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REDOX BIOLOGY OF CANDIDA ALBICANS: SURVIVAL IN HOSTILE CONDITIONS

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ABSTRACT

Candida albicans, the causative agent of most of the fungal infection in humans has been attributed to estimated 400,000 deadly infections world-wide each year involving immunocompromised patients. Innate immune cells use the reactive oxygen species (ROS) to eliminate the infection from the host. But the Candida species have evolved some sophisticated pathways to scavenge the ROS and evade the ROS mediated killing by macrophages and neutrophils. In recent years, the incidences of fungal infections have increased tremendously and so are the efforts to understand the pathogenesis. The recent findings have unveiled the mechanism employed by C. albicans to sense and respond to ROS produced by phagocytes. It has been illustrated that the ROS regulates the yeast to hyphae transition, how biofilms resist ROS toxicity and killing by immune system. In this review, we try to cover the recent findings in ROS sensing and signaling and their mechanisms in clinically important fungal pathogen Candida albicans.

KEY WORDS

Candida pathogenesis; Candida albicans; oxidative stress; biofilms; Hog1 pathway

1) Introduction

Primitive earth's atmosphere was filled with molecular oxygen (O_2) by the invasion of cyanobacteria (Schopf, 1993). Atmospheric oxygen has played a major role in the evolution and is responsible for catabolic activities of living organisms. On one hand, reactive oxygen species (ROS), as we know it can prove lethal to the living organisms. But on the other hand, ROS can also play a major role as a second messenger in the cell and control many essential processes from cell death, cell differentiation, cell survival and host immune response. The main source of ROS is the electron transport chain during aerobic respiration (Nohl et al., 2004; Nohl et al., 2003; Sedensky and Morgan, 2006). The most interesting redox regulated phenomenon is the "respiratory burst" also known as "oxidative burst", in which a large amount of ROS is produced in order to kill the microbial pathogen entering the host cell phagosome (Fang, 2011). The defective oxidase activity of NADPH oxidase can lead to chronic granulomatous disease (CGD) followed by deadly, systematic, life-threatening infections displaying the essentiality of ROS in microbicidal defense system (de Oliveira-Junior et al., 2011). But the processes and mechanisms involved in the killing of pathogen are still partially understood and open to debate (Slauch, 2011). In order to combat, survive in these hostile conditions, the intracellular microbial pathogens have developed some of the most sophisticated arsenal of antioxidant systems (Missall et al., 2004; Paiva and Bozza, 2014). Moreover, higher concentrations of ROS can lead to oxidation of host macromolecules also. To protect the cellular machinery from these detrimental effects of oxidation, cells have developed some complex sensing and response mechanisms to scavenge these ROS.

The fungal pathogens is fumigated when inside the host and interestingly, fungal pathogens have also developed one of the complex protective responses to protect its components from killing from ROS (Brown et al., 2014). The mechanisms involved have been

thoroughly deciphered in *Saccharomyces cerevisiae* due to availability of versatile and genetic tools to manipulate its genome. Pre-conditioning with lower doses of ROS can lead to trigger the expression of antioxidant genes to scavenge ROS (Jamieson, 1992), protecting the yeast from cell death due to high levels of ROS inside the cell. This baker's yeast has proved to be a valuable model system to study human fungal pathogens like *Candida albicans*, Candida glabrata, etc, in the absence of genetic tools for these organisms. According to evolutionary history, *S. cerevisiae* and *C. albicans* got diverged about 300 million years ago (Stajich et al., 2009). Although, they share some common characteristics but are genetically and phenotypically different in many respects and hence makes baker's yeast a "not so genuine" model for studying fungal pathogens (Karathia et al., 2011; Mohammadi et al., 2015). *C. albicans* and *C. glabrata* are the major fungal pathogens responsible for causing life-threatning infections in immunocompromised individuals with mortality rate of more than 50% among fungal infections and rising due to rise in immunocompromised patients (McNeil et al., 2001; Yang et al., 2017; Yapar, 2014). Thus it becomes incumbent upon us to understand the molecular mechanisms of survival of these candida species inside the host, flourish and cause systemic invasive infections. The toolkit of fungal pathogens, *C. albicans* or *C. glabrata* to neutralize and survive the damage caused by ROS during respiratory burst inside the phagocytes can prove a promising drug target for combating the spread of fungal infections. This review will be focused on the redox biology in the context of fungal pathogenesis with special reference to Candida. The studies on *S. cerevisiae* will be complemented in relation to antioxidant response in fungal pathogenesis.

2) Oxidative stress response pathways

2.1) Transcriptional regulators

The highly reactive superoxide radical $O_2^{\bullet-}$ is the primary ROS species produced during oxidative burst. In less than a second of its production, it gets converted to hydrogen peroxide H_2O_2, a highly reactive species responsible for killing of microbes inside an immune cell.(Halliwell and Gutteridge, 2007). The oxidative stress responses employed by *C. albicans* are similar to those found in non-pathogenic fungi, such as S.cerevisiae and S. pombe (Nikolaou et al., 2009). Interestingly, *C. albicans* is tolerant to milimolar concentrations of ROS (20 mmol l^{-1} of H_2O_2) (Jamieson, 1992). The resistance to oxidative stress is dependent on a bZip Transcription Factor Cap1 (an orthologue of *S. cerevisiae* Yap1). Cap1 transcriptional response regulation is the main pathway involved in Oxidative Stress resistance of *Candida albicans* and *C. glabrata*, facilitating the multidrug resistance response (Alarco and Raymond, 1999). Cap1 is regulated through Skn7 protein (Cuellar-Cruz et al., 2008). *Candida* species have been reported to adapt to a high level of H_2O_2 and establish infection. This resistance is also partially dependent upon two other stress transcription factors Msn2 and. Msn4. Interestingly, the only catalase gene, *CTA1* of *C. glabrata,* shown to be essential for H_2O_2 resistance *in vitro* has no role in providing virulence advantage during survival inside the mouse model of systemic infection (Cuellar-Cruz et al., 2008). The nuclear translocation of Cap1 due to oxidation on its redox sensitive cysteines leads to transcriptional activation of target genes by binding to Yap1-responsive elements (YRE) (Enjalbert et al., 2007; Zhang et al., 2000; Znaidi et al., 2009). Cap1 activates antioxidant genes involved in redox homeostasis and oxidative damage such as catalase (CAT1), superoxide dismutase (SOD1), gamma-glutamylcysteine synthetase (*GCS1)*, glutathione reductase (GLR1) and thioredoxin (TRX1) (da Silva Dantas et al., 2010). Among these antioxidant genes, CTA1, TRX1 and TTR1 are only upregulated only when in contact with neutrophils (Enjalbert et al., 2007; Lorenz et al., 2004) et al., 2007, Lorenz et al., 2004).

2.2) Two- component signal transduction pathways

The Hog1 MAPK dependent stress response signaling is also found to play a major role in resistance to oxidative stress in *C. albicans*. Like Skn7 mutant, Hog1 inactivation and its upstream components mutants renders *C. albicans* sensitive to oxidative stress (Alonso-Monge et al., 2003; da Silva Dantas et al., 2010). The two-component systems in *Candida* species are involved in most of stress adaptation pathways. CaSln1, Chk1 and Nik1/Cos1 are the three histidine kinases with homology to three different fungi. For example, CaSln1 has homology to Sln1 in *S. cerevisiae* (Nagahashi et al., 1998), Chk1 is homologous to Mak2 and Mak3 of S. pombe(Calera and Calderone, 1999) and Nik1 is structurally homologous to Nik-1 in Neurospora crassa (Alex et al., 1998). Interestingly like Hog1 mutation, the

mutations in above mentioned two-component genes results in the loss of virulence in *Candida* (Kruppa and Calderone, 2006). Interestingly, cells lacking the CaSsk1 response regulator, have lower level of CaHog1 phosphorylation under oxidative stress, but shows no effect upon osmotic stress (Chauhan et al., 2003). A point mutation in response regulator Ssk1, changing from aspartate to asparagines (D556N) renders the fungal cells more sensitive to peroxide stress than the cells lacking CaSsk1. Interestingly, Hog1 fails to translocate to the nucleus despite being phosphorylated in cells expressing CaSsK1D556N protein under oxidative stress (Menon et al., 2006). Although, Chk1 has been found to regulate the cell wall biosynthesis of mannan and glucan components, its potential role in peroxide sensing cannot be ignored due to its homology to Mak2 and Mak3 of S. pombe acting as peroxide sensing protein in two- component system (Buck et al., 2001; Kruppa et al., 2004). Chk1 deletion mutant cells have increased sensitivity to oxidative stress, but surprisingly, in *chk1* Δ cells there is no impairment of peroxide induced activation of Hog1 (Li et al., 2004; Roman et al., 2005). Moreover, *chk1* Δ*Casln1* Δ and *chk* Δ*nik1* Δ mutants show no impairment of Hog1 phosphorylation in presence of oxidative stress. The mechanism for the activation of peroxide induced phosphorylation of Hog1 in absence of D556N key residue points towards the redox relay to activate Hog1 that is independent of two-component system mediated phosphorylation and hence needs further investigation. Peroxidoxin Tsa1 may be playing a role in redox relay to activate Hog1. A new player in peroxide resistance in *Candida* is *Candida* response regulator 1 (Crr1) protein belonging to *Candida* CTG clade. Deletion or functional mutation (D to N) of CRR1 in *C. albicans* impairs the peroxide resistance. The localization of Crr1 in nucleus or cytoplasm is not affected by the functional mutation of aspartate residue or redox stress in *Candida*. Moreover, H2O2 induced activation of Hog1 is also independent of Crr1 dependent protein kinase pathway and has no role in virulence of *C. albicans* in mice model of infection. Taken together, two-component systems Chk1, Crr1 provides resistance to peroxide stress in Hog1-independent manner and is not required for virulence (Bruce et al., 2011; Smith et al., 2010). Another protein involved in providing oxidative resistance in *Candida* is Cor33 having no homolog present in S.cerevisiae. COR33 gene gets induced under peroxide stress and is dependent upon the Cap1 binding as it fails to get induced in CAP1 mutant strains. COR33Δ strains have impaired capacity to H2O2 resistance (Sohn et al., 2005). The oxidative stress response in *C. albicans* revolving around the Hog1 activation and resistance to H_2O_2 remains to be an active area of research. The mechanism of oxidative stress response of Cap1 and Hog1 dependent manner is still in infancy and more efforts need to be made to elucidate the involvement of these pathways in *Candida* sp. (Gonzalez-Parraga et al., 2010).

Similarly, *C. albicans* cap1 and hog1 also play a major role in resistance to oxidative stress induced killing during phagocytosis by host cells. Thus, hog1, cap1 and *trx1* mutants have been shown to have attenuated virulence (Cheetham et al., 2011; da Silva Dantas et al., 2010). Hence, the antioxidant genes equip the *C. albicans* with an arsenal of strategies to fight against the killing by phagocytes during early phase of infection. While, the oxidative stress response has less role to play after the development of systemic infections.

3) Oxidative stress response during infection

3.1) *Candida albicans* inside phagocytes

After internalization of *C. albicans* in phagocytes, it has been observed that the target fungal pathogen like any other microbial pathogen follows the path from phagosomes to phagolysosomes and gets fumigated and killed. During infection, *Candida* species are exposed to higher levels of reactive oxygen species (ROS), reactive nitrogen species (RNS) and antimicrobial peptides, low pH and reactive chloride species (HOCl) inside macrophages and neutrophils, and survival through these harsh conditions is essential for establishing disease and virulence. *C. albicans* evolved systems to directly scavenge the ROS produced by host cells and establish systemic infection. *C. albicans* is carrying six superoxide dismutase (SOD) genes. SOD genes along with other antioxidatnt genes are induced during exposure to host macrophages, neutrophil environments (Fradin et al., 2005; Lorenz et al., 2004) and in mucosal cells (Zakikhany et al., 2007). Interestingly, the transcriptional profiling performed by single cell analysis of *C. albicans* reveals that antioxidant gene induction is higher in case of ex vivo

condtioons as compared to infection in tissues (Walker et al., 2009; Wilson et al., 2009).

3.2) Superoxide dismutase and catalase

The importance of these antioxidant genes in virulence can be estimated from the fact that inactivation of SOD or catalase (CAT1) genes results in the impairment of ROS detoxification and *C. albicans* becomes sensitive to ROS killing and attenuated virulence (Fradin et al., 2005). *C. albicans* cells overexpressing CAT1 have been reported to tolerate higher concentrations of oxidants and resistant to killing by phagocytic cells. They also showed the inhibitory effect on amphotericin B or ciclopiroxolamine generating ROS accumulation in fungal cells. Although there was no change in MIC of amphotericin B and increases MIC of caspofungin two-fold, but in mouse model of infection, the CAT1 overproducing strain shows no effect on virulence (Roman et al., 2016).

3.3) Glutathione system

The stress response involving the glutathione redox system is ubiquitous to almost all living organisms and so is the case with fungal speicies where glutathione tightly regulates the redox homeostasis during different stress conditions (Missall et al., 2004). The increased sensitivity to oxidative stress and growth defect in minimal medium of *S. cerevisiae gsh1* mutant cells displays the importance of GSH in fungal cell survival (Grant et al., 1996). The killing or growth defect by oxidants, disulfiram, hypochlorite (HOCl), and heavy metals is also rescued by using exogenous GSH in medium (Kwolek-Mirek et al., 2011; Kwolek-Mirek et al., 2012; Thorsen et al., 2009). Consequently, the deletion mutant of GCS1 (homologue of *S. cerevisiae GSH1)* have imapaired tolerance to ROS, decreased killing by phagocytes, and diminished virulence in systemic candidiasis mouse model (Yadav et al., 2011). Moreover, the other enzymes in GSH system glutathione reductase (Glr1) of *C. albicans* have been shown to have reduced resistance to hydrogen peroxide and play a major role during infection in host (Tillmann et al., 2015).

4) Morphogenesis of *Candida* under the control of oxidative stress response

The killing of phagocytosis after the infection by activating apoptosis, necrosis and recently discovered phenomenon known as pyroptosis has been attributed to the ability of *C. albicans* to undergo morphogenesis from budding yeast to filamentous fungal cells. This change in form provides it with tools to escape from phagocytosis and resistance to oxidative stress meditated killing by macrophages and ultimately leading to death of macrophage. Interestingly, *C. albicans* cells with robust and dynamic oxidative stress response can only undergo morphogenesis to form filaments unlike the oxidant sensitive *C. albicans* cells, which fail to make filamentous cells in phagosomes. The ROS sensitive cells undergo phagocytosed and fail to evade killing machinery of phagocytes and are cleared from the host cells. (Lorenz et al., 2004; Miramon et al., 2014; Patterson et al., 2013). *C. albicans* cells lacking Cap1, Ybp1, or Gpx3 genes are not able to change to filamentous form inside macrophages and thus are essential for virulence in murine model of infection (Patterson et al., 2013). Interestingly, NADPH oxidase produces ROS, which is essential for inhibiting filamentation in *C. albicans* and recruitment of innate immune cells to the site of infection. Thus, *C. albicans* evades this NADPH oxidase response and completes yeast to hyphae transition and evades the signals necessary for chemotaxis of phagocytes to fight the infection (Brothers et al., 2013). It is interesting to note that the in vitro exposure of *C. albicans* to ROS triggers the yeast to hyphae switching and this hypha is very different from the true hypae or pseudohyphae and is known as hyperpolarized budding. The hyperpolarized bud is formed by mutations in the cell cycle pathway leading to cell cycle arrest of *C. albicans*. The filamentation inside macrophages to escape the immune response is different from hyperpolarized buds. As already stated above, *C. albicans* cells sensitive to ROS cannot undergo filamentation in macrophages but are hyperpolarized under H2O2 stress in vitro (Bachewich et al., 2005; da Silva Dantas et al., 2010; Patterson et al., 2013). Although the role of these hyperpolarized buds is unknown, we suspect it to play a role in interactions with other microbiota species in oral cavity or gut.

5) Regulation of DNA damage response by ROS

Although, the mechanisms involved in hyperpolarized budding in *C. albicans* is unknown, the H_2O_2 exposure mediated hyperpolarized bud formation does not involve key hyphal regulators, Efg1 and Cph1, but is regulated by DNA damage checkpoint pathway involving Rad53 (da Silva Dantas et al., 2010; Shi et al.,

2007). *C. albicans* Rad53 protein kinase gets activated on exposure to DNA damaging agents like UV, hydroxyurea, methyl methanesulfonate (MMS) and is responsible for the regulation of hyperpolarized budding formation. ROS leads to oxidation of DNA bases and is genotoxic leading to damage to DNA. The DNA damage checkpoint Rad53 gets activated and phosphorylation of Rad53 leads to downstream signaling to form hyperpolarized bud formation in *C. albicans*. Cells lacking Rad53 fail to elicit the DNA damage response and inhibit the hyperpolarized bud formation on exposure to ROS (Leroy et al., 2001; Loll-Krippleber et al., 2014; Shockley et al., 2013). Thus, Rad53 is activated by Trx1 in response to H_2O_2 and controls hyperpolarized bud formation (da Silva Dantas et al., 2010).

Rad53 is constitutively phosphorylated in cells lacking Trx1 and the cells undergo hyperpolized bud formation. Moreover, overexpression of thioredoxin reductase in cells to reduce Trx1 and activate it inhibits the hyperpolized bud formation in *C. albicans* by inhibition of Rad53. We already know the mechanism (Stajich et al., 2009), Trx1 uses to regulate the activity of proteins is by reducing them, thus we hypothesize that the same will be applied to Rad53. Chk1 is a cell cycle checkpoint protein similar to Rad53 reduced by Trx1 inhibiting its phosphorylation in mammalian cells. These findings provide an indirect proof for the regulation of Rad53 by redox relay in which oxidation leads to activation of the Rad53 and result in ROS mediated filamentation (Muniyappa et al., 2009). More efforts are needed to put in to understand the mechanism of ROS mediated filamentation of *C. albicans*.

6) Oxidative stress regulation in *Candida* biofilms

It has been widely illustrated that *Candida* spp. form biofilms on medical devices increasing the financial burden of medical treatment. *C. albicans* are the major fungal pathogen to form biofilms in immunocompromised patients. It is also established that neutrophils which are the main player in clearing of fungal infection are embedded in fungal biofilms to increase the thickness (Chandra et al., 2007). Such infections are not easy to get treated. The situation is worsened by the resistance of *Candida* biofilms to most antifungal drugs (LaFleur et al., 2006; Ramage et al., 2009). Although, it is unclear, why neutrophills (the professional killer cells) co-exist with *Candida* in a biofilm and not able to kill the pathogens, but recent study by Zhihong Xie et. al.(Xie et al., 2012) demonstrated that *Candida* cells in a biofilm impair the function of neutrophils by inhibition of ROS production. The inhibition of ROS leads to reduced activation of neutrophils and chemotaxis. Furthermore, the β-glucans present in extracellular matrix of *Candida* biofilm prevent the neutrophil activation by acting as a shield between biofilm cells and phagocytes (Xie et al., 2012). The antifungal agents are known to induce ROS in planktonic cells, but the biofilm cells are resistant to ROS induction by antifungal drugs.

7) Conclusions

Following the infection in host phagocytes, *C. albicans* cells are exposed to different myriad of oxidative reactive oxygen species and reactive nitrogen species. The presence of this fungal species in common host niches like oral cavity, gut and lungs as a commensal organism illustrates its unique tendency to combat the oxidative damage and evade the innate immune system to survive and thrive in that environment. *Candida* spp. have developed some of the sophisticated response regulators to avoid killing by ROS produced by macrophage NADPH oxidase. Moreover, immunocompromised patients are prone to *Candida* infections and result in the formation of drug tolerant biofilms inside the host. Thus, ROS plays an important role in eliminating the infection from the host and adding the potentiator to induce ROS in phagocytes could drastically change the MIC of anitmycotics. More indepth studies are needed to understand the relation of ROS production and *Candida* pathogenesis.

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