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Deciphering the oxidative stress response in *Candida albicans*

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ABSTRACT

Candida species are the leading cause of invasive fungal infections, with *Candida albicans* being the most common one. Consequently, the World Health Organization has included *C. albicans* in its fungal priority pathogens list. Following infection, phagocytes (mostly macrophages) initiate a respiratory burst, producing oxidant compounds, such as hydrogen peroxide. In response, *C. albicans* activates a robust oxidative stress response to catalyze the oxidant molecules produced by the immune system and counteract their oxidative effects within the cell. The oxidative stress response of *C. albicans* implies proteomic changes, both in abundance and in post-translational modifications, that are not fully described yet. Proteins with immediate antioxidant properties, the MAPK signaling pathways, and transcription factors are involved in the response. In this review, we discuss the role of these factors and the interactions among them in *C. albicans*. Many of these mechanisms act as virulence traits that favor the invasive candidiasis and can be used as potential targets for antifungal drugs.

1. Introduction

Candida albicans is a dimorphic fungus found as part of the microbiota of the skin and mucosal surfaces in 60% of the human population. Oral candidiasis is more common in immunocompromised patients, whereas vaginal candidiasis is common in immunocompetent women (Brandt, 2002). However, the importance of this opportunistic microorganism lies in its ability to cause invasive infections by disseminating through the bloodstream and colonizing internal organs (Talapko et al., 2021; Tsui et al., 2016). The origin of invasive candidiasis (IC) could be exogenous through colonized hospital workers or biofilm growth in medical devices, such as catheters; however, most cases are of endogenous origin (Suleyman and Alangaden, 2021). The transition of commensal *C. albicans* to a pathogen involves different, and sometimes coincidental, factors, such as disruption of microbiota balance, mucosal barrier damage, or immune system disorders. For this reason, IC is one of the main nosocomial diseases, and it is particularly prevalent in immunocompromised and intensive care unit patients (Dadar et al., 2018; Zhai et al., 2020). IC could be caused by different *Candida* species, the most common of which is *Candida albicans* (~65%), followed by *Candida glabrata* (~15%) (Guinea, 2014; Turner and Butler, 2014). The incidence of the disease varies between regions due to differences in healthcare practices, patient populations, or local epidemiological factors. The overall incidence of IC was 9 cases per 100,000 persons in the United States from 2013 to 2017, with no significant increase over time (Cleveland et al., 2015; Ricotta et al., 2021; Toda et al., 2020). On the other hand, the incidence decreased in Europe between 2000 and 2019 to a rate of 3.88 cases per 100,000 persons (Koehler et al., 2019; Tortorano et al., 2004).

The number of *C. albicans* strains resistant to several antifungal treatments, including azoles (e.g., fluconazole) and echinocandins (e.g., caspofungin), has increased, leading to multidrug-resistant strains that have rapidly spread around the world, becoming a considerable challenge (Costa-de-oliveira and Rodrigues, 2020; Lee et al., 2021). The limited effectiveness of standard antifungal treatments against resistant strains has led to increased morbidity, mortality, and healthcare costs (Ksiezopolska and Gabaldón, 2018; Sanyaolu et al., 2022). For this reason, the World Health Organization (WHO) has included *C. albicans* in the fungal priority pathogens list (FPPL) within the critical priority group ("WHO fungal priority pathogens list to guide research, development and public health action," n.d.). Thus, the discovery of new targets for antifungal treatments is a priority. Among the virulence traits of *C. albicans* are its mechanisms for responding to oxidative stress induced by phagocytes. In this review, we discuss the anti-oxidative mechanisms of *C. albicans* as a possible source of new antifungal targets.

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2. Immune response to invasive candidiasis

2.1. C. albicans-macrophage interaction

To counteract IC, the immune system interacts with *C. albicans,* particularly via neutrophils and macrophages (Molero et al., 2005). This interaction involves a complex process of surface recognition, phagocytosis, and immune response. Macrophages have surface receptors known as pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) and C-type lectin receptors (CLRs). PRRs recognize pathogen-associated molecular patterns (PAMPs) of *C. albicans,* such as β-glucans, mannans, or chitin (Erwig and Gow, 2016; Godoy et al., 2022; Qin et al., 2016). This recognition initiates the phagocytosis of *Candida* and an oxidative burst (Destin et al., 2009). Through this process, immune cells attempt to eliminate the pathogen by generating reactive oxygen species (ROS) and reactive nitrogen species (RNS) (Halliwell, 2006; Miranda et al., 2019; Nathan and Shiloh, 2000). ROS are generated in macrophages through the NADPH oxidase enzyme complex, which produces superoxide radicals (O_2^-) on the phagosomes. These radicals are converted into hydrogen peroxide (H_2O_2), hydroxyl radicals (OH^-), and other ROS (Fig. 1) (Brothers et al., 2013; Thomas, 2018). RNS are generated by the nitric oxide synthase (NOS) enzyme complex, but only NOS2 is induced in macrophages after interaction with *Candida*. NOS2 (iNOS), produces nitric oxide radicals (·NO) that are converted to nitrite (NO_2^-) and nitrogen dioxide (·NO_2) (Fig. 1) (Nathan and Shiloh, 2000). Nitric oxide is an oxidant molecule, but it does not exhibit the same strong oxidative properties and reactivity as ROS, though ·NO can also react with O_2^-, resulting in peroxynitrite ($ONOO^-$) (23, 28). The inhibition of NOS2 by overexpression of *Hdac11* (Wu et al., 2022) or the treatment of mice with aminoguanidine, an iNOS inhibitor (MacFarlane et al., 1999), substantially diminishes the antifungal capacity of macrophages and dendritic cells, increasing the virulence of wild-type *C. albicans* strain or less virulent mutant strains of *C. albicans*, such as the 92' or *mkc1Δ*-deleted strain. The same *C. albicans* strains, both wild-type and mutants, have demonstrated susceptibility to the NO and peroxynitrite donor SIN-1 (Vazquez-Torres et al., 1996) that is proportional to the virulence shown in a murine model of IC (Diez-Orejas et al., 2001; Molero et al., 2005). Alive *C. albicans* cells respond to ROS by inhibiting NADPH oxidase in untreated or IFN-α and IFN-γ treated dendritic cells (Donini et al., 2007). Moreover, *C. albicans* can inhibit NOS2 in macrophages activated by IFN-gamma and LPS via soluble factors (Chinen et al., 1999) and by direct contact with macrophages (Fig. 1) (Schröppel et al., 2001). This ability is also proportional to the virulence shown in a murine model of IC (Diez-Orejas et al., 2001; Molero et al., 2005).

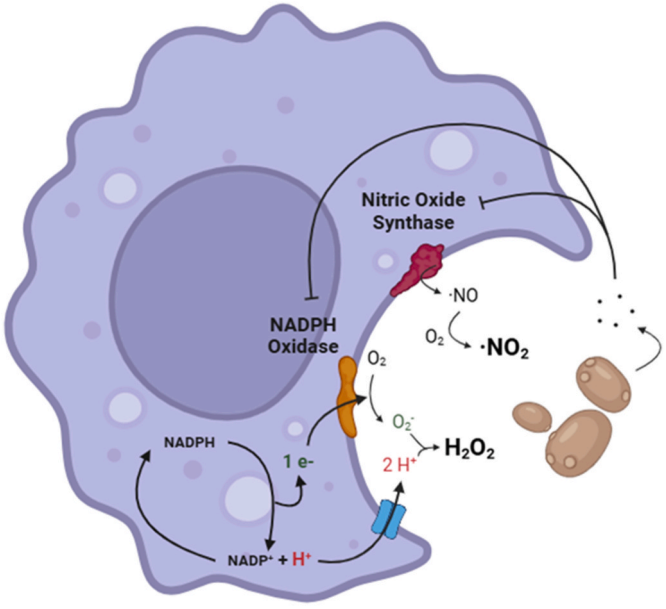

Fig. 1. Graphical illustration of ROS and RNS production by phagocytes. NADPH oxidase generates ROS by catalyzing the transfer of electrons from NADPH to molecular oxygen (O_2), leading to the production of superoxide anion (O_2^-). The superoxide radical reacts with two protons (H^+) to produce one molecule of hydrogen peroxide (H_2O_2). Nitric oxide synthase generates RNS by producing nitric oxide radicals (·NO), which reacts with molecular oxygen (O_2) to form nitrite (NO_2^-) and nitrogen dioxide (·NO_2). *C. albicans* releases soluble molecules to inhibit nitric oxide synthase and NADPH oxidase. This figure was created with BioRender.

Nevertheless, ROS species play an important role in the respiratory burst. After phagocytosis, macrophages release cytokines and chemokines that recruit other immune cells to the site of infection and activate an adaptive immune response. ROS released by immune cells also mediate different signaling pathways involved in regulation of the innate immune response. In this way, ROS also promote immune cell activation, contributing to the coordination of the overall immune response against IC (Brothers et al., 2013; Thomas, 2018). Consequently, ROS production by immune system cells is a pivotal defense mechanism to kill the invading *C. albicans* cells.

2.2. ROS effect on C. albicans

ROS generated during the respiratory burst have various direct effects on *C. albicans*. Highly reactive oxygen molecules react with cellular DNA, proteins, and lipids, ultimately leading to cell death (Juan et al., 2021). ROS result in DNA oxidation that can induce double-strand breaks that cause cell death. Oxidated nucleotides also increase the risk of DNA mutations due to mismatches impairing the modified nucleotides during replication. Moreover, oxidized DNA disrupts its interaction with different proteins, such as transcription factors or replication machinery proteins (Fig. 2) (Juan et al., 2021; Poetsch, 2020; Yao et al., 2021). ROS also result in the oxidation of amino acid residues, causing protein misfolding, with the consequential loss of its third structure, function, and interactions. In addition, dysfunctional oxidized proteins could aggregate or fragment, promoting their degradation (Fig. 2) (Stadtman and Levine, 2003; Zhang et al., 2013). ROS lipid peroxidation drives the production of reactive lipid peroxides. This process damages cell membranes, compromising their fluidity, permeability, and integrity, disrupting cellular functions and eventually inducing cell death (Fig. 2) (Vázquez et al., 2019; Yadav et al., 2019). Finally, ROS accumulation within *C. albicans* cells can trigger apoptosis, programmed cell death contributing to the elimination of invasive *Candida* cells (Amador-García et al., 2021; Cabezón et al., 2016).

3. Oxidative stress response signaling in *C. albicans*

Although ROS production by macrophages and neutrophils during the respiratory burst is an effective tool against *C. albicans* infection, this yeast has developed different mechanisms to counteract oxidative stress, contributing to its virulence. *C. albicans* defense mechanisms against oxidative and nitrosative stresses include the activation of signaling pathways. Currently, three signaling pathways have been described in response to oxidative stress, including mitogen-activated protein kinases (MAPKs), transcription factors, and DNA damage checkpoint signaling. These pathways regulate the cell cycle, DNA damage repair systems, and the expression and activation of antioxidant enzymes, such as catalase, or thioredoxin and glutathione systems.

3.1. MAPK signaling pathways

The MAPK pathways regulate different cellular processes, including signal transduction, cell growth, differentiation, and the response to environmental stimuli. The high osmolarity glycerol (HOG) MAPK pathway is the major signaling cascade that responds to oxidative stress

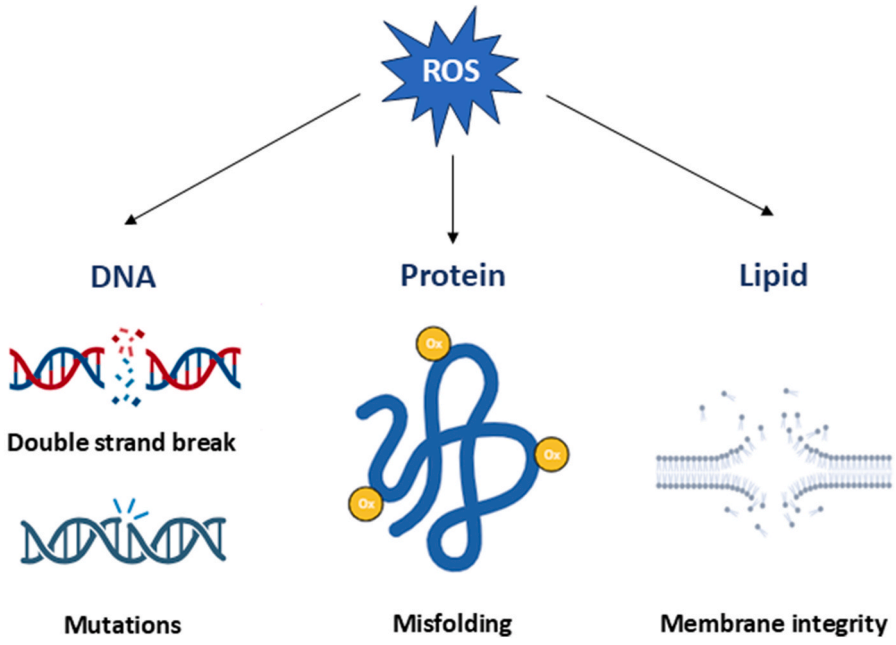

Fig. 2. Graphical illustration of ROS effects in *C. albicans*. ROS result in double-strand breaks and oxidation of nucleotide bases, which could induce DNA mutations. In proteins, ROS result in oxidation of amino acid residues, causing protein misfolding that leads into its loss of enzymatic activity or the disruption of their protein interactions. Finally, ROS result in lipid peroxidation compromising membrane fluidity and integrity, thereby disrupting cellular functions. This figure was created with BioRender.

in *C. albicans* (Alonso-Monge et al., 2003). Inactivation of the other MAPK signaling pathways does not increase the susceptibility of the *hog1Δ* mutant strain to oxidative stress (Correia et al., 2020). In *S. cerevisiae*, the HOG pathway can be activated by either the SLN1 branch or the SHO1 branch converging at Pbs2 MAPK. However, in *C. albicans*, Sln1 is the main branch involved in the activation of Hog1 after oxidative stress, while the Sho1 branch has a minor role (Chauhan et al., 2003; Román et al., 2005, 2020). H_2O_2 signals through the Sln1 branch, promoting Ssk1 phosphorylation and, consequently, Hog1 phosphorylation and activation (Chauhan et al., 2003). Although Hog1 phosphorylation is observed in the non-phosphorylatable *ssk1* mutant strain, it is not observed in the null-mutant when exposed to H_2O_2, while observed when grown in a hyperosmotic medium (Chauhan et al., 2003; Menon et al., 2006). *C. albicans* two-component system includes the

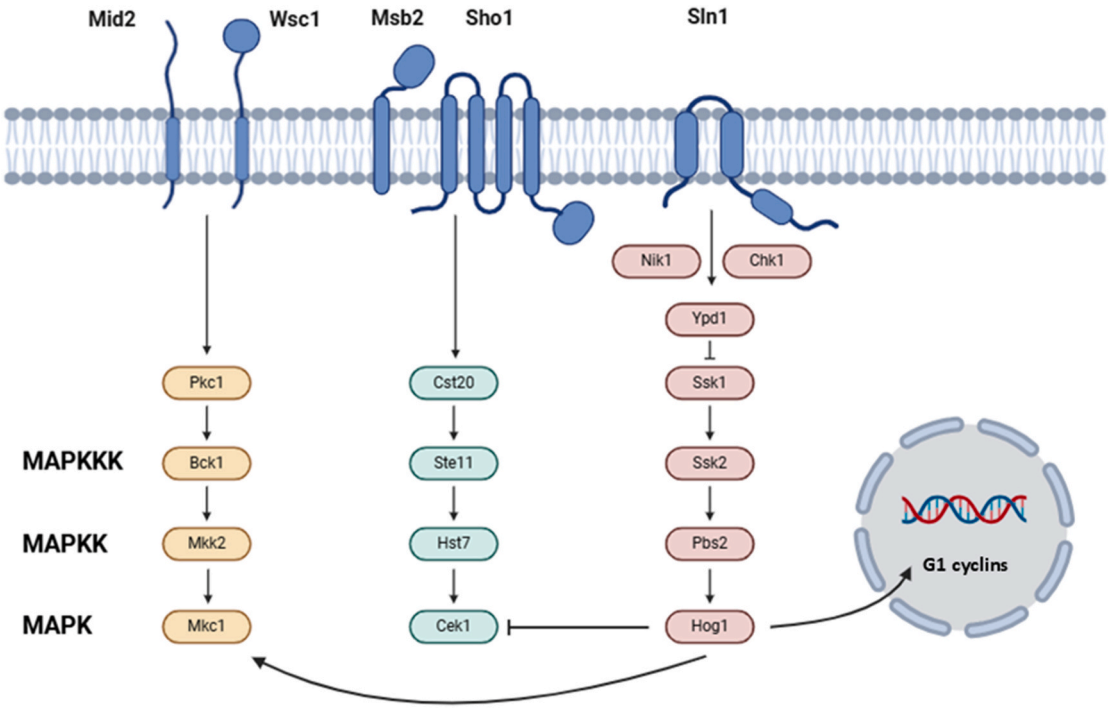

Fig. 3. Graphical illustration of MAPKs regulation after oxidative stress in *C. albicans*. Exogenous H_2O_2 diffuses through the membrane and promotes HOG MAPK signaling pathway activation. Phosphorylated Hog1 translocates to the nucleus and regulates the expression different proteins. Hog1 also mediates crosstalk with other MAPKs signalling pathways, phosphorylating Mkc1 and inactivating Cek1. This figure was created with BioRender.

histidine kinases Sln1, Chk1 and Nik1 (Liao et al., 2021). Chk1 is significantly upregulated following H_2O_2 and menadione treatment. Although Hog1 is phosphorylated in the *chk1Δ* mutant strain, the temporal events of phosphorylation differed slightly in mutant cells (Li et al., 2004). *C. albicans* two-component system includes the intermediate phosphorelay signal transduction protein Ypd1 (Liao et al., 2021). *YPD1* depletion promotes Hog1 constitutive phosphorylation, thus showing its role as inhibitor of the activation of Hog1 MAPK signalling pathway (Mavrianos et al., 2014) (Fig. 3). Trx1 and Tsa1 proteins from the thioredoxin system, complementary to its antioxidant function, have also been shown to be critical for Hog1 phosphorylation after H_2O_2 treatment (da Silva Dantas et al., 2010). Fzo1, a mitochondrial biogenesis factor, is also related to Hog1 phosphorylation after oxidative stress (Thomas et al., 2013).

Once activated, phosphorylated Hog1 translocates from the cytoplasm to the nucleus, regulating the oxidative stress response. Unexpectedly, transcription profile analyses have indicated that Hog1 phosphorylation is not essential for the expression of antioxidant genes (Enjalbert et al., 2006). Moreover, after treatment with 5 mM H_2O_2, Hog1 deletion does not promote significant changes to the *C. albicans* proteome, in contrast to salt or cadmium stress (Yin et al., 2009). These results suggest that, in addition to Hog1 activation, other more relevant mechanisms are involved in the antioxidant response. However, *hog1* mutants showed an altered expression of G1 cyclins after hydrogen peroxide treatment, modulating cell cycle progression (Correia et al., 2017). Hog1 also mediates important cross-talk between MAPK pathways, promoting Mkc1 phosphorylation and Cek1 pathway inactivation. In this way, Hog1 might be implicated in the cell wall integrity pathway and filamentation regulation after oxidative stress (Eisman et al., 2006; Navarro-García et al., 2005) (Fig. 3).

3.2. Transcription factor-mediated signaling

3.2.1. Cap1

Cap1, a bZip transcription factor of the AP-1 family, is the main regulator of the oxidative stress response attenuating *C. albicans* cell death by apoptosis (Dai et al., 2013). However, combined exposure to oxidative and cationic stress inhibits Cap1 nuclear localization through hyperoxidation of the transcription factor and the consequent reduction in catalase activity (Kaloriti et al., 2014; Kos et al., 2016). Cap1 has a conserved ortholog in *S. cerevisiae*, Yap1, which is also involved in the oxidative stress response (Alarco and Raymond, 1999). Yap1 has a nuclear export sequence (NES) on its C-terminal domain, which is conserved in *C. albicans*. This sequence is masked by its interaction with the Crm1 factor, preventing Yap1 from localizing to the nucleus. (Delaunay et al., 2000; Kos et al., 2016). Yap1 also needs to bind Ybp1 to form a complex that stabilizes it, avoiding ubiquitin-mediated degradation by the proteasome (Gulshan et al., 2012; Patterson et al., 2013). In *C. albicans*, upon H_2O_2 exposure, specific cysteine residues in Cap1 undergo oxidation, forming disulfide bonds that modify its structure. This conformation change prevents its binding to Crm1, promoting its accumulation in the nucleus (Zhang et al., 2000). Cap1 is oxidated by the glutathione peroxidase-like enzyme Gpx3, promoting its nuclear localization. In the nucleus, Cap1 is phosphorylated, inducing the expression of Cap1-dependent antioxidant proteins, including Tsa1 and Trx1 thioredoxins. In addition, Trx1 reduces oxidized Cap1, reversing its activation (da Silva Dantas et al., 2010) (Fig. 4).

Chromatin immunoprecipitation (CHiP) analysis has shown that, in the nucleus, Cap1 not only binds to gene promoters, but is also present in their upstream regions. Thus, Cap1 also associates with the transcriptional and chromatin remodeling machinery to induce antioxidant gene expression (Znaidi et al., 2009). Specifically, Cap1 mediates the recruitment of Ada2, a component of the SAGA/ADA histone acetylase complex, which is critical for the oxidative stress response (Ramírez-Zavala et al., 2014; Sellam et al., 2009). Under oxidative stress, Cap1 mainly regulates three ROS detoxication systems: catalase, thioredoxin, and glutathione (Komalapriya et al., 2015). In addition, Cap1-regulated genes have been implicated in other pathways, including carbohydrate metabolism (e.g., glucose-6-phosphate dehydrogenase), protein degradation (e.g., 26S proteasome regulatory subunit), and ATP-dependent RNA helicase (e.g., DEAD box protein ATP-dependent RNA helicase) (Wang et al., 2006). In summary, Cap1

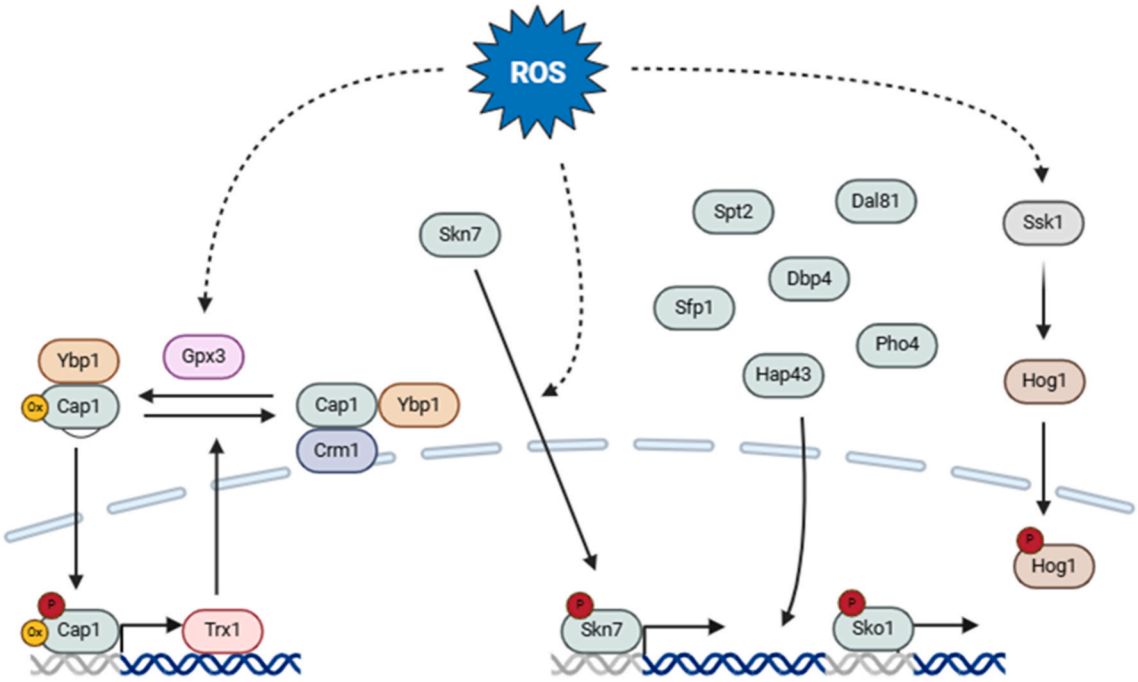

Fig. 4. Graphical illustration of *C. albicans* oxidative stress transcription factors signalling. Oxidative stress response takes place through two main transcription factors: Cap1 and Skn7. In addition, other transcription factors, such as Hap43, Sko1, Sfp1, and Pho4, have also been implicated. This figure was created with BioRender.

is the main transcription factor implicated in the oxidative stress response, but the existence of other Cap1-independent mechanisms that modulate the oxidative stress response have also been investigated (Gónzalez-Párraga et al., 2010).

3.2.2. Skn7

Suppressor of Kre Null (Skn7) is a transcriptional regulator that regulates ROS accumulation through antioxidant gene expression during filamentous growth (Basso et al., 2017; Singh et al., 2004). Skn7 increases the expression of different antioxidant proteins, including Tsa1, Trr1, and Gpx2, together with other genes related to hyphal growth and morphogenesis (Basso et al., 2017). The upstream regulation and activation of Skn7 in *C. albicans* are still unknown. However, as described in *S. cerevisiae*, Skn7 D427 is susceptible to phosphorylation in a Sln1-Ypd1 branch-dependent manner (Fassler and West, 2011). Furthermore, Skn7 T484 and T486 may be phosphorylated during regulation of the oxidative stress response (Basso et al., 2017). Cap1 and Skn7 are the main regulators of the oxidative stress response in yeasts, and their interaction has been proven in *S. cerevisiae* (Fig. 4) (Mulford and Fassler, 2011).

3.2.3. Hap43

Hap43, also known as Cap2, is a negative transcriptional repressor induced under low iron conditions that represses iron-dependent proteins involved in mitochondrial respiration (Hsu et al., 2011). Hap43 expression is increased after *Candida* and neutrophil interaction (Niemiec et al., 2017). In addition, Grx3, a putative glutaredoxin, interacts and regulates Hap43, linking this protein to the oxidative stress response (Alkafeef et al., 2020). Hap43 has been implicated in the regulation of oxidative stress genes in response to iron availability, including Cat1, Sod4, Grx5, and Trx1. In this way, Hap43 links iron obtainability to the oxidative stress response (Chakravarti et al., 2017).

3.2.4. Other oxidative stress transcription factors

The transcription factor Sko1 is implicated in Hog1 phosphorylation and regulation of the Mkc1 MAPK signaling pathway. In this way, Sko1 plays an important role in hyphal growth regulation during the oxidative stress response (Alonso-Monge et al., 2010). Another transcription factor, Sfp1, is also implicated in the oxidative stress response and in the cell wall integrity pathway (Chang et al., 2022; Hsu et al., 2021). In a *sfp1Δ* mutant strain, the Hog1 MAPK pathway is phosphorylated and, consequently, activated, which is accompanied by increased expression of Cap1 and several antioxidant proteins (Lee et al., 2019). Pho4, a transcription factor required for phosphate acquisition, is involved in osmotic stress signaling, but also indirectly in oxidative stress by mediating copper bioavailability to activate the superoxide dismutase Sod1 (Ikeh et al., 2016; Urrialde et al., 2016). Pho4 regulates the expression of the high-affinity phosphate transporter Pho84, which has also been implicated in *C. albicans* virulence and regulates Sod3 expression through TORC1 activation (Liu et al., 2018) (Fig. 4).

Recently, a genetic screen of transcription factor mutants together with genome-wide transcriptional profiling after H_2O_2 treatment revealed new putative transcription regulator proteins in response to oxidative stress, including Dal81, Stp2, and Dbp4. Null mutant strains of these proteins have increased sensitivity to H_2O_2 (Cui et al., 2023). Dal81 is involved in the regulation of different genes under starvation conditions (Ramachandra et al., 2014) and filamentation (Wakade et al., 2023) but is also related to Aox2 oxidase-regulated expression (Liu et al., 2023). Spt2 is a transcription factor that regulates the expression of amino acid and peptide permeases (Miramón et al., 2020). Dpb4 is a positive transcriptional regulator of Goa1, an oxidative stress-related mitochondrial protein (Khamooshi et al., 2014; Li et al., 2011).

3.3. Oxidative stress DNA damage signaling

ROS activate the DNA damage checkpoint that leads to Rad53 phosphorylation, inducing expression of the DNA repair system genes, hyperpolarized bud formation, and cell cycle arrest (Leroy et al., 2001; Loll-Krippleber et al., 2014; Shi et al., 2007). Mec1 has been the classical kinase implicated in DNA damage-Rad53 activation in *C. albicans* (Legrand et al., 2011) and, in combination with Tel1, in *S. cerevisiae* (Vialard et al., 1998). Recently, Mec1-Rad53 activation has been proven to be necessary for DNA damage-induced autophagy, enabling Atg1 and Atg13 recruitment to the phagophore assembly sites. Moreover, DNA damage-induced autophagy regulators Psp2 and Dcp2 regulate Rad53 and Mec1 protein levels (Du et al., 2023). In addition to its main role in Hog1 and Cap1 activation, thioredoxin Trx1 is a key factor in the regulation of Rad53 kinase phosphorylation activation in response to oxidative stress-induced DNA damage, though the exact mechanism has not yet been elucidated (Dantas et al., 2010).

4. ROS scavenging mechanisms and antioxidant proteins

Oxidative stress signaling pathways promote the expression and activation of several antioxidant systems implicated in ROS clearance to protect cells from oxidative injury. These signaling pathways also promote significant changes to the relative quantitative abundance of numerous proteins, including oxidoreductases and heat shock proteins. These changes in protein abundance are also an important part of the cellular response to counteract the intracellular oxidation of nucleotides, amino acids, and lipids by ROS. Both antioxidant system activation and proteome remodeling are critical for the cellular response to ROS and increasing cell survival after oxidative stress.

4.1. ROS scavenging systems of C. albicans

Upon H_2O_2 exposure, *C. albicans* induces the expression of key components of the three main ROS scavenging systems: catalase, thioredoxin, and glutathione (Fig. 5) (Komalapriya et al., 2015). The catalase system catalyzes H_2O_2 into water and oxygen, contributing to ROS detoxication. In *C. albicans*, catalase is coded by one gene, *CAT1*, which is regulated by the transcription factors Cap1 and Hap43 (Chakravarti et al., 2017; Znaidi et al., 2009). The thioredoxin system involves three proteins (Tsa1, Trx1, and Trr1) that are also induced by Cap1 (Urban et al., 2005; Wang et al., 2006; Znaidi et al., 2009). Peroxyredoxin Tsa1 disrupts H_2O_2 through oxidation of the conserved peroxidatic cysteine residue and then forms a disulfide bond with the resolving cysteine residue of another Tsa1 partner protein. Subsequently, thioredoxin Trx1 reduces Tsa1 homodimers, forming a disulfide bond in its active site sequence, Trp-Cys-Gly-Pro-Cys. Oxidized thioredoxin is then reduced through the action of thioredoxin reductase Trr1 using NADPH (da Silva Dantas et al., 2010; Komalapriya et al., 2015) (Fig. 5). In contrast to *S. cerevisiae*, which has two redundant, fully functional thioredoxins (Trx1 and Trx2), *C. albicans* Trx1, but not Trx2, contains the essential active site to reduce Tsa1. Thus, Trx1 is the only thioredoxin that mediates the oxidative stress response, playing a pivotal role in the regulation of Hog1 and Rad53 signaling pathway activation (da Silva Dantas et al., 2010). The glutathione system consists of glutathione peroxidases (Gpx1-3), which disrupt H_2O_2, and the glutathione (GSH) tripeptide as a reductant molecule. GSH is oxidized to GSSG, which is subsequently reduced back to GSH by glutathione reductase (Glr1) using NADPH (Fig. 5). Gpx1 is the main glutathione peroxidase involved in the oxidative stress response, whereas the gamma-glutamylcysteine synthetase Gcs1 synthesizes GSH; both are regulated by Cap1. In addition, the glutathione system repairs oxidatively damaged proteins through Grx1, Grx3, and Ttr1 glutaredoxins (Komalapriya et al., 2015; Miramón et al., 2014).

Pentose phosphate pathway (PPP) activation following oxidative stress exposure leads to an increase in NADPH production to support H_2O_2 detoxification by the glutathione and thioredoxin systems. In *C. albicans*, Zwf1 enzyme from the PPP is regulated through the transcription factor Cap1 (Fig. 5). In this way, this protein serves as a

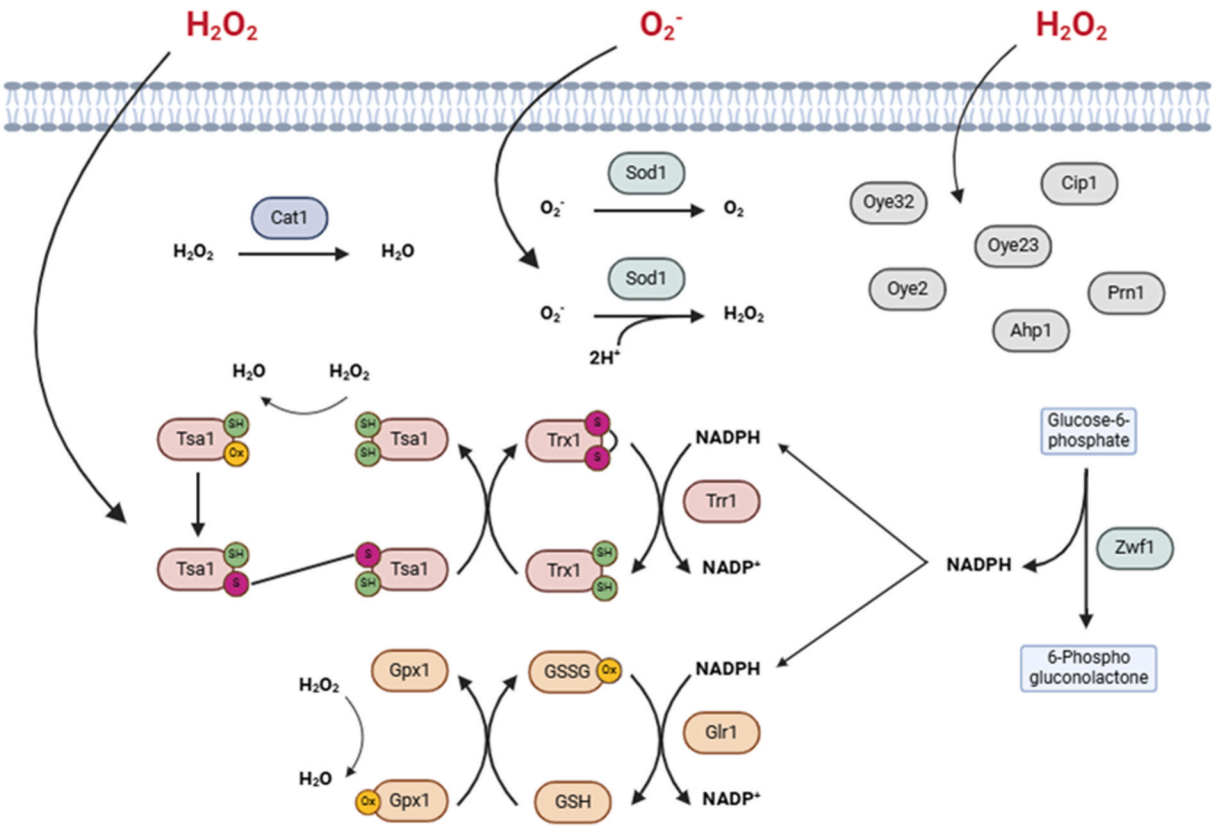

Fig. 5. *C. albicans* ROS **scavenging.** The catalase system consists of the Cat1 protein regulated by Cap1 and Hap43 transcription factors. The thioredoxin system involves three proteins: Tsa1, Trx1, and Trr1, also induced by Cap1 and Hap43. The glutathione system includes glutathione peroxidases (Gpx1-3) and glutathione (GSH) tripeptide. The pentose phosphate pathway protein Zwf1 acts as a regulatory mechanism to enhance the production of NADPH. Superoxide dismutase catalyzes the conversion of superoxide radicals into oxygen or hydrogen peroxide. Other oxidoreductases (e.g. Oye32, Cip1), dehydrogenases (e.g. Oye2, Oye23), and reductases (e.g. Ahp1) also increase their abundance to detoxify ROS. This figure was created with BioRender.

regulatory mechanism to enhance the production of NADPH, which is crucial for optimal functioning of the ROS scavenging systems during the oxidative stress response (Komalapriya et al., 2015; Strijbis et al., 2012).

Superoxide dismutases catalyze superoxide radical (O_2^-) into oxygen or hydrogen peroxide (Fig. 5). The genome of *C. albicans* has six putative superoxide dismutases. Sod1 and Sod4-6 are Cu/Zn-dependent, whereas Sod2 and Sod3 are Mn-dependent. Sod1 and Sod3 are in the cytosol; Sod2 is in the mitochondria; and Sod4, Sod5, and Sod6 are on the cell surface. At early stages of *C. albicans* infection, host Cu levels rise concurrently with the expression of Cu-Sod1 in the yeast. Later, Cu levels decline, leading to a switch to Mn-Sod3 expression. This adaptation allows *C. albicans* to respond to host Cu fluctuations, promoting superoxide dismutase activation as part of the oxidative stress response. Among surface-located superoxide dismutase, Sod5 is the only one that can detoxify extracellular ROS after the yeast-host interaction (Frohner et al., 2009; Martchenko et al., 2004).

Catalase is present at relatively high levels under basal conditions and is involved in immediate ROS detoxication after oxidative stress exposure, carrying out the major role in the oxidative stress response. Moreover, catalase is the only one of the three systems that also reduces extracellular H_2O_2 levels. On the other hand, the thioredoxin and glutathione systems also participate in the initial H_2O_2 detoxication steps, but they may play a more prominent role in the later stages (Komalapriya et al., 2015). The thioredoxin system may also play a main role at higher oxidative stress levels, with peak expression at 5 mM H_2O_2, whereas the catalase and glutathione systems reach their maximum peak at 2 mM H_2O_2 (Enjalbert et al., 2007).

4.2. Quantitative changes in protein abundance

The *C. albicans*-macrophage interaction promotes significant proteome changes in the yeast, including protein metabolism, deoxidation, and degradation. Glutathione system proteins (Gpx1), thioredoxin system proteins (Tsa1), and PPP regulators (Zwf1) significantly increase in abundance after interaction, as do other scavenging proteins, such as Sod1 or Sod3 superoxide dismutases (Fernández-Arenas et al., 2007). Further proteomic analysis confirmed the increased expression of thioredoxin system proteins (Prx1) and superoxide dismutases together with dehydrogenase proteins (Gdh3, Tdh3, and Adh3), reductases (e.g., Ahp1), which are regulated by Hog1 activation, and other metabolism and translation-related proteins. The levels of antioxidant proteins after the *C. albicans*-macrophage interaction are summarized in Table 1. In addition, pro-apoptotic proteins increase in abundance in response to the interaction (Cabezón et al., 2016). Transcriptomics analysis after macrophage interaction has also revealed significant reprogramming of the yeast proteome in two steps. First, *C. albicans* shifts to a starvation mode, inducing gluconeogesis, fatty acid degradation, and down-regulation of translation, together with the expression of DNA damage repair and oxidative stress genes. Later, *C. albicans* switches to hyphal growth, allowing escape from the macrophage and the restart of glycolytic growth (Lorenz et al., 2004).

The exposure of *C. albicans* cells to 5 or 10 mM H_2O_2 also promotes significant quantitative changes in the abundance of three main ROS scavenging system proteins, as well as superoxide dismutases. Other oxidoreductases (e.g., Oye32, Cip1), dehydrogenases (e.g., Oye2, Oye23, Fdh3), reductases (e.g., Ahp1, Gre3), and heat shock proteins (e.g., Hsp12 and Hsp104) also increase in abundance (Amador-García et al., 2021; Yin et al., 2009). Antioxidant proteins that are increased

Table 1
Significantly increased *C. albicans* antioxidant-related proteins after *C. albicans*-macrophage interaction or H_2O_2 treatment.

	Significant increased antioxidant-related proteins after *C. albicans*-macrophage interaction	Significant increased antioxidant-related proteins after H_2O_2 treatment
Catalase system	–	Cat1
Glutathione system	Gpx1	Glr1, Glx3, Grx3, Gst1 and Gst2
Thioredoxin system	Tsa1, Prx1,	Tsa1, Trr1, Trx1 and Ttr1
Pentose phosphate pathway	Zwf1	Zwf1
Superoxide dismutase	Sod1, Sod3	Sod1 and Sod2
Dehydrogenase proteins	Gdh3, Tdh3 and Adh3	Oye2, Oye23 and Fdh3
Reductase proteins	Ahp1	Ahp1, Mcr1 and Gre3
Oxidoreductase proteins	–	Oye32, Cip1, Pst1 and Ccp1
Heat shock proteins	–	Hsp12 and Hsp104

after H_2O_2 exposure are given in Table 1. Most of these proteins are regulated by Cap1 or Hap43 transcription factors in response to oxidative stress (Chakravarti et al., 2017; Znaidi et al., 2009). Moreover, oxidative stress promotes a significant relative increase in the abundance of proteasome-dependent catabolism, amino acid biosynthesis, and ribosome biosynthesis proteins (Amador-García et al., 2021). Other proteins, such as Prn1, a protein similar to mammalian pirin, or Cub1 also significantly increase in relative abundance and are implicated in the oxidative response, however, the exact function remains to be determined (Arribas et al., 2024). Oxidative stress also promotes significant changes in cell wall proteins, including moonlighting or heat shock proteins (Ramírez-Quijas et al., 2015; Serrano-Fujarte et al., 2016). Moreover, recent studies have shown that oxidative stress leads to significant changes in the abundance of proteins in extracellular vesicles, including proteins involved in the glycerophospholipid and sphingolipid pathways (Trentin et al., 2023).

5. Cell survival mechanisms in the oxidative stress response

In addition to antioxidant systems and other increased detoxication proteins that neutralize intracellular ROS, *C. albicans* also activates additional mechanisms to promote cell survival after oxidative stress. These mechanisms are related to oxidized DNA, protein or lipid repair, and degradation.

5.1. DNA damage induced by oxidative stress repair

Oxidative stress-induced DNA damage stimulates Rad53 signaling pathway activation, which promotes activation of DNA repair mechanisms, including base excision repair (BER), nucleotide excision repair (NER), and homologous recombination (HR), all of which are necessary for cell survival (Yao et al., 2021). BER system proteins Ntg1, Apn1, and Ogg1 have been characterized in *C. albicans*, of which, Apn1 significantly increases in abundance after treatment with 5 or 10 mM H_2O_2 (Table 2) (Amador-García et al., 2021; Legrand et al., 2008). In contrast to *S. cerevisiae*, the deletion of a single component does not affect *C. albicans* survival after treatment with 4 mM H_2O_2, pointing to an overlapping function of these genes in *C. albicans* (Legrand et al., 2008). Rad family proteins are the key components of the NER system. Rad1 and Rad2 significantly increase after *C. albicans*-macrophage interaction (Fernández-Arenas et al., 2007), whereas Rad6 and Rad23 significantly increase after 10 mM H_2O_2 treatment (Table 2) (Amador-García et al., 2021; Leng et al., 2000). In both *C. albicans* and *S. cerevisiae*, single deletion of *RAD2* or *RAD10* NER genes does not lead to increased H_2O_2 sensitivity (Legrand et al., 2008). In the HR process produced by oxidative stress, Rad52 plays a prominent role. Its homozygous mutant presents increased susceptibility to 5 mM H_2O_2 treatment (Ciudad et al., 2004; García-Prieto et al., 2010). *C. albicans* Rad52 operates through two different Rad51-dependent or -independent pathways (García-Prieto et al., 2010). Rad51 levels significantly increase in abundance following 5 mM H_2O_2 treatment (Table 2) (Amador-García et al., 2021) and its homozygous mutant shows increased sensitivity to this treatment (García-Prieto et al., 2010). Similarly, Rad50 abundance increases after 5 mM H_2O_2 treatment (Amador-García et al., 2021) and its homozygous mutant strain is slightly sensitivity to H_2O_2 treatment (Legrand et al., 2007). The N-terminal domain of Rad52 shares partial similarity with that of Rad59, with both proteins physically interacting and operating within the same recombination pathway (Davis and Symington, 2001, 2003). However, in *C. albicans*, *Rad59* mutant does not present decreased recovery after H_2O_2 or menadione treatment, in contrast to *rad52* or r*ad51* mutants as mentioned previously, suggesting a secondary role of Rad59 in the *C. albicans* oxidative stress response (García-Prieto et al., 2010).

Table 2
Significantly increased *C. albicans* BER, NER, and HR proteins after *C. albicans*-macrophage interaction or H_2O_2 treatment.

	Significant increased antioxidant-related proteins after *C. albicans*-macrophage interaction	Significant increased antioxidant-related proteins after H_2O_2 treatment
BER system proteins	–	Apn1
NER system proteins	Rad1 and Rad2	Rad6 and Rad23
HR system proteins	–	Rad51, Rad52 and Rad50

5.2. Other oxidative stress cell survival mechanisms

H_2O_2-induced oxidative stress leads to proteasome activation, correlating with a significant increase in the expression of proteasome component proteins that are regulated by Cap1. Proteasome activation is a key mechanism for cell survival, enabling the degradation of misfolded and aggregated oxidized proteins produced by ROS (Amador-García et al., 2021; Wang et al., 2006). In addition, oxidative stress promotes cell membrane lipid oxidation, compromising their fluidity and integrity. Analysis of the proteomic content of the extracellular vesicles of *C. albicans* after oxidative stress has revealed an increase in glycerophospholipid and sphingolipid membrane metabolism proteins that may be necessary for membrane lipid degradation and biosynthesis (Trentin et al., 2023).

6. Conclusion

During IC, the interaction between *Candida* and phagocytes, mainly macrophages, induces an oxidative burst, one of the main pathogen-killing mechanisms. The oxidative burst induces changes in yeast cells that favor survival. The oxidative stress response of *C. albicans* implies proteomic changes, both in abundance and in post-translational modifications , that are not fully described yet. The current review intended to show different aspects of this response, as new targets for antifungal drugs that may enable the development of new effective therapeutic strategies to manage invasive candidiasis, are always being sought.

Conflict of interest

The authors declare no conflict of interest.

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