SODs are classified in three families: copper/zinc (Cu,ZnSOD), iron or manganese SODs (FeSOD and MnSOD) and nickel SODs (NiSOD).[7] Most eukaryotes contain two SODs, a MnSOD localized in the mitochondrial matrix[37] and a highly abundant Cu,ZnSOD present in cytosol and mitochondrial inter-membrane space.[26] *C. glabrata* has two SOD genes, Cg*SOD1* (Cu,ZnSOD) and Cg*SOD2* (MnSOD) (Table 1). Interestingly, it has been shown that *Cryptococcus neoformans*, *C. albicans* and *Histoplasma capsulatum* SODs are required for survival against macrophages[13,24,40]; however, the survival rate of *C. glabrata sod1*△ mutant in macrophages was not diminished.[29]

In *S. cerevisiae*, *Schizosaccharomyces pombe* and *C. albicans*, *SOD1* expression is induced by oxidative stress,[6,18] and regulated by Yap1, a key transcriptional regulator of the OSR.[16,17,42] In contrast, *C. glabrata* Cg*SOD1* and Cg*SOD2* are constitutively expressed even in the presence of oxidative stress and independent of CgYap1.[29] Cg*SOD1* and Cg*SOD2* expression are highly induced under glucose starvation. Interestingly, the survival rate of *C. glabrata sod1*△ mutant in macrophages was diminished only in combination with a mutation in CgYap1.[29]

Glutathione and thioredoxin

Redox homeostasis is necessary to support important cellular processes. The oxidation status of thiols is maintained and rapidly

Table 1
Oxidative stress response genes in *Candida glabrata*.

Gene name	Systematic name	Function	Null mutant phenotype			
			Oxidative stress sensitivity	Phagocytes survival?	Important to virulence?	Ref.
CTA1	CAGL0K10868g	Catalase	H_2O_2	Yes	No	5
SOD1	CAGL0C04741g	Superoxide dismutase	MD	Yes	ND	31
SOD2	CAGL0E04356g	Superoxide dismutase	ND	ND	ND	31
TRR1	CAGL0A02530g	Thioredoxin reductase	No	ND	ND	12
GSH1	CAGL0L03630g	γ Glutamyl-cysteine synthetase	H_2O_2, MD, Cd	ND	ND	12,42
GSH2	CAGL0F00825g	Glutathione synthetase	H_2O_2, MD, Cd	ND	ND	12
YAP1	CAGL0H04631g	bZip transcription factor	H_2O_2, ONOO−	Yes	No	5,4,31
SKN7	CAGL0F09097g	Transcription factor	H_2O_2, t-BuOOH	Yes	Yes	5,34
MSN2	CAGL0F05995g	Cys_2-His_2 zinc finger transcription factor	H_2O_2	ND	No	5,29
MSN4	CAGL0M13189g	Cys_2-His_2 zinc finger transcription factor	H_2O_2	ND	No	5,29

Abbreviations: ND = not determined; H_2O_2 = hydrogen peroxide; t-BuOOH = tert-butyl hydroperoxide; ONOO− = peroxynitrite; MD = menadione; Cd = cadmium; bZIP = basic leucine zipper transcription factor.

restored by the action of two redox-balancing systems: glutathione (GSH) and thioredoxin pathways.[12] In yeast, the GSH system is constituted by GSH, glutaredoxins and a glutathione reductase. Similarly, the cytoplasmic thioredoxin pathway comprises two thioredoxins and a thioredoxin reductase.[35] *C. glabrata* has the majority of the components of both systems (Table 1); however, their role in the OSR of *C. glabrata* has recently been described.[10,39]

GSH is an essential tripeptide composed of glycine, cysteine and glutamate synthesized by the sequential action of Gsh1 and Gsh2.[21] Through its thiol group, GSH reacts directly with reactive species or acts as cofactor with specific enzymes (glutaredoxins, glutathione peroxidases or glutathione transferases) to detoxify ROS or xenobiotics. In *C. glabrata*, *GSH1* is essential[39]; however, a suppressor mutation in *CgPRO2* was isolated in the absence of *GSH1*. The *pro2-4* suppressor mutation could be acting through the synthesis of residual amounts of GSH.[10] Additionally, *C. glabrata* cells lacking glutathione are sensitive to oxidative stress and have a reduced late chronological life span.[10] Surprisingly, the *S. cerevisiae* specific GSH transporter (Sc*OPT1*) is not present in *C. glabrata*; however, there is evidence suggesting external uptake of GSH by an unknown transporter.[10] The differences between *S. cerevisiae* and *C. glabrata* in the GSH pathway and the absence of the GSH specific transporter suggest that GSH may play an important role during pathogenesis.

The thioredoxin system is a pivotal player in the redox homeostasis since some components affect the oxidative stress resistance in many microorganisms. In *C. glabrata*, there is evidence that suggest that the cytoplasmic thioredoxin system plays a minor role in H_2O_2 adaptation; however, the inability to disrupt simultaneously the three systems (GSH, thioredoxin and catalase) in *C. glabrata* suggests that these pathways could be complementing each other in order to respond to oxidative stress.[10]

Metallothioneins, phytochelatins and pigments

Some metals are essential micronutrients for physiological processes. Copper, zinc and other non-essential heavy metal ions, such as cadmium, lead, and mercury, are highly reactive and can produce oxidative stress. To diminish the toxic effects of heavy metals, some yeast synthesize phytochelatins (PCs), which are enzymatically synthesized cysteine-rich peptides derived from GSH and metallothioneins (MT), oligomeric thiolated molecules that act as chelators.[11] In the *C. glabrata* genome, two MT isoforms have been identified: MT-I (CAGL0D01265g) and MT-II (CAGL0H04257g).[19] *C. glabrata* appears to chelate cadmium with phytochelatin-like molecules[20]; however, the phytochelatin synthase coding gene has not been identified.

Pigments are important factors in pathogenic fungi for survival in their host. Production of the dark pigment melanin has been linked to pathogenicity. Recently it was shown that *C. glabrata* produces a pigment that protects against H_2O_2 and the attack by human neutrophils. This pigment is a by-product of the Ehrlich pathway of tryptophan degradation and its production is mainly driven by the aromatic aminotransferase I (Aro8).[3]

Transcriptional regulation by reactive oxygen species

CgYap1

A number of well-conserved transcription factors have been identified that control the OSR in *C. glabrata*.[5,28,29] Yap1 is a bZip transcription factor that contains cysteine rich domains in its N- and C-terminal portions. The transcription factor Yap1 of *C. glabrata* controls the OSR and accumulates transiently in the nucleus during phagocytosis.[28,29] In a genome wide analysis in *C. glabrata*, one set of genes (*CTA1*, *TRR1/2*, *TSA1/2*, *TRX2*, *GPX2* and *CCP1*) were dependent on the presence of both, Skn7 and Yap1, and defined the core of the OSR. A second Yap1-regulated group included genes encoding proteins with aldo-ketoreductase and oxidoreductase activities (*ADH6*, *GRE2*, *SCS7* and *OYE2*).[29] Interestingly, the loss of CgYap1 had no impact on virulence in both primary mouse macrophages or in a murine model of systemic infection.[4,29] It is possible that either the genes controlled by CgYap1 are dispensable to survive within the host or there are redundant mechanisms that compensate the lack of the genes controlled by this transcription factor.

CgSkn7

Skn7 is an oxidative and cell wall stress-responsive transcription factor highly conserved among fungi. It has been shown that in *C. glabrata* Skn7 controls the expression of a set of genes including *TRX2*, *TRR1*, *TSA1* and *CTA1* in response to the presence of H_2O_2 and is required for the adaptation response to oxidative stress.[5,30,34] Skn7 has been shown to be important for virulence in a murine model of systemic infection[31]; however, Skn7 was dispensable for prolonged survival in macrophages.[29]

CgMsn2 and CgMsn4

The Cys_2-His_2 zinc finger transcription factors Msn2 and Msn4 mediate the general stress response and functions in parallel with Yap1 and Skn7 to mediate the OSR in *C. glabrata*.[5,27] However, the function of Msn2 and Msn4-like proteins has diverged significantly among fungi. In a *Drosophila melanogaster* infection model, it was shown that Msn2 does not have a major impact on virulence.[27] Genes functionally connected to stress response, such as *HSP12*, *HSP42*, *DDR48*, *GPH1*, *GDB*, *TPS1*, *TPS2* or *PGM2* displayed a CgMsn2 and Msn4-associated upregulation.[27,41]

Concluding remarks

In the past 10 years, some of the *C. glabrata* virulence factors that contribute to pathogenesis have been identified, and in particular specific efforts have been made to study the interplay between *C. glabrata* and the host. As a successful fungal pathogen, *C. glabrata* quickly detects and responds to metabolic changes and to oxidative stress through the induction of protective enzymes against oxidative stress (catalase and SODs) and non-enzymatic defense systems (GSH) (Fig. 1). The transcription factors, Msn2, Msn4, Skn7 and Yap1, play a central role in the regulation of OSR. The fact that these transcriptional factors are dispensable for virulence (except for Skn7) suggests that *C. glabrata* survival depends on redundant pathways that can compensate each other (Fig. 1). It is possible that the ability of *C. glabrata* to suppress the production of ROS ensures its survival during phagocytosis.[33] Interestingly, although the structure of the MAP kinase pathways is relatively conserved among fungi, the role of MAPK pathways in *C. glabrata* remains largely unexplored despite the fact that these pathways are important for virulence.[9] The identification and characterization of the proteins involved in the detection of the oxidative signal will be essential to understand how *C. glabrata* evades killing by the phagocytic cells. Our knowledge about the OSR of *C. glabrata* is increasing rapidly and, in the next few years, future research will reveal major new insights into the regulatory networks and signal transduction pathways that regulate and coordinate the stress regulons in *C. glabrata*.

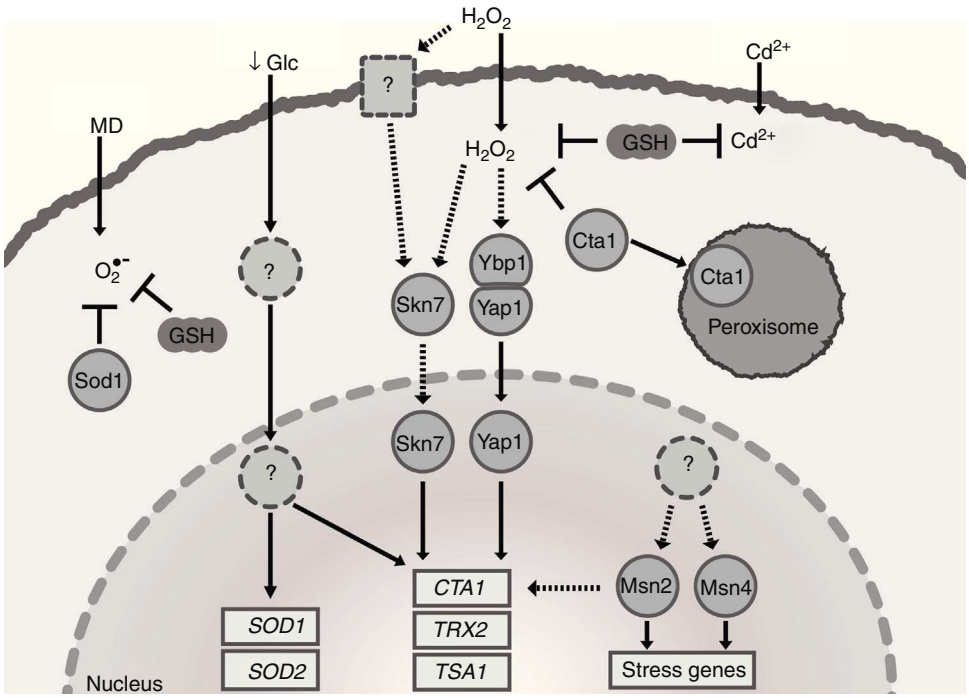

Fig. 1. Pathways of the OSR in *Candida glabrata*. *C. glabrata* responds with antioxidant defenses against external sources of oxidative stress such as menadione (MD), hydrogen peroxide (H_2O_2) and cadmium (Cd^{2+}). The peroxide-induced signal transduction pathway of *C. glabrata* is still unknown, but data suggest that H_2O_2 activates the transcription factors Yap1, Skn7 and Msn4. Yap1 response to H_2O_2 requires Ybp1. Yap1 and Skn7 activate transcription of the catalase (*CTA1*), thioredoxin (*TRX2*), and thioredoxin peroxidase (*TSA1*). The catalase detoxifies H_2O_2 in cytoplasm and peroxisomes. To neutralize the superoxide (O_2^-), *C. glabrata* induces the superoxide dismutase (Sod1) and the synthesis of glutathione (GSH). Sod1 converts O_2^- to H_2O_2. GSH participates in maintaining the redox balance. The transcription of *CTA1*, *SOD1* and *SOD2* is induced by glucose starvation (↓Glc). *SOD1* and *SOD2* do not respond to H_2O_2. Msn2 and Msn4 are involved in the activation of the general stress response. The discontinuous arrows and dashed-line circles represent not-well established pathways.

Conflict of interest

The authors declare that they have no conflict of interests.

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