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REVIEW

Oxidative stress response pathways in fungi

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Abstract

Fungal response to any stress is intricate, specific, and multilayered, though it employs only a few evolutionarily conserved regulators. This comes with the assumption that one regulator operates more than one stress-specific response. Although the assumption holds true, the current understanding of molecular mechanisms that drive response specificity and adequacy remains rudimentary. Deciphering the response of fungi to oxidative stress may help fill those knowledge gaps since it is one of the most encountered stress types in any kind of fungal niche. Data have been accumulating on the roles of the HOG pathway and Yap1- and Skn7-related pathways in mounting distinct and robust responses in fungi upon exposure to oxidative stress. Herein, we review recent and most relevant studies reporting the contribution of each of these pathways in response to oxidative stress in pathogenic and opportunistic fungi after giving a paralleled overview in two divergent models, the budding and fission yeasts. With the concept of stress-specific response and the importance of reactive oxygen species in fungal development, we first present a preface on the expanding domain of redox biology and oxidative stress.

Keywords Oxidative stress · Fungal adaptation · Fungal pathogens · Hog1 · Yap1 · Skn7

Introduction

Fungi are acknowledged for being able to sense and adapt to a wide range of extracellular stimuli found in their different biotopes [1, 2]. Although not to an equal degree, same stimuli can be encountered in divergent fungal territories. This is the case of oxidative stress that results from exposure to biotic and artificial agents come across in nature or to the immune cells during host attack. Such stress, when coupled with compromised antioxidant systems, can deleteriously and irreversibly impact cells, leading to fungal death. Evading oxidative stress is therefore crucial for fungi to survive, a process called "adaptation". Adaptive response to oxidative stress is often multilayered since cellular reprogramming happens on transcriptional, post-transcriptional, and metabolomic levels.

Literature on fungi responding to oxidative stress abounds. It highlights prominent roles of three major modulators: the high osmolarity glycerol pathway (HOG), the yeast-activating protein 1-like (Yap1) basic-leucine zipper (bZIP)-containing transcription factor (TF), and the response regulator (RR) and TF Skn7. Of particular significance is the degree of conservation of these regulators. Hog1, the central mitogen-activated protein (MAP) kinase (MAPK) in the HOG pathway, is the most conserved regulator of osmotic and oxidative stress across the fungal kingdom (identity of 80 to 100%) [3]. While Yap1 and Skn7 are less conserved on the fungal kingdom scale (identity of 20–29%) [3], both are the only conserved TFs in pathogenic species [4]. This might explain the pronounced resistance to oxidative stress found in these species compared to environmental counterparts [3]. Nevertheless, the role of these pathways in fungal response to oxidative stress is not uniformly conserved, meaning that there are always species-specific aspects of the mounted response.

To gain insight into molecular mechanisms in which the HOG pathway, Yap1, and Skn7 perceive and respond to oxidative challenges in different fungal species, we wanted to compile current knowledge in this paper. Given that a recent

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review on this topic in phytopathogenic fungi has been published [5], the current review discusses relative knowledge in human pathogenic and opportunistic fungi while taking the budding and fission yeasts as reference models. A table summarizing the involvement of each regulator in fungal virulence is also presented (Table 1). We find here necessary to provide first a glimpse of developing knowledge concerning oxidative stress and related areas, particularly in the fungal kingdom.

Redox biology

Biological processes are regulated in part by the chemical modifications underwent by key biomolecules that are nucleic acids, proteins, and lipids. Redox (oxidation–reduction) reactions prevail over the types of reactions through which such modifications occur. In the biological systems, these reactions are spatiotemporally positioned according to a set of principles called "redox code", a matter that applies to all eukaryotes [33]. Redox species are the main effectors of redox reactions and correspond to reactive oxidant molecules that constantly interact in biological systems according to the physicochemical environment [34]. They are diverse and categorized into reactive electrophile, nitrogen, sulfur, and most importantly, oxygen species (ROS) [34, 35]. The need for oxidoreductases is therefore critical to sustain and control interactions. Here comes redox homeostasis, a term that is mostly conceived on the cellular scale, denoting the capacity of the cell to constantly deal with challenges generating oxidants, in other word, the antioxidant capacity [36]. Of interest is that redox species themselves play roles in cellular signaling for the maintenance of redox homeostasis [36]. Thus, a healthy physiological state does not refer to a

Table 1 Involvement of major oxidative stress response regulators in fungal virulence assessed ex vivo and in vivo

Species	Regulators	Ex vivo survival assays	In vivo virulence assays	References
S. cerevisiae	Yap1	NT	**Yes—WMI**	[6]
C. albicans	Hog1	**Yes—MM, HL60, PMNs**	**Yes—MMI**	[7–9]
	Cap1	**Yes—MM**	No—MMI **Yes—WMI**	[10, 11]
	Skn7	NT	**Yes—MMI**	[12]
C. glabrata	Hog1	**Yes—MM**	Conflicting—MMI	[13, 14]
	Yap1	No—MM, PMNs	No—MMI	[15–17]
	Skn7	No—PMNs	**Yes—MMI**	[17, 18]
C. neoformans	Hog1	NT (Ssk2: Yes—MM)	**Yes—MMI**	[19, 20]
	Yap1	NT	No—MMI **Yes—WMI**	[21–23]
	Skn7	No—PMNs, PBMC, MM **Yes—HUVEC**	Conflicting—MMI No—WMI	[21, 24, 25]
C. gattii	Hog1	NT	**Yes—MMI**	[26]
	Yap1	NT	NT	
	Skn7	NT	NT	
A. fumigatus	SakA/MpkC	NT	**Both MAPKs: Yes—MMI** Single MAPK: No—MMI	[27]
	Yap1	No—PMNs	No—MMI	[28, 29]
	Skn7	No—PMNs, MM	No—MMI	[30]
T. marneffei	SakA	**Yes—MM, THP1**	NT	[31]
	Yap1	**Yes—THP1**	NT	[32]
	Skn7	NT	NT	

To highlight cases of eventual contribution of regulators (Hog1, Yap1, and Skn7) in fungal virulence are shown in bold

Yes and No denote contribution or no contribution of the pathway in fungal virulence. The term "Conflicting" is used when both observations (contribution and no contribution) are reported by different studies. HL60, human myelomonocytic cell line; HUVEC, human umbilical vein endothelial cells; MM, murine macrophages; MMI, murine models of infection; PBMC, peripheral blood mononuclear cells; PMNs, human polymorphonuclear cells; THP1, human macrophages; WMI, worm models of infection. NT, not tested

balanced flux of redox reactions (balance between production and elimination of redox species), but rather to a steady-state flux deviating from equilibrium. So practically, stress occurs only when an additional deviation takes place [37].

Among reactive species, ROS have the greatest imprint on redox biology. Knowledge regarding ROS and oxidative stress has been largely gathered elsewhere. The preface given here will focus on the most recent related papers.

Reactive oxygen species (ROS)

Endogenous sources

Oxygen (O_2) is the key electron acceptor during aerobic respiration [38]. As illustrated in Fig. 1, the process of electron transfer to O_2 that generates water by the cytochrome oxidase (complex IV) within the mitochondrion occurs in a stepwise manner. Leaking electrons by the preceding components of the respiratory chain, particularly complex I and III, gives rise to partially reduced derivates of O_2 named ROS intermediates that can accumulate in mitochondrion or diffuse to the cytosol [39, 40]. ROS are more reactive than oxygen in its ground state

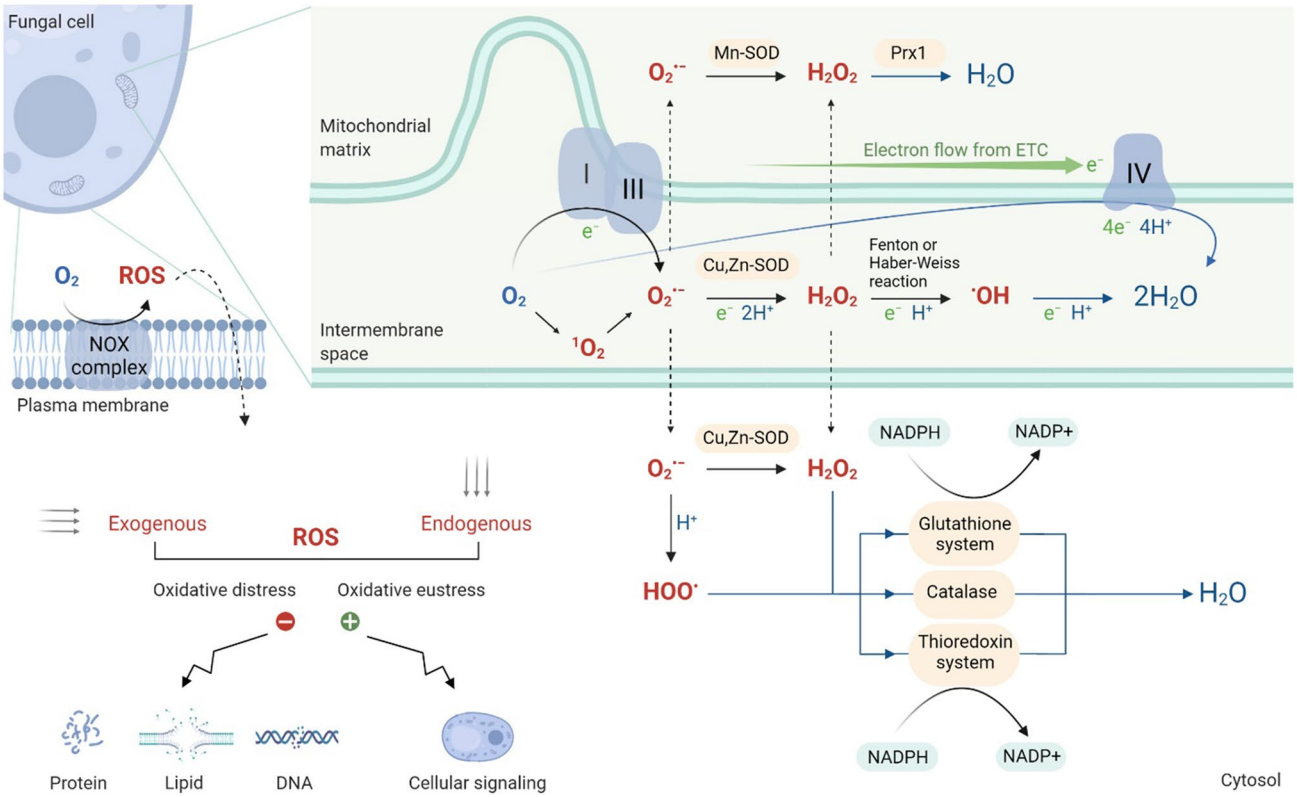

Fig. 1 Schematic representation of ROS metabolism in fungal cells. The main source of ROS production in cells is mitochondria, followed by the plasma membrane-embedded NADPH oxidase (NOX) complex. Electrons may leak during the gradual reduction process of oxygen (O_2) to water by the mitochondrial respiratory chain, mainly from complexes I and III, leading to the formation of superoxide anion $O_2^{\cdot-}$. The latter constitutes the main precursor for the formation of other ROS, including hydrogen peroxide (H_2O_2) by the activity of superoxide dismutase (SOD), hydroxyl radical ($OH^{\cdot}$) via the Fenton or Haber–Weiss reaction favored by metal catalysts, and hydroperoxyl radical ($HOO^{\cdot}$) via the protonation of $O_2^{\cdot-}$. The oxygen singlet ($^1O_2$) corresponds to the oxygen molecule in an electronically excited state due to inputs of energy that rearrange the electrons. These ROS can diffuse from the intermembrane space to (*i*) the mitochondrial matrix, where the mitochondrial Mn-SOD (known as Sod2) converts $O_2^{\cdot-}$ to H_2O_2 which is further reduced to water by the mitochondrial peroxiredoxin Prx1; or to (*ii*) the cytosol, where they are neutralized by the predominantly cytosolic Cu, Zn-SOD (known as Sod1), catalase, and components of the NADPH-dependent systems, the glutathione and thioredoxin systems. High concentrations of ROS molecules (oxidative distress), whether produced endogenously or exogenously, may damage vital macromolecules, including nucleic acids, proteins, and lipids. Nontoxic concentrations are still beneficial for cellular signaling in growth and differentiation (oxidative eustress). e^-, electron; H^+, proton; ETC, electron transport chain. Undashed black arrows refer to reactions allowing ROS formation. Dashed black arrows signify diffusion across compartments. Blue arrows point final neutralization step of ROS into water. This figure was created using BioRender

and exist in two types, radical and nonradical. They are very diverse in chemical nature, though molecules with the most significant roles in biology are a few, such as superoxide anion ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), and the highly reactive hydroxyl radical ($OH^{\cdot}$) [41]. The production of ROS in eukaryotes is compartmentalized. As such, fungi exhibit additional but less metabolically active cellular compartments producing ROS: these include the plasma membrane due to the activity of the embedded NADPH (nicotinamide adenine dinucleotide phosphate) oxidase (NOX) complex that produces outward ROS diffusing intracellularly [42, 43], peroxisomes due to fatty acid oxidation [44], and the endoplasmic reticulum owing to protein folding [45].

Exogenous sources

The formation of ROS can additionally be enhanced during exposure to physical and physiological stressors, including biotic agents, xenobiotics, high temperatures, heavy metals, UV-radiations, and high light intensities [40, 41], all are nowadays referred as "exposome" [46]. Excessive exposure to ROS also occurs during the oxidative burst response of phagocytes, which is critical for fungal, bacterial, and viral clearance [47, 48]. Of note that part of fungal clearance is due to the host NOX modulating fungal physiology in favor of the host [49, 50]. On the applied front, some natural antimicrobial agents that disrupt redox homeostasis by inducing the ROS buildup are believed to constitute promising candidates for therapeutic applications, including in medical mycology [51, 52]. Also, ROS-inducing xenobiotics are of importance for research use. As shown in yeast, they invoke different cellular responses reflecting distinct modes of action [53, 54]. For example, redox cycling compounds such as menadione and paraquat accept electrons from a respiratory carrier and deliver them to oxygen to produce $O_2^{\cdot-}$. In contrast, the inorganic peroxide H_2O_2 leads to the formation of reactive hydroxyl radicals $OH^{\cdot}$ via Fenton and Haber–Weiss reactions. As for organic peroxide stressors, including cumene hydroperoxide and *tert*-butyl hydroperoxide (*t*-BOOH), they are thought to induce lipid oxidation and generate highly reactive free radicals. Thiol-reactive agents such as diamide are quite different: they disrupt redox balance by depleting the reduced glutathione pool [40].

Positive and negative effects

A growing body of evidence supports that ROS act as physiological signaling molecules in aerobic organisms, with a particular relevance of H_2O_2 [55–57]. ROS entities have been shown to exert roles in fungal differentiation, specifically those NOX-derived [42]. For instance, Yno1 NOX-mediated production of ROS in the budding yeast *Saccharomyces cerevisiae* was associated with the formation of actin fibers [58], which is consistent with $O_2^{\cdot-}$ inhibiting quiescence in this species [59]. Likewise, ROS allow intercellular signaling within *S. cerevisiae* and the opportunist yeast *Candida albicans* populations to promote biofilm formations [60]. Accordingly, observations in *C. albicans* showed that subtoxic concentrations of H_2O_2 promote hyperpolarized bud growth via thioredoxin (Trx) [61, 62]. This feature seemed to depend on H_2O_2 derived from the activity of Fre8 NOX, in addition to Sod5, a Cu-only superoxide dismutase (SOD) [63]. High concentrations of H_2O_2 may also result in the development of pseudohyphae in *C. albicans* [64]. While high concentrations of ROS-inducing biotic agents inhibited the growth of *Aspergillus* species, mild concentrations promoted asexual conidiation, and this induction required Yap1 homolog [65]. At an earlier stage of development of *Aspergillus fumigatus*, the activity of NOX and RacA GTPase mediated the phialide formation and elongation via the generation of ROS in conidiophores [66]. Similarly, mild concentrations of ROS activated the Ras GTPase pathway, resulting in the induction of proliferation for the dimorphic fungus *Paracoccidioides brasiliensis* [67]. Most recent findings in *Cryptococcus neoformans* proved that nitrosative stress prompted the intracellular accumulation of $O_2^{\cdot-}$ and both stresses contributed to the formation of titanic cells [68]. In phytopathogenic fungi, special attention is paid to the roles of fungal ROS and NOX-derived ROS in mediating plant-fungal interactions [69, 70]. On the other hand, the pathological impacts of ROS on cells are well recognized and constitute the root of diverse human diseases related to aging and inflammation [71, 72]. Still, the damage itself can act as a signaling product [37]. Classical events include different types of damage to DNA and RNA, alteration of protein folding and activities, and peroxidation of lipids [40]. The majority of these events have been registered in various fungal species exposed to ROS, including yeasts and filamentous fungi [73–76]. Research was very informative in setting the concept of positive and negative effects of ROS, but what remains fog is the cellular thresholds above which ROS switch behaviors from signaling to damaging.

Oxidative stress and antioxidants

Oxidative stress

Stress is known as "the nonspecific response of the body to any demand" [77]. The first description of oxidative stress as "an imbalance between the oxidant and antioxidant in favor of oxidants" [78] has evolved with the increased awareness of ROS in signaling. This gave rise to two new terms: oxidative eustress and distress. With both corresponding to the deviation of redox balance to the oxidative side, eustress

refers to a physiological deviation that maintains redox signaling so that specific cellular targets are being addressed, whereas distress signifies a supraphysiological (or pathophysiological) deviation that causes disrupted redox signaling leading to damage of unspecified targets (Fig. 1) [71]. Since the cellular response to increasing concentrations of ROS depends on their type, a single oxidant cannot be representative of oxidative stress [79]. Thereby, it is suggested to replace the annotation "ROS" with the specific chemical species whenever this is possible [37]. Although particular attention has been paid to classify oxidative stress according to different categories, including those related to the intensity of stress, the form of stress, and cellular response to stress [37, 80], there is still no consensus agreement over the terms that should be used in the scientific literature. So in the following sections, oxidative distress will be referred to as oxidative stress.

Antioxidant defense

As important as ROS are in signaling are the antioxidants in maintaining redox homeostasis. An antioxidant is defined as "any substance that delays, prevents, or removes oxidative damage to a target" [40]. The antioxidant defense is a network of enzymatic and nonenzymatic scavengers, with some having overlapping roles in intercepting ROS and in turning over the cellular buffer of reductants. The first category includes SODs, catalases, the thioredoxin system [comprising Trx, thioredoxin reductase (TrxR), and peroxiredoxin (Prx)], and the glutathione system [formed by glutathione (GSH), glutathione reductase (GR), glutathione peroxidase (GPx), and glutaredoxin (Grx)]. The non-enzymatic molecules principally include melanin and vitamin E. The fact that some encoding genes belong to evolutionarily conserved eukaryotic H_2O_2-responsive genes depicts the importance of their protective functions [81]. In fungi, all of them have been shown to be required to evade endogenous and exogenous ROS [82–84]. More importantly, there are obvious links between tolerance to oxidative stress and fungal pathogenesis. This is illustrated in the attenuated virulence profiles of strains lacking such enzymes [50, 85], with TrxR and Prx performing the most persistent roles, which highlighted their importance as alternative therapeutic targets favored by the structural divergence between fungal antioxidant enzymes and their higher eukaryote counterparts [86–88]. In this regard, recent findings reinforced such approaches by showing the involvement of a conidia-specific Cu,Zn-SOD, as well as TrxR and Prx in tolerance to chemically-derived oxidants and phagocytes-mediated killing of the opportunistic filamentous fungus *Scedosporium apiospermum* [89, 90]. Besides replenishing their antioxidant defense to offset redox homeostasis, fungi respond in various ways. These include events of cell cycle arrest and DNA repair mediated by the Rad53 checkpoint pathway, though the response is less conserved across fungi [91, 92]. Additionally, fungi can hijack the host antioxidant armament to ensure more protection against host-derived ROS, a stealth behavior mostly restricted to phytopathogens [93]. Other effectors or mechanisms employed by fungal cells in scavenging ROS include melanin [94], the induction of NADPH flux by switching to the pentose phosphate pathway (PPP) [83], and the production of some secondary metabolites, such as aflatoxin, gliotoxin, and ochratoxin [95, 96]. Fungal response to oxidative stress is therefore complex and necessitates distinct but also collaborative involvement of cognate regulators: the HOG pathway, Yap1, and Skn7 (Fig. 2). These regulators are either activated via canonical phosphorelay systems and/or via redox relays. *Saccharomyces cerevisiae* and the fission yeast *Schizosaccharomyces pombe* constitute the fungal prototypes in which regulatory mechanisms are the best studied and serve for comparative views.

The HOG pathway-mediated regulation

It is now admitted that the HOG pathway, corresponding in mammals to p38 and JNK pathways, is one of the most evolutionally conserved pathways in eukaryotic life [97, 98]. The structural conservation extends to the functional and architectural levels, as the pathway constitutes the backbone of stress signaling facilitated by a two-component system (TCS)-dependent activation of serine/threonine kinases and consists of tiers of MAP kinase kinase kinase (MAPKKK), MAP kinase kinase (MAPKK), and Hog1 MAPK. With the exception of not being identified in mammals, the eukaryotic TCS system is a multi-step histidine-aspartate phosphorelay system formed by a hybrid histidine kinase (HK) and a histidine-containing phosphotransfer protein (HPT) acting as a mediator between HK and a RR (Fig. 2) [99]. This culminates in the activation of Hog1, represented by dual phosphorylation on its TGY (Threonine-Glycine-Tyrosine) motif, which allows Hog1-mediated metabolic and/or transcriptional regulation of target genes. The fact that Hog1 is highly conserved in the fungal kingdom regardless of the species niche [3] may be traced back to its significant contribution in guarding adaptation to a wide range of stresses potentially encountered in fungal niches, encompassing antifungals, antimicrobial peptides, osmotic and oxidative stresses, as well as in virulence [100]. In contrast to its key role in osmotic stress adaptation in fungi, the role of the HOG pathway in protecting against oxidative stress is somehow divergent.

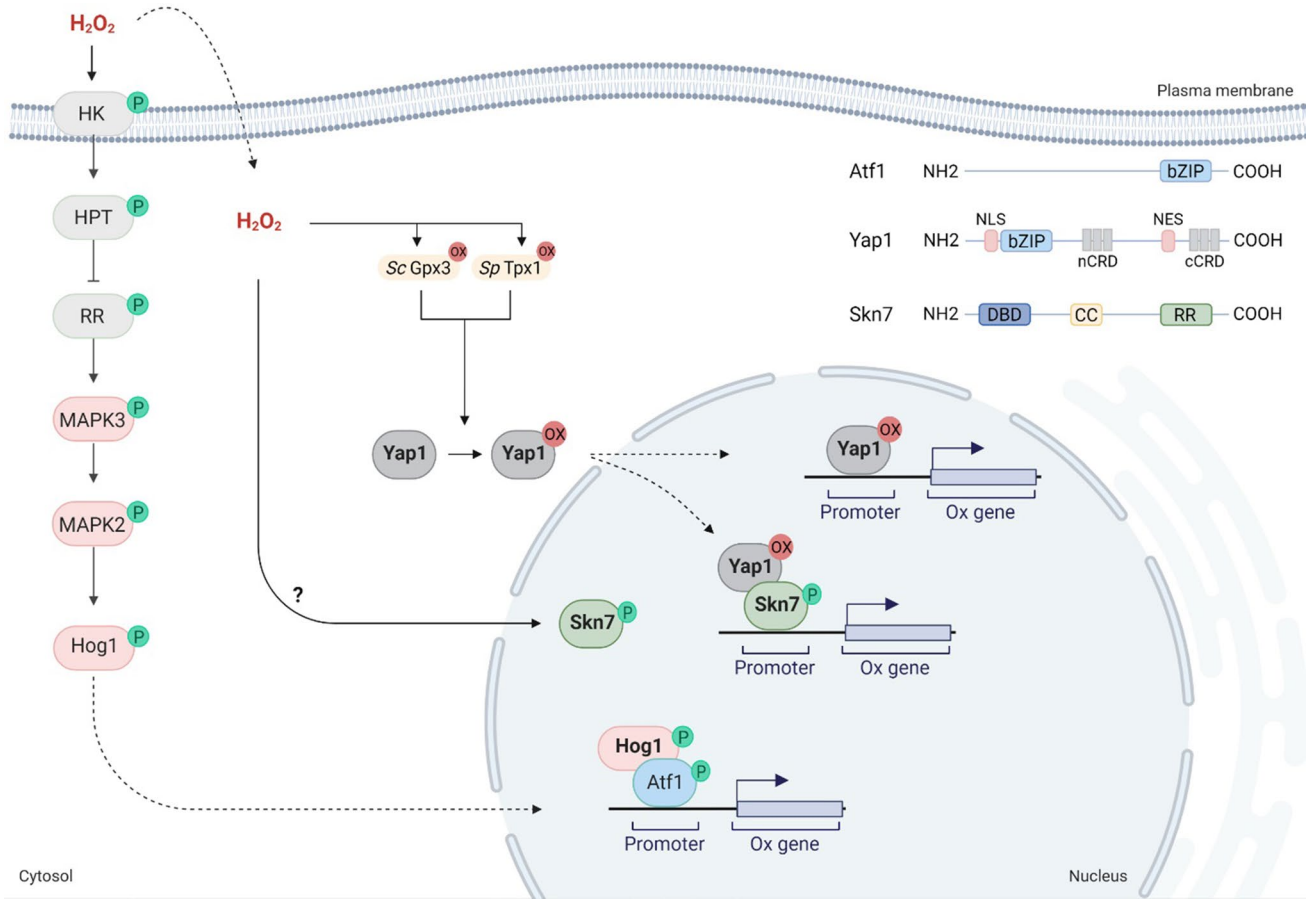

Fig. 2 Graphical illustration of oxidative stress response pathways in fungi. Oxidative stress signals are detected by TCS and transduced to the HOG pathway. Activated Hog1 MAPK translocates to the nucleus and phosphorylates the nuclear-resident Atf1 TF, which alongside Hog1, induces the translational programs, mainly consisting of oxidative stress-responsive genes (abbreviated as Ox gene). On the other hand, Yap1 and Skn7 TFs detect the cues of oxidative stress by means of non-canonical signal transduction. It is still obscure how oxidative stress induces the activation (phosphorylation) of Skn7. Yap1 is activated via oxidation by redox-sensitive Gpx3 (in the case of *S. cerevisiae*) or Tpx1 (in the case of *S. pombe*). Oxidized Yap1 accumulates in the nucleus and triggers the expression of Ox gene(s). Once the nuclear-resident Skn7 is activated, it cooperates and forms a complex with oxidized Yap1 on the promoter of Ox gene(s). Undashed black arrows refer to reactions that activate regulators. Dashed black arrows signify diffusion across compartments. Abbreviations not used in the text: MAPK3, MAPKKK; MAPK2, MAPKK; *Sc*, *S. cerevisiae*; *Sp*, *S. pombe*; P, phosphorus group; OX, oxidized; Ox gene, oxidative stress-responsive genes. This figure was created using BioRender

The HOG pathway in *S. cerevisiae*

Studies on the response to oxidative stress on *S. cerevisiae* revealed differential functions of a few pathways, among which the HOG pathway appears the least involved [101]. The sole Sln1 HK and the transmembrane sensor Sho1 are more influencing in sensing osmostress than oxidative stress signals [102]. Hog1 is still responsive to oxidative stress indicated by its phosphorylation through the Ssk1-Ssk2-Pbs2 (RR-MAPKKK-MAPKK) pathway and the mutant sensitive phenotype, though it only localizes throughout the cytoplasm in such conditions [103, 104]. This mirrors the transcriptional behaviors, where Hog1 and its candidate Sko1 bZIP TF, which belongs to the family of ATF (activating transcription factor)/CREB [cAMP (*c*yclic-*a*denosine-*m*ono*p*hosphate)-responsive element binding protein], have no identifiable role in the H_2O_2-induced transcriptome [105]; however, contradictory results were reported concerning the dependency on Hog1 of H_2O_2-activated stress-responsive elements [104, 106]. Components of this pathway perform secondary roles in the global cellular response to oxidative stress, such as in the crosstalk with the cell-wall integrity pathway (CWI) [107, 108], the regulation of ergosterol [109], and the regulation of cadmium-induced ROS accumulation [110]. There are else poorly explored roles of *S. cerevisiae* Hog1 in the regulation of mitochondria, the major ROS-producing sites, as suggested by the responsiveness of Hog1 to mitochondria-disrupting molecules, such as honokiol [111], clotrimazole [112], and zinc oxide nanoparticles [113], as well as the

implication of Hog1 in the dysfunction of mitochondria and the deficiency in mitochondrial and peroxisomal catalase A (Cta1) in cells lacking inositol phosphosphingolipid phospholipase C (Isc1) known to impact mitophagy [114].

The HOG pathway in *S. pombe*

Oppositely to *S. cerevisiae*, *S. pombe* is an excellent model representative of how critical the HOG pathway is in adaptation to oxidative stress [115]. Interestingly, the TCS, headed by three redox sensing-containing HKs termed as Mak1-3, appears H_2O_2-specific and is not responsible for the relay of other insults to Sty1 (Hog1 ortholog) [116–118]. The phosphorylation state of Sty1 is proportionate to H_2O_2 levels, and Sty1 becomes transcriptionally involved when the concentration exceeds 0.25 mM [118, 119]. Upon high peroxide stress, some auxiliary events participate in promoting the activation of Sty1. For example, Tdh1 is a glyceraldehyde-3-phosphate dehydrogenase (GAPDH) that enhances the interactions between TCS components, thus additionally feeding into Sty1 [120]. Also, oxidization of Sty1 on the cysteinyl residues 153 and 158 is essential for Sty1-dependent response and survival to high doses of H_2O_2 [121]. Moreover, oxidization of Sty1 on Cys35 by oxidized Tpx1 (a 2-Cys Prx) is important to reinforce its phosphorylation, even though Tpx1 becomes inactivated by hyperoxidation at high concentrations of H_2O_2 (> 1 mM) [122]. The role of Tpx1 extends to switch off the H_2O_2-induced activation of Pap1 (Yap1 homolog) to allow Sty1 to take over the transcriptional regulation. On the other hand, keeping Sty1 inactivated at low concentrations of H_2O_2 seems to rely on the constitutively oxidized Cys458 of Wis1 MAPKK, which restrains the activity of Wis1 and prevents unnecessary activation of Sty1 [123]. The activation of Sty1 enriches its nuclear accumulation and the phosphorylation of nucleus-resident Atf1 ATF/CREB bZIP TF, which in turn regulates target genes by binding to CRE (cAMP-responsive element), either acting as homodimer or heterodimer with another bZIP TF named Pcr1 [124, 125]. Indeed, CRE motifs are found in most of the core environmental stress response (CESR) genes, where the Sty1-Atf1 pathway predominates their regulation [126]. Most of these genes belong to core oxidative stress response (COSR) genes modulated by this pathway during strong H_2O_2 stress (> 0.5 mM), whereas during *t*-BOOH stress, the regulation of COSR genes is only marginally dependent on Sty1-Atf1 [119]. Importantly, the recruitment of Sty1 by Sty1-activated Atf1 and their direct interaction with RNA polymerase II (Pol II) are prerequisites to activate their target genes [127]. It is explainable, therefore, why Sty1-mediated phosphorylation of Atf1 is crucial for roles of the Sty1-Atf1 pathway in the regulation of other biological functions, such as the meiotic recombination [128, 129]. Mitotic cell-cycle arrest occurring during oxidative and nitrosative stress is believed to depend on the pathway [130, 131]. For further regulatory roles of Atf1 in fungi, please see a recent review by Leiter et al. [132]. Otherwise, Sty1 has additional tasks in regulating the translational program post oxidative stress [133, 134]. The governing of autophagy and chronological lifespan by Sty1, along with other pathways, further emphasizes its role in preventing endogenous ROS accumulation that often associates dysfunctional autophagy and aging [135–138].

The HOG pathway in pathogenic and opportunistic fungi

Some of the biological aspects of *S. cerevisiae* Hog1 are customary for *C. albicans* Hog1, including the mitochondrial regulation [139] and the Hog1-Sko1-independent regulation of transcriptional response to oxidative stress [140, 141]. Whether TCS is involved in shuttling oxidative stress signals to *C. albicans* Hog1 is suspicious. This is because (*i*) Ssk1 is required for the activation of Hog1 in oxidative but not osmotic stress [142] and (*ii*) upstream sensors supposed to route stress signals to Ssk1, *i.e.* three HKs (Sln1, Chk1, Nik1) and Sho1, are feasibly not involved in the oxidative stress-induced activation of Hog1 [143]. This suggests the existence of other mechanisms activating the phosphorylation of *C. albicans* Hog1. Indeed, three mechanisms have been proved so far, *i.e.* those involving Trx1, Tsa1 (a 2-Cys Prx, Tpx1 homolog), and Fzo1 (a mitochondrial biogenesis factor) [62, 144]. These mechanisms were evidenced in cells challenged with high concentrations of H_2O_2, which may explain the fact that the H_2O_2-induced phosphorylation of Hog1 happens only at high concentrations (> 2 mM) [145]. Also, Hog1 undergoes additional oxidation on two Cys residues (corresponding to Cys153 and Cys158 of Sty1) when cells are subjected to nitrosative stress (known to induce ROS), which allows the protein to induce the expression of both oxidative and nitrosative responsive genes [146]. Recent reports showed that Hog1 is phosphorylated upon treatment of *C. albicans* cells with ROS-inducing antimicrobial peptide (LfcinB15) [147]. Beside phosphorylation of the protein, expression of *HOG1* is also rapidly increased following exposure to H_2O_2 [148]. Observations of *C. albicans* Hog1 being responsive to oxidative stress but not transcriptionally involved in the cognate response give rise to the question of types of involvement. To date, the involvement of *C. albicans* Hog1 in oxidative stress-induced cellular events is prominently seen in promoting cell recovery both on the transcriptional and post-transcriptional levels [149, 150] and in the activation of the CWI pathway [151]. However, this is not sufficient to explain the predominant involvement of Hog1, among other MAPKs, in the survival of *C. albicans* under different types of oxidants, including

ROS-mediated phagocyte killing [9]. Recent work suggested the contribution of Sln1-Ssk2-Pbs2-Hog1 in the regulation of genes involved in ROS accumulation, such as *SOD2* [152]. The pathway is as well required along with Cap1 (Yap1 homolog) to resist the photodynamic inactivation (PDI), which is known to trigger ROS intracellular levels [153]. Future research may hold answers on where does reside the utility of Hog1 in oxidative stress tolerance of *C. albicans*.

The HOG pathway in *C. glabrata* is phylogenetically similar to that of *S. cerevisiae*, but it functionally diverges regarding involvement in response to oxidative stress. Mutants lacking Hog1 were sensitive to oxidant agents and accumulated ROS, which is the basis for decreased survival in mutants exposed to macrophages [13, 14]. The phosphorylation of Hog1 has not been detected in such conditions, probably because only the nontypical strain ATCC 2001 (possessing unfunctional Ssk2) was used when testing the phosphorylation [154]. Hog1 is alike important to adapt to stress in the opportunistic species *C. auris*, including oxidative stress [155]. The activation of *C. auris* Hog1 is typically Ssk1-dependent, though single mutants did not phenocopy each other in terms of sensitivity to oxidative stress [156]. In *Meyerozyma* (*Candida*) *guilliermondii*, the presence of Hog1 conferred protection against oxidative stress insults [157]. In contrast, comparable roles could not be detected for the HOG pathway in *Clavispora* (*Candida*) *lusitaniae* [158], despite that its upstream HKs are significantly protective [159].

Common *C. neoformans* serotype A is peculiar in evolving an opposite way to activate Hog1 upon stress, which occurs by dephosphorylation [19], but also in being resistant to environmental stress, including oxidative stress represented by H_2O_2 [20]. These features are specifically due to a polymorphic change in Ssk2 N-terminal region of serotype A strains [20]. Among the seven owned HKs, only Tco2 exhibits partial responsiveness to oxidative insults [160]. However, the Ssk1-Ssk2-Pbs2-Hog1 pathway is tightly involved in protecting against such stress, as indicated by the even hypersensitivity of each of the deletion mutants to oxidants [20, 160] and the critical regulation of oxidative stress and CESR genes co-performed by Ssk1 and Hog1 [161]. For the former response, genes included those encoding catalase Cta1, Sod2, Trr1 (a TrxR), Tsa1, and Srx1, of which both basal and inducible expressions were dependent on the pathway [161]. Atf1 is only assumed to be driven by Hog1 in targeting these genes [162, 163]. The repression of ribosomal biogenesis during oxidative threats, which is a feature commonly seen in fungi, is also dependent on Hog1 in this species [161]. However, global cellular response to such conditions results rather from a cooperative collaboration of the HOG, Skn7, and Yap1 pathways [23, 161]. A recent study in *C. gattii* showed that resistance to oxidative stress was spared in the deletion of Hog1. However, the mutant was less virulent in a murine model and less able to propagate in infected lung tissues, which is thought to be due to the reduced production of capsule and melanin [26].

Albeit less is known about the HOG pathway in filamentous fungi, it is clear that the pathway functioning against oxidative stress in these species is enigmatic. This is exemplified in *A. fumigatus* and *Aspergillus nidulans*. First, their genomes harbor two paralogs of Hog1, called SakA and MpkC, displaying unequal and overlapping roles in stress resistance in *A. fumigatus* [27, 164], whereas, in the case of *A. nidulans*, they perform opposing roles in oxidative stress resistance even though this stress induces both their phosphorylation and nuclear translocation [165, 166]. A recent phosphoproteomic study suggested these opposing behaviors might be due to H_2O_2 promoting differential phosphosites of SakA and MpkC [167]. Second, none of the 13 *A. fumigatus* HKs nor the 15 *A. nidulans* HKs, including those orthologous to Mak1-3, appeared responsible for tolerance to oxidative conditions [168, 169]. However, genetic interactions between SlnA and components of SHO1, as well as presumable crosstalk between a G-coupled protein and SakA, are supposed to impact the activation of *A. fumigatus* SakA in such conditions [170, 171]. Third, the involvement of the pathway components in stress resistance is growth-dependent. In *A. nidulans*, conidial tolerance to H_2O_2 and *t*-BOOH is principally taken over by the SskA-SakA-AtfA pathway, relating to the dependence of conidia-specific catalase (CatA) on this pathway [165, 172, 173], whereas the ability to trigger hyphae-specific catalase (CatB) in response to H_2O_2 is partially dependent on the SskA-SakA-AtfA pathway, and additionally requires NapA and SrrA (Yap1 and Skn7 orthologs, respectively) [172–174]. Still, the paraquat-induced activity of CatB requires SakA-AtfA [165]. Similarly, hyphal resistance of *A. fumigatus* depends predominantly on SakA without AtfA being involved, but the latter is required for conidial resistance and expression of CatA [164]. Fourth, the genome of *A. fumigatus* harbors AtfA homologs (AtfB, C, and D), which all have been shown to interact with SakA even under normal conditions and to translocate to the nucleus upon H_2O_2 exposure [175], probably to compensate the lack-of-function of AtfA in mycelial resistance to oxidative stress. Among the transcriptional programming driven by oxidative stress, *A. fumigatus* SakA regulates genes encoding cytoplasmic Prx1 and mitochondrial PrxB and PrxC [176], in addition to those encoding dehydrin-like proteins, DprA and DprB, both displaying peroxisomal functions [177]. The HOG pathway is also believed to act as a salvage pathway in amphotericin B-resistant clinical isolates of *Aspergillus terreus*, as its late phosphorylation following exposure to amphotericin B (4 h) synchronizes the dephosphorylation of CWI MAPK and the induced expression of catalases and SODs [178]. In contrast,

the HOG pathway exhibits no protective role against oxidative stress in *Aspergillus flavus* [179] nor in *Fusarium oxysporum* [180].

As for dimorphic species, mutations in the Hog1 sequence of *Sporothrix brasiliensis* were suggested to account for its higher resistance to H_2O_2 and menadione compared to *Sporothrix schenckii* [181]. In the latter, transcripts of the components of the HOG pathway in addition to Skn7 and proteins involved in the oxidation–reduction process and signaling pathways were identified among the transcriptomic changes that occur during yeast-to-hyphae switching [182], suggesting possible accumulation of ROS prior to transition. In *P. brasiliensis*, Hog1 and Ssk1 were upregulated in response to PDI treatments [183], and the crosstalk between the Ras GTPase and the HOG pathways was essential to survive nitrosative stress [184]. Similarly, *Talaromyces marneffei* (formerly *Penicillium marneffei*) SakA invokes nitrosative stress response [185], and each of TCS, AtfA, and SakA contributes to surviving inside macrophages [186, 187]. Nevertheless, it appears that the function of the HOG pathway in oxidative stress tolerance is again restricted to conidia [31].

YAP1-mediated regulation

Yap1 belongs to the AP-1 subfamily of bZIP TFs found in all fungi [188, 189]. The AP-1 family comprises other TFs that are distinctively involved in stress adaptation, but Yap1 is the major regulator of the oxidative stress response [188]. Although identified as homologous to mammalian Jun/Fos bZIP TFs, Yap members of the AP-1 family (Yap1-8) exhibit different bZIP-containing DNA binding domains (DBD), which bind to the Yap response element (YRE) consensually identified as TTACTAA [188]. Subcellular localization of fungal Yap1 is regulated by the oxidation of conserved Cys residues located in the C-terminal (cCRD) and N-terminal cysteinyl-rich domains (nCRD) [189]. The redox state of these residues allows proper recognition of the N-terminal nuclear localization sequence (NLS) or the C-terminal nuclear exportation sequence (NES) of Yap1 by importin or exportin machinery, thus permitting the shuttling of Yap1 between nucleus and cytoplasm and the fulfillment of its roles in the maintenance of cellular homeostasis and fungal adaptive responses to oxidative stress, mainly H_2O_2 (Fig. 2) [189]. Yap1 is also subjected to H_2O_2-induced phosphorylation, as reported for *S. cerevisiae* Yap1 [190], *C. albicans* Cap1 [191], and *A. nidulans* NapA [167].

Yap1 in *S. cerevisiae*

Studies in the *S. cerevisiae* have provided insights into how Yap1 governs oxidative stress response in fungi independently of the HOG pathway. Yap1 was the first regulator to be described and identified among the Yap members. Yeast Yap1 contains three Cys residues in the nCRD (Cys-303, Cys-310, and Cys-315) and three others in the cCRD (Cys-598, Cys-620, and Cys629) [189]. Under physiological conditions, Yap1 predominantly localizes in the cytoplasm owing to Crm1 (chromosomal region maintenance 1)-dependent nuclear export. More precisely, it is translocated into the nucleus by the importin Pse1 and rapidly exported once the exportin Crm1 interacts with NES [192, 193]. The activation of Yap1 is believed to occur in two distinct ways, one triggered by hydroperoxides and superoxide anions and the other by thiol-reactive chemicals, with menadione being able to operate both ways [194]. Exposure to H_2O_2 oxidizes Cys36 of the GPx protein Gpx3 (also known as Orp1), resulting in the oxidation of Yap1 Cys598 and subsequent formation of inter-molecular Cys598-Cys303 disulfide bonds [190, 195]. Yap1-binding protein (Ybp1) is meanwhile needed to bring Gpx3 to Yap1 and prevent Gpx3 auto folding, thus operating as a scaffold protein [196, 197]. The Prx Tsa1 can operate as the redox transducer similarly to Gpx3 but only in a specific background strain (harboring truncated version of Ybp1) [198, 199]. On the other hand, the oxidation by diamide is Gpx3-independent and involves residues of cCRD [190, 200]. Consequently, folding events of Yap1 mask NES, hindering its recognition by Crm1 and thereby promoting Yap1 nuclear accumulation [190, 201]. The importance of these redox-sensitive enzymes in signaling is elaborated by the finding that yeast cell lacking all of its Prx and GPx was not able to transcriptionally respond to H_2O_2 signals, although the mutant was not as sensitive as *yap1Δ* to H_2O_2 [202].

Approximately 70 genes belonging to CESR are differentially modulated by Yap1 following H_2O_2 exposure; most of them encode components of the glutathione system, such as the glutathione transferase Gtt2, Gpx2, Ttr1 (a Grx), and of the thioredoxin system, including Trr1/2 (TrxRs) and Trx2 [203]. Those encoding SOD1, SOD2, and membrane transporters belonging to ATP-binding cassette (ABC) family and the major facilitator superfamily (MFS), renowned for involvement in drug resistance, have been reported as Yap1 targets according to several transcriptional studies reviewed in Lushchak [73] and Farrugia and Balzan [204]. Some of these antioxidants, in addition to Yap1, participate in tolerance to methyl- and ethylmercury-induced oxidative stress, suggesting a consistent regulatory role of this TF [205]. The *Mmt1* gene, encoding a mitochondrial

protein for the export of iron to the cytosol, was also identified among H_2O_2-triggered genes co-regulated by Yap1 and Atf1 [206]. Furthermore, Yap1 increases the expression of cytosolic catalase Ctt1 to compensate for the loss of glucose-6-phosphate dehydrogenase (G6PD) that belongs to PPP, which leads to increased tolerance to oxidative and nitrosative stress in the *g6pdΔ* mutant [207]. Other oxidative stress-triggering agents were reported as activators of yeast Yap1, such as menadione, various genotoxic agents [208], vanillin [209], metalloid stress [210, 211], linoleic acid hydroperoxide [212], thiol-reactive electrophiles [213], and garlic-derived allicin [214]. It is all of these special biochemical features that made the Yap1 exploitable in usage in oxidative stress biosensors [215, 216]. As *S. cerevisiae* can rarely be a pathogen [217], findings of in vivo assays may give insights into fungal pathogenesis. It was shown that *yap1Δ* mutant failed to induce Dar phenotype (an indicator of infection) in infected *Caenorhabditis elegans*, but when worms were deficient in NOX-encoding *bli-3* gene, *yap1Δ* cells succeeded to establish infection, supporting that role of Yap1 in virulence is based on its ability to incapacitate host defense [6].

Pap1 in *S. pombe*

The unique characteristic of Pap1 resides in being rapidly oxidized and accumulated in the nucleus under H_2O_2 concentration as low as 0.07 mM and in its delayed activation upon higher concentrations (> 1 mM) [118, 218]. While H_2O_2-induced activation of *S. cerevisiae* Yap1 requires Gpx3, the fission yeast Pap1 depends completely on Tpx1 (the complete model of Tpx1-mediated regulation of Pap1 is described in [219]). Pap1 contains a total of 7 Cys residues, but they are not all involved in its regulation [220]. Low concentrations of peroxide (< 1 mM) are believed to initiate interaction between Tpx1 Cys48 and one residue of Pap1 cCRD (either Cys501 or Cys532), consequently allowing the formation of an intramolecular disulfide bond between Cys278 of nCRD and one of the cCRD Cys residues [221, 222] and then the dissociation of Pap1 NES from Crm1 [223, 224]. However, the essential role of Tpx1 in responding to low H_2O_2 is not the direct oxidation of Pap1 but rather the oxidation of a proteasome-associated thioredoxin-like protein (Txl1). This prevents the Txl1-mediated reduction of Pap1 and allows its nuclear accumulation [225]. At higher concentrations (> 1 mM), Tpx1 becomes temporarily hyperoxidized and thioredoxin-resistant, therefore allowing the thioredoxin pool to repair oxidized protein, such as Pap1 [226, 227]. In this case, the accumulation of Pap1 in the nucleus is not totally prevented but only delayed [218, 221], the time by which activated Sty1-Atf1 triggers the expression of Srx1, the only enzyme capable of reducing the hyperoxidized Tpx1, thus resuming the Tpx1-mediated activation of Pap1 [221, 222]. The intricacy of these behaviors could be seen transcriptionally. The basal and the inducible expressions of most of COSR genes are critically dependent on Pap1 at weak H_2O_2 concentrations, and this dependency is shifted to Sty1-Atf1 as doses go higher [119]. COSR genes encode typical antioxidant enzymes, including Srx1, Tpx1, Trx1, Trr1, Ctt1, but also ABC and MFS membrane transporters. The induction of COSR in response to menadione is as well dependent on Pap1 [119]. However, data concerning mechanistic activation of Pap1 upon such stress are still lacking. Other agents reported as oxidizers of Pap1 are the toxic metabolite methylglyoxal, which activates Sty1 as well [228], and the glutathione-depleting agent diethylmaleate [224]. Otherwise, endogenous oxidative stress induced by glucose deprivation has been reported to activate the nuclear accumulation of Pap1 following activated Sty1 [229].

Yap1 in pathogenic and opportunistic fungi

In contrast to Hog1 in *C. albicans*, Cap1 plays a pivotal role in oxidative stress tolerance and multi-drug resistance (MDR), and these roles are pronounced on all omic levels. From a genomic point of view, Cap1 binding sites are present in the promoters of many COSR genes, encompassing those encoding SODs, catalases, and components of the thioredoxin and glutathione systems, in addition to promoters of genes with drug resistance functions, phospholipid transport, and nitrogen utilization [140, 230]. Findings support that while H_2O_2 induces chromatin accessibility in upstream regions of genes with functions in oxidative stress response to facilitate their upregulation, these regions are significantly enriched in Cap1 binding sites [230, 231]. Accordingly, H_2O_2 induces the expression of many COSR genes in a Cap1-dependent fashion, such as *GTT1* (encoding a glutathione S-transferase), *GLR1* (encoding a GR), *TRR1*, *SOD2*, as well as genes encodings components of PPP and ABC- and MDR-efflux pumps [232–234]. Findings associating ROS-induced DNA instability with activated Cap1 further emphasize its cognate role in protection from damages [75, 235]. Regulatory roles of Cap1 are also needed to maintain redox balance under normal conditions [236]. *Candida albicans* Cap1 and its counterpart in *S. cerevisiae* are structurally and functionally very similar [237]. Similarity also applies to the way of activation; Ybp1 and Gpx3 are critical for the oxidation, phosphorylation, and nuclear accumulation of Cap1 following exposure to H_2O_2 but not to diamide [11]. Same as Hog1 is dispensable for the launch of antioxidant defense in *C. albicans*, the H_2O_2-induced nuclear accumulation of Cap1 is independent of Hog1 [140]. On the epigenetic level, Cap1 is believed to mediate chromatin remodeling by recruiting a component of the SAGA (Spt-Ada-Gcn5 acetyltransferase) complex,

Ada2, to the promoters of oxidative stress-responsive genes and fluconazole-resistance genes [238, 239]. Likewise, Cap1 regulates antioxidant machinery on proteomic levels [240]. The induction of *CAP1* in cells exposed to human polymorphonuclear cells [241] and the vulnerability of mutants lacking Cap1, Ybp1, or Gpx3 to killing by murine macrophages [11] provide obvious proofs of involvement of Cap1 in the pathogenesis of *C. albicans*. The type of such involvement is directly related to Cap1 triggering antioxidant machinery to break down host-produced ROS, as it was shown that deletion of *NOX* in nematode cells and macrophages obviated the need for Cap1 in virulence (in nematodes) and resistance to macrophages killing [10]. For these multiple reasons, Cap1 is considered an attractive target in therapy that is based on inducing oxidative stress, such as PDI [242, 243]. Nevertheless, the virulence of *cap1*, *ybp1*, *gpx3* deletion mutants in a murine model of infections was found to be intact [11]. This discrepancy might owe to Cap1 being inactivated in vivo due to the complexity of defense like the imposing of multiple stressors, such as cationic and oxidative stress, the same combinatorial stress that accounted for inactivated Cap1 in vitro [191, 244].

Same observations were reported in *C. glabrata* in regard to the involvement of Yap1 in oxidative stress and drug resistance and lack of involvement in virulence in mouse models of infection [15, 245]. Although not required to survive phagocytes attack [16], Yap1 transiently localizes to the nucleus following engulfment by murine macrophages [246]. DNA binding motifs of *C. glabrata* Yap1 are enriched in genes encoding generic antioxidant enzymes [247]. The Yap1-mediated targeting of these genes upon oxidative challenges was confirmed transcriptionally, and some of them are cooperatively regulated by Skn7 [16] (details in the Skn7 section). The regulation of *C. glabrata* Yap1 is still unknown, and only *Ybp1* mutant has been characterized so far [248]. In *C. lusitaniae*, Cap1 is responsible for inducing fluconazole resistance via exposure to methylglyoxal (an electrophile species), probably through mechanisms engaging MDR-efflux pumps [249].

The contribution of Yap1 to antifungal resistance, mainly to azole drugs and flucytosine, is a conserved function in *C. neoformans* [22, 23, 250], but its function otherwise is divergent. First, the sensitivity of null mutant is reported to a broader range of oxidants, in addition to osmotic agents and membrane disrupting agents, and this is reflected by increased expression of Yap1 following exposure to these drugs and the Yap1-mediated basal expression of genes with different oxidoreductase and membrane stability functions [23]. Second, Yap1 enriches to the nucleus following diamide stress but not any other stress [23]. Third, none of Trx and Prx appear to regulate Yap1 as in other yeasts [23]. Another divergent aspect is the protein structure which lacks the nCRD and its inability to restore growth of *S. cerevisiae yap1Δ* cells in the presence of H_2O_2 [22]. Even the cCRD does not or poorly contributes to oxidative stress resistance [23]. Therefore, other unconventional mechanisms are assumed to regulate Yap1 functions, one example being Mpk1 (CWI MAPK) [23]. Genes of which inducible expression depends on *C. neoformans* Yap1 have not yet been investigated. A recent report demonstrated that dynamic superoxide production and detoxification during the formation of titan cells is mediated by SOD1/2, of which regulation during exposure to H_2O_2 is lost in mutant lacking Yap1 [68]. Interestingly, Srx1, identified as a major marker of oxidative stress response in *C. neoformans* and a target of the Hog1-Atf1 pathway [162], is not regulated by Yap1 [23]. This, along with the double mutant *atf1Δyap1Δ* being as sensitive as either single mutant to oxidative stress, suggests that Hog1-Atf1 pathway and Yap1 operate separately in response to such a stress. The relationship between Yap1 and the pathogenicity of *C. neoformans* is not totally discarded. Yap1 is not required for virulence in murine models, but it accounts for significant fungal burdens in lungs and brain of infected mice [23]. This can be construed as Yap1 negatively affecting fungal clearance by residual immune cells. Of note is that *C. neoformans yap1Δ* mutant exhibits reduced thickness of the capsule [21]. As such, the role of Yap1 in fungal clearance might not exclusively be attributable to the function of Yap1 in oxidative tolerance but also to its putative role in capsule synthesis.

Yap1 in *A. fumigatus* is likewise believed to mediate resistance to azole antifungals [251], and it was shown to translocate to the nucleus upon exposure to ROS-inducing antifungal amphotericin B [252]. The TF is required to tolerate peroxide and menadione stress, and unlike *S. cerevisiae* Yap1, it does not contribute to tolerance to diamide [28, 29]. As it occurs in *S. pombe*, recent reports demonstrated that H_2O_2-induced nuclear accumulation of *A. fumigatus* Yap1 and activation of its regulon necessitate functional 2-Cys Prx Asp f3 [253]. Yap1 regulon comprises Asp f3 itself, mycelial catalase Cat2, cytochrome C peroxidase Ccp1, cytoplasmic Prx1, and p-nitroreductase family protein Pnr1 [28]. Mitochondrial PrxC also belongs to Yap1 paraquat-induced targets [176]. In addition, Yap1 mediates the production of redox-active gliotoxin [254]. Nonetheless, hyphae defective in Yap1 did not show attenuated virulence in a murine model of invasive aspergillosis, nor reduced survival in human neutrophils [28, 29]. This could partly be explained by the fact that ROS-produced neutrophils could not be used for killing *A. fumigatus* hyphae [28]. As Asp f3 is critically involved in virulence [255], it is possible that separate functions of Asp f3 other than regulation of Yap1 account for *A. fumigatus* pathogenesis. The link between ROS detoxification and cellular development is clearly seen in *A. nidulans*. NapA regulates germination, secondary metabolites production (including melanin), and iron scavenging [173]. It is also

required for conidiation mediated by the action of phenazine (bacteria-derived toxic metabolite)-induced ROS [65], as well as for mycelial resistance to H_2O_2 and, unlike Srr1 and SakA, to menadione [173, 256]. Notably, its subcellular translocation upon these stresses happens very slowly [173]. Induced expression of Yap1 following oxidation of CCAAT-binding factor HapC is believed to activate the TF, allowing the activation of Yap1-dependent transcriptional program, involving mainly CatB and components of the thioredoxin system (TrxA/B, TrxR, and PrxA) [173, 256, 257]. In *A. flavus*, a point mutation in the *YAP1* gene lagged behind the voriconazole-resistant phenotype resulting from successive subcultures on subinhibitory concentrations of voriconazole. The mutant strains showed remarkably increased expression of an ABC transporter (AtrF) and antioxidant enzymes, suggesting a gain-of-function mutation [258]. Along with SrrA, Yap1 is also involved in anti-aflatoxigenic mechanisms in *A. flavus* (see Skn7 section).

Finally, in *F. oxysporum*, Yap1 is activated upon exposure to the DNA damaging agent methyl methanesulfonate [259], and in *T. marneffei*, Yap1 is more critically involved in oxidative stress tolerance in conidia than in hyphae but also contributes to conidial development and conidial survival in THP1 macrophages [32].

SKN7-mediated regulation

Skn7 features a helix-turn-helix type of DNA binding motif, which characterizes the family it belongs to. The DBD shares a high degree of similarity with the heat shock transcription factor (HSF) and locates in the N terminus, whereas the C-terminal region consists of the RR domain [260]. Even though Skn7 overall size is variable within fungal species, each of the feature domains is highly conserved, with orthologous HSF-like domains and RR domains being 41–71% and 42–92% identical to those of *S. cerevisiae* Skn7, respectively [260]. The HSF-like DBD, therefore, justifies the involvement of Skn7 in heat tolerance in some fungal species. One characteristic region that follows the DBD named "coiled-coil" (CC) is predicted to mediate protein–protein interaction, though documented evidence is not enough to assume its function (Fig. 2). Skn7 is typically regulated via two independent phosphotransfer events that have been mainly investigated in *S. cerevisiae*. The aspartyl residue at position 427 (D427) of RR constitutes the first phospho-accepting residue, regulated by the histidine-aspartate phosphorelay signaling of the osmostress Sln1-Ypd1 pathway, which culminates into Skn7 acting as osmotic stress, and to some extent, as cell-wall regulator. Other residues located in the RR are putative targets of Sln1-Ypd1-independent phosphorylation and thought to be responsible for the activity of *S. cerevisiae* Skn7 as oxidative stress response regulator [260]. Functions in the cell wall often associate regulation of morphogenesis and cellular development. However, it is clear that this function is not as conserved as involvement in tolerance to oxidative stress.

Skn7 in *S. cerevisiae*

Several functions have been assigned to Skn7 in the budding yeast besides the regulation of oxidative stress response. What makes Skn7 functions distinguishable in all of these responses is its mechanistic regulation and/or its activity with a stress-specific auxiliary believed to drive Skn7 to the stress proper genes. In osmotic stress adaptation, Skn7 transcriptional activity is crucially dependent on D427; osmotic stress activates Ypd1, which in turn shuttles signal from transmembrane Sln1 to D427 of the predominantly nuclear Skn7 [261–264], thereby activating interaction with the Ran-binding protein Mog1 on the promoter of responsive genes, such as *OCH1* [265, 266]. On the other side, the role of Skn7 in thermal stress is only related to the existence of the HSF-like domain but not directly related to Skn7 being a cognate mediator. Transcriptional studies showed that only upon oxidative stress, Skn7 activates expression of heat-responsive genes (for instance, *SSA1*) by binding to heat-shock element (HSE) [267]. Interactions between CC domains of Skn7 and Hsf1 and cooperative binding to the HSE are believed to be essential for maximal induction of heat-shock genes in response to oxidative challenges [267]. A mutual aspect of this cooperation can be seen in Hsf1 being required for induction of oxidative stress genes at concentrations of oxidants higher than those inducing Skn7-Yap1-regulated transcription [268]. Mutant lacking Skn7 is hypersensitive to oxidative agents, including peroxides and menadione but not diamide [269, 270]. Meanwhile, D427 is dispensable for the tolerance of cells to H_2O_2 and induction of Skn7-Yap1-dependent gene *TRX2* [270]. Still, the RR domain itself is required for oxidative stress tolerance [270], which suggested the existence of other phosphosites with regard to evidence of oxidant-specific induction of phosphorylation occurring in the RR [271]. Cumulative data on cellular response against oxidative stress prove that Skn7 acts in concert with Yap1. The loss of one TF gene rendered cells almost as sensitive as either single mutant to oxidative stress, but proteomic and transcriptional studies indicated the existence of distinct targets [272–274]. Thus far, there is no gene that showed exclusive dependency on Skn7. Common H_2O_2-induced targets include those encoding Trr1, Trx2, Tsa1, Ccp1, SOD1/2, Ctt1, and the alkyl hydroperoxide reductase Ahp1 [270, 272, 275]. Although the majority of oxidative stress genes contain in their promoters the response elements for Skn7 and Yap1 [276], biochemical studies using electrophoretic mobility gel shifts

assays documented the presence of Skn7-Yap1 complex on the promoters of some of these genes [270, 271, 276]. In a study aiming to identify oxidant-specific phospho-accepting residue, He et al. [271] showed that the threonyl residue Thr437 is the oxidant-specific but not the sole phosphor-accepting residue, and its replacement by alanine eliminates the formation of Skn7-Yap1 complex at promotors of oxidative genes. Other residues in the RR domain (isoleucyl I428 and valyl V429) were completely responsible for the formation of the binding complex as well as for oxidant-induced phosphorylation of Skn7 [271]. Since Yap1 regulates the phosphorylation of Skn7, the authors suggested that Yap1 interacts with the RR domain of unphosphorylated Skn7, allowing its phosphorylation by unknown kinases, and thus stabilizing the complex on the promoter of the target genes [271]. Indeed, Cdk8 kinase is identified as a modulator of Skn7 activity in oxidative stress, including phosphorylation, promoter occupancy, and transcriptional activity [277]. Later identification of Yap1 determinants required for interaction with Skn7 revealed that both cCRD and nCRD are involved [278]. Findings on Trx2 reporting its role in the induction of Skn7-Yap1-dependent targets upon H_2O_2 but not that of Yap1-dependent targets further suggest the implication of Tpx2 in the complex formation [279]. Yap1-dependent but Skn7-independent H_2O_2-induced genes comprise genes encoding components of the glutathione system, PPP, NADPH dehydrogenase, and enzymes of the trehalose pathway required for maintaining cellular reducing power [272]. In yeast, the upregulation of NADPH or GSH appears required for initial cell survival upon oxidative insults, while an adaptative response requires induction of ROS scavengers by Skn7 and Yap1 [280]. Consistently, only during exponential growth, where cells are metabolically active and prone for increased endogenous ROS accumulation, Yap1 and Skn7 are essential to maintain redox homeostasis in all active compartments (cytosol, mitochondria, and peroxisomes), whereas GSH is always required independently of growth phase [281].

As part of their role in protecting against oxidative stress, Skn7 and Yap1 genetically interact with Rad51 to prevent the DNA checkpoint signaling upon oxidative challenges [282], and they induce expression of Srx1 to survive hyperoxia (100% O_2) [283]. Furthermore, both are involved in anaerobic-to-aerobic adaptive response [284] and required to survive cyanide stress that associates elevated ROS accumulation [285] and to prevent H_2O_2-induced protein carbonylation [286]. Otherwise, they contribute to anti-aging effects exerted by anti-aging molecules [287–290] and induce yeast antioxidant capacity when cells are grown with *Lactobacillus plantarum* [291].

Skn7 in *S. pombe*

In a spark contrast to D427 being dispensable for the activity of *S. cerevisiae* Skn7 in oxidative stress, the homolog residue in *S. pombe* Prr1 (D418) is indispensable for such a function [292]. Substitution of asparagine to aspartic acid (which prevents phosphorylation) led to a higher sensitivity to H_2O_2 and *t*-BOOH compared to the parent strain, but lower than that of *prr1Δ* mutant [292]. However, the residue was needed, like Prr1, for the induction of *CTT1* and *TRR1* in response to H_2O_2 [292]. The regulation of Prr1 by upstream HKs (Mak2 and Mak3) is only inferred by the fact that the triple mutant is more sensitive than *prr1Δ* to peroxide [117]. In contrast to Pap1 and the Sty1-Atf1 pathway being required for adaptation to low and high concentrations of peroxide, respectively, Prr1 transcriptionally behaves in a wide range of doses, from 0.2 to 6 mM [119, 292, 293]. At low concentrations (0.07 mM), while Pap1 predominates inducible and basal expression of COSR genes, Prr1 is as important as Pap1 for basal expression but required for the induction of only 13 genes (including genes encoding Ctt1, Trr1, Trx1, and the zinc finger protein Hsr1) [119]. Notably, as in the case of *S. cerevisiae*, no single gene requires Prr1 without Pap1 for its induction. Upon medium doses (0.5 mM), induction of genes becomes jointly dependent on Prr1 [119]. Interestingly, Prr1 is not required for H_2O_2-induced oxidation of Pap1, but its interaction with oxidized Pap1 is required for proper transcription of *SRX1*, *CTT1*, and *TRR1* [294]. At the same time, oxidized Pap1 favors recruitment of Prr1 to promotors of these genes [294], suggesting the formation of Prr1-Pap1 complex as in the case of *S. cerevisiae*. Another function linking Prr1 to oxidative stress tolerance is the positive D418-dependent involvement in meiosis by the regulation of the *STE11* gene [295–297], a gene reported as being required for chronological lifespan extension in a Prr1-dependent manner [298].

Skn7 in pathogenic and opportunistic fungi

While *C. albicans* Ssk1 is responsible for the adaptation to osmotic and a broad range of oxidative agents [142], Skn7 appears involved only in the case of peroxide agents [12], but its deletion mutant is even more sensitive to H_2O_2 than mutant defective in the third RR Srr1 [299, 300]. Accordingly, genes encoding peroxidases (Tsa1 and Tsa1B), Trr1, Gpx3, and Ccp1 are upregulated in an Skn7-dependent manner [301]. This regulation, along with regulation of genes with functions in hyphal growth, belongs to Skn7-mediated cellular reprogramming that follows growth on hyphae-inducing solid medium, translating into yeast-to-hyphae transition [301]. Skn7 can bind directly to some of these

genes, and it is required for the full functioning of some of the major regulators of morphogenesis (*i.e.* Cph1, Tec1, and Ume6). Indeed, Skn7 over accumulates during such transition [302], which may justify the involvement of the protein in virulence [12]. The other function of Skn7 during hyphal growth is assumed to help to avoid the intracellular accumulation of ROS; however, these two functions appear uncoupled [301]. To exemplify, the conserved phenylalanyl and leucyl residues in the HSF-like domain (F76 and L83, corresponding to F135 and L142 in *S. cerevisiae*) mediate Skn7 function in hyphal growth, but they do not influence its function in intracellular ROS accumulation, even though the residues are required for surviving peroxide stress. On the other hand, the target Asp residue of Ypd1 located in the RR domain (D474, corresponding to D427 in *S. cerevisiae*) is crucial for the activity of Skn7 in ROS accumulation but has no role in oxidative adaptation nor morphogenesis. As for the other conserved threonyl residues in the RR (T484 and T496, corresponding to T437 and T449 in *S. cerevisiae*), they are only required for oxidative stress tolerance, all suggesting that Skn7 senses internal and external oxidative stress in distinct ways [301]. There is still to uncover the upstream regulators of Skn7.

In *C. glabrata*, in silico interactome analysis predicted interactions between Sln1-Ypd1 and Skn7 during oxidative stress [303]. More evidently, phenotypic and transcriptional studies support the collaborative involvement of Skn7 and Yap1 in oxidative stress tolerance. In mutant lacking Skn7, the H_2O_2-inducible expression of Trx2, Trr1, Tsa1, and Cta1 was either abolished or delayed, which correlates with the increased sensitivity toward H_2O_2 [18, 245]. In response to H_2O_2 and menadione, COSR genes are cooperatively regulated by Skn7 and Yap1, with the exception of genes encoding SODs, which probably explains the intact susceptibility of TF deletion mutants to superoxide generators [16]. Skn7- and Yap1- dependent COSR genes include those encoding Trr1/2, Trx2, Tsa1/2, Gpx2, Cta1, Srx1, and others encoding oxidoreductase enzymes [16, 17]. This transcriptional cooperative behavior is explained in part by the interdependency of Skn7 and Yap1 in their recruitment to their proximate target promoters [16]. Transcripts of a gene encoding the cell-wall adhesin Epa2 were also prompted in peroxide stress under the control of both TFs [304]. Albeit the target genes of Skn7 and Yap1 are involved in survival to neutrophils (*i.e.* Tsa2 and Cta1), both TFs are not required for this feature [17]. Nevertheless, the involvement of Skn7 but not Yap1 in virulence of *C. glabrata* assessed in mouse models of candidiasis [15, 18] suggests undiscovered roles of Skn7 in pathogenesis other than regulation of antioxidant defense.

In the case of *C. lusitaniae*, phenotypic studies support that Skn7 but not the other RR Ssk1 is crucial for the survival to H_2O_2 challenges, while the latter RR is involved in resistance to a wide range of stresses [305]. Skn7 has not been deleted in *M. guilliermondii*. It is only known as exclusively localized in the nucleus [306].

Genome-wide transcriptional studies in *C. neoformans* elicited that Skn7 negatively affects cellular differentiation, melanin production, and resistance to azole antifungals and fludioxonil and promotes oxidative stress tolerance [161]. This set of results is in agreement with the phenotype of the mutant, which exhibits increased melanin production and increased resistance to antifungal drugs [19, 21]. Mutant defective in Skn7 is also extremely sensitive to NaCl, even more than mutants deficient in the HOG pathway [20, 56], although the TF is poorly involved in transcriptional regulation of osmoresponsive genes [161]. When it comes to oxidative stress, mutant is selectively sensitive to *t*-BOOH but not any other oxidants [21]. Transcriptional investigation yet reported oxidative stress-responsive genes among H_2O_2-induced targets of Skn7, including those encoding Trr1, Tsa1, Ccp1, and Gpx2 [161], in addition to Trr1 and SOD1 as *t*-BOOH-induced targets of Skn7 [24]. The use of different background strains and infection models and the set of intricate phenotypes of mutant made in vivo and ex vivo observations less interpretative. Given as an example, Skn7 is required to survive phagolysosomal killing in endothelial cells but not in human nor murine phagocytes [24, 25]. Also, the loss of protein promoted fungal burden in lungs and brain of infected mice [25], and contradictory results were reported concerning its implication in virulence in murine models (see Table 1). It is worth noting in this context that a recent phosphoproteomic study demonstrated that Mpk1-mediated phosphorylation of Skn7 on Ser335 is required for glucosamine-induced filamentation, which relates Skn7 to the pathogenesis of this species [307].

Finally, in the opportunistic yeast *Rhodotorula mucilaginosa*, the response to treatment with chitosan mimicked oxidative stress response and showed an increased abundance of Skn7 and proteins with antioxidant functions [308].

Not much is known about Skn7 in *A. fumigatus*. Based on two phenotypic studies, defective mutants are sensitive to peroxide stress even more than mutants defective in the HOG pathway, but not to menadione nor thiol-disrupting agents [30, 309]. Nevertheless, this sensitivity was not enough to significantly reduce phagocytes-mediated killing or to attenuate virulence in a murine model of pulmonary aspergillosis [30]. Novel findings from Schruefer et al. [309] showed that Skn7 mediates fludioxonil effects, which translated into enhanced resistance in *skn7Δ* cells. In *A. nidulans*, SrrA predominantly contributes to tolerance of hyphae to H_2O_2, while both SrrA and NapA regulate CatB activity [173, 256]. Otherwise, SrrA modulates the activity of another catalase (CatD) during the stationary phase of growth, the ability to use glycerol as the sole carbon source, and resistance to osmostress and cell-wall stress [173, 310]. Also notable is its role in regulating asexual growth [310].

This, along with similar reports on NapA, suggests that morphogenesis functions in *A. nidulans* are tightened to oxidative stress regulators. None of SrrA functions seemed to depend on NikA HK, with the exception of role in fludioxonil sensitivity [310, 311]. Of note, *A. nidulans* SrrA undergoes H_2O_2-induced phosphorylation on T244 [167]. SrrA in *A. terreus* is believed to mediate the production of the secondary metabolite lovastatin through the regulation of ROS [312]. As the HOG pathway is dispensable for oxidative stress tolerance in *A. flavus*, the fungus relies on SrrA to survive peroxide stress and drive expression of Cu,Zn-SOD and GR. Additionally, SrrA regulates both sexual and asexual reproduction and promotes aflatoxin production [313]. At the same time, SrrA, along with Yap1, is involved in anti-aflatoxigenic mechanisms induced by cinnamaldehyde [314], probably in relation with these regulators being important to alleviate the cinnamaldehyde-induced oxidative stress rather than being negative regulators of aflatoxin biosynthesis. This is supported by the fact that two anti-aflatoxigenic molecules, ethanol and eugenol, triggered differential expression of SrrA and Yap1 [315, 316]. Both regulators were also induced in expression following exposure to perillaldehyde, a natural compound causing the accumulation of ROS [317]. Similar findings were reported in *A. oryzae* exposed to oxidative agents [318].

Oxidative stress response in *F. oxysporum* is also heavily dependent on Skn7. Transcriptomic and biochemical analysis showed that Skn7 plays a critical role in the regulation of a subset of genes encoding antioxidants, including catalases and components of the thioredoxin and glutathione systems [319]. Finally, *T. marneffei* Skn7 was also shown to protect conidia against H_2O_2 stress [320].

Conclusion and future perspectives

Oxidative burst is critical in immune clearance, so targeting protective pathways may help incapacitate fungi and tackle relative infections. Conclusive evidence reviewed here on functions of the HOG pathway, Yap1, and Skn7 in oxidative stress response indicate different aspects of involvement and settle the groundwork for therapeutic development. For the HOG pathway, the involvement is rather species-specific, changing from putative mitochondrial-related functions in *S. cerevisiae* to heavy antioxidant and anti-aging functions in *S. pombe*. With the fact that the pathway is a critical nexus modulator of other types of stress and governs many virulence determinants in fungi, its implication in the survival of phagocyte killing and in vivo virulence might not only relate to its role in the mediation of ROS scavenging. Targeting a multi-operational pathway like the HOG pathway promises to have a great impact on fungal adaptation. In the view of high homology between Hog1 MAPK and the human counterparts, targetting of the HOG pathway via components of TCS, particularly Ypd1, should take center stage in the mining for antifungals. The heavily conserved function of Yap1 in oxidative stress response does not appear sufficient to drive fungal pathogenesis. Considering the obvious link between Yap1 and antifungal resistance, exploiting Yap1 in therapy is still proposed. One would consider approaches addressing reactive cysteine in targeting both Yap1 and enzymes that drive its dynamicity, such as thioredoxin and glutaredoxin-related enzymes. Fungal Skn7 operating in oxidative stress response is obviously demanding of Yap1. However, Skn7 appears more related to virulence than Yap1, and similarly to the HOG pathway, its involvement in fungal development might account for the mutant reduced in vivo virulence. The druggability of Skn7 should be appreciated regardless of its constitutively nuclear nature, mainly because its regulators are quite poorly discovered and could constitute suitable substitutes. Nonetheless, the concept of collaborative rather than individual tasks performed by each regulator in favor of the whole cellular response to oxidative stress must be kept in mind. One way to support this concept is the characterization of a triple mutant devoid of genes encoding these effectors (if not lethal), which has never been reported in fungi.

Although gathered data on fungal response to oxidative stress are sufficient to prioritize translational research, dissection of some unexplored biological aspects will help usher the antifungal discovery. First, the identification of novel actors of the response and relative mechanistic fashion of activation needs to be addressed by means of omic tools. Technologies of chromatin immunoprecipitation sequencing (ChIP-Seq), ARN sequencing (ARN-Seq), and phosphoproteomic ensued with functional genomic approaches like CRISPR-Cas9 would refine data on eventual regulators and effectors of a given pathway. The meager literature on the interconnection between the HOG pathway, Skn7, and Yap1 should also spur investigational efforts toward physical interactions of components of these pathways, principally via yeast two-hybrid system (Y2H) and the bimolecular fluorescence complementation assay (BiFC). Second, researchers should be aware of the issue that fungal response to host-imposed oxidative threats may be largely overlooked. This is because conditions applied during in vitro studies, from which current knowledge is founded, lack the spatiotemporal dynamism and complexity that feature human hosts. Therefore, more in vivo studies integrating mathematical modeling are warranted to provide credible information on fungal response during infections. A third aspect that remains uncharted is the evolutionary aspects of oxidative stress response across fungi. Some questions could be raised in this regard as to which extent evolution drives patterns of adaptation. As more fungal genomes are becoming publicly available and with the emergence of sophisticated and

inexpensive big-data tools, large-scale phylogenetic analyses are expected to deliver answers. Finally, besides transcriptional and proteomic levels of response regulation, attention should be paid to metabolic regulation. Numerous functions of secondary metabolites in fungal pathogenesis and development have been reported to date, though roles in oxidative stress tolerance are still restricted to some mycotoxins (such as gliotoxin) and pigments (melanin). Genome mining studies, as well as biochemical screening, are yet to depict more secondary metabolites with functions in protection from free radicals. A better understanding of these aspects will help unveil the different layers of the regulatory network employed by fungi during oxidative stress, consisting of sensors, modulators, transcription factors, effector genes, and non-proteinous actors. The foreseeable research will enrich the knowledge on these regulatory pathways and provide scalable approaches for therapeutic innovation.

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