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Review article

Molecular pathways of generation and detoxification of reactive oxygen species and induction of apoptosis in yeasts

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A B S T R A C T

Reactive oxygen species (ROS) can trigger cell death in *Saccharomyces cerevisiae* and other lower eukaryotic organisms. Protein structure and function may be altered by ROS produced by cellular metabolism or by exposure to environmental oxidants. This happens regardless of whether peroxidases, superoxide dismutases, or catalases are active. Depending on the redox state of cysteine residues, oxidative alteration of sulfhydryl groups in proteins may inhibit protein activity or begin alternative pathways that affect cell function. Redox control is made possible by conserved, interdependent thioredoxin and glutaredoxin systems, which may play a comparable function in metal homeostasis in eukaryotic organisms. In response to oxidative stress, gene expression in *S. cerevisiae* is regulated by several transcription factors, including Yap1, and Gpx3 peroxidase, and one function of Yap1 is to regulate gene expression. Notwithstanding this information, many issues about the link between ROS production and apoptosis remain unsolved. ROS may disrupt cells or activate certain molecular and cellular pathways during cell death, promoting apoptosis. This review aims to elucidate ROS's essence, their harm to cells, how *S. cerevisiae* reacts to ROS, and how ROS might affect cell integrity and cause cell death.

1. Introduction

Reactive oxygen species (ROS) are acknowledged as unstable, partially reduced, and highly reactive derivatives of oxygen with unpaired electrons that are generated in various cellular physiological pathways as a by-product (Qamer et al., 2021). Oxygen (O_2) is relatively inert despite having two outer-shell unpaired electrons. This is because the usual criteria for higher reactivity are not met since each of these electrons has the same spin. When an unpaired electron becomes excited and changes its spin, the resultant species, what we call singlet O_2, sets off an extremely strong oxidant. The result of the reactive oxygen species (ROS) includes a range of molecules acting as either reductants or oxidants, such as superoxide anion (O2−) and hydrogen peroxide (H_2O_2). These molecules can impact the cellular redox homeostasis (Nazir et al., 2024).

ROS may produce beneficial and/or detrimental effects depending on the cell's internal conditions (Zhang et al., 2018). Secondary ROS molecules and radicals with varying degrees of reactivity are produced when primary ROS interact with different parts of cells. Therefore, it has been proven that the mechanism responsible for cellular damage is associated with ROS. ROS plays an important physiological role of ROS in the normal functioning of the cells. Various diseases may arise where the concentration of ROS exceeds and overwhelms the body's natural defense against them. Moreover, ROS may induce genomic alterations

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that affect cellular homeostasis and result in diseases including cancer. The present review describes toxicity generated by ROS and protective systems including antioxidant enzymes and antioxidant molecules to combat ROS toxicity in yeast cells (Fig. 1).

2. Reactive nitrogen species

Cells initiate the synthesis of reactive nitrogen species (RNS) and generate ROS via the interaction of oxygen with the nitric oxide radical (NO). Byproducts of this process include nitrogen dioxide radical (NO_2) and reactive peroxynitrite ($ONOO^-$). Peroxynitrator activation of aromatic amino acid residues can (Taysi et al., 2019; Gong et al., 2024), result in DNA lesion formation and thiol group oxidation. Peroxynitrite has higher reactivity than H_2O_2 when it comes to protein damage and thiol oxidation. Peroxynitrite has higher reactivity than H_2O_2 when it comes to protein damage and thiol oxidation (Mandal et al., 2022). $ONOO^-$ is a very active compound that forms when NO reacts with superoxide anions (O-2). It can modify thiol groups, resulting in the production of S-nitrosothiols, as well as nitrate tyrosine residues (Pérez de la Lastra et al., 2022). *S. cerevisiae* appears to generate NO in a hypoxic situation in mitochondria (Sunyer-Figueres et al., 2020). A reduction of nitric oxide generation lowers the risk of damage to the S-nitrosylation of glyceraldehyde-3-phosphate dehydrogenase (GAPDH), reduces ROS generation, and increases cell existence (Muronetz et al., 2017). NO can also be produced via reducing nitrite, in addition to NO synthase. These kinds of operations would be facilitated through mitochondrial nitrite reductase or cytochrome *c* reductase (Lancellotti et al., 2020; Zhan et al., 2024). Yeast hemoglobin (YHb) is an important enzyme that helps control levels of NO and protects the cell from harmful quantities of nitric oxide, especially when it comes from outside the cell. This provides further evidence that NO production is going on inside yeast cells as well (Poole, 2020).

3. Yeast cell-mediated production of reactive oxygen species

3.1. Mitochondria

The evolutionary history of oxygen's emergence has ushered in the rage of stresses due to the various reactive species as the result of metabolism or sensitive metabolites' reaction with oxygen. Throughout the redox reaction, the ROS production is directly coupled with the concentration of oxygen (Sachdev et al., 2021). In yeast, the substantial intracellular source of ROS involves the extraction of electrons from the mitochondrial electron transport chain (ETC) during aerobic respiration (Fig. 2) under typical physiological circumstances (Payen et al., 2019). Despite numerous valid debates regarding the precise measurement of ROS production at the alternate site of the respiratory chain, there is a consensus on the controversy (Nair et al., 2018).

The inner membrane space of mitochondria in yeast cells contains three nicotinamide adenine dinucleotide dehydrogenases that are not sensitive to rotenone, regardless of whether complex 1 is present or not (Fig. 3) (Brambilla et al., 2020). NDI1 also known as internal NADH ubiquinone oxidoreductase, oxidized NADH which is generated in the mitochondrial matrix. Ndi1p, in addition to an oxidizing Nicotinamide adenine dinucleotide which is generated through ethanol oxidation via ethanol/acetaldehyde shuttle, has been hypothesized to also play a part in modulating the redox balance at the extent of mitochondrial NADHA, which is generated through the citric acid cycle (Signorile et al., 2019). Contrary to mammalian mitochondria yeast mitochondria are like plant mitochondria which oxidize cytosolic NADH directly (Zhao et al., 2020). Nde1 and Nde2 are two external NADH dehydrogenases found on the inner membrane of mitochondria, showing five active sites opposite the mitochondrial intermembrane gap. They facilitate the oxidation of cytosolic NADH, generated in the course of glycolysis because of the mitochondrial inner membrane's inability to transport NADH, but some scientists hypothesized that they are predominantly jumbled in respiration when cells were vegetated on ethanol (Mancebo et al., 2022). Due to the rotenone-insensitive status of Nde1p and Nde2P, they cannot pump protons (Fedoseeva et al., 2017). On the other hand, the glycerol-3-phosphate de-hydrogenase shuttle comprises cytosolic Nicotinamide adenine dinucleotide link G3PDH (Gpd1/2), and membrane-bound G3P; Ubiquinone, oxidoreductase can oxidize cytosolic NADH which is produced through glycolysis (Gut2) (Costa et al., 2021). In the ETC, the succinate dehydrogenase also called succinate dehydrogenase or complex II through FADH2 is liable for shifting the electron from succinate to coenzyme Q (ubiquinone). In *S. cerevisiae* all enduring pathways of

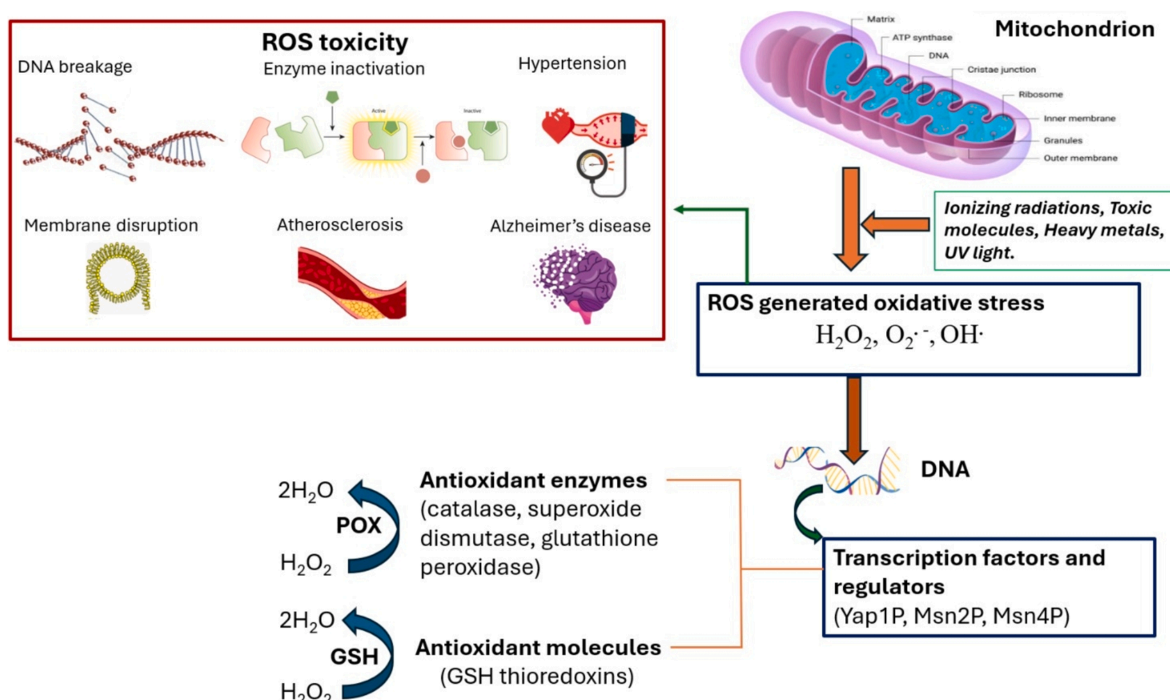

Fig. 1. Schematic diagram showing ROS toxicity and protective systems to combat ROS toxic effects.

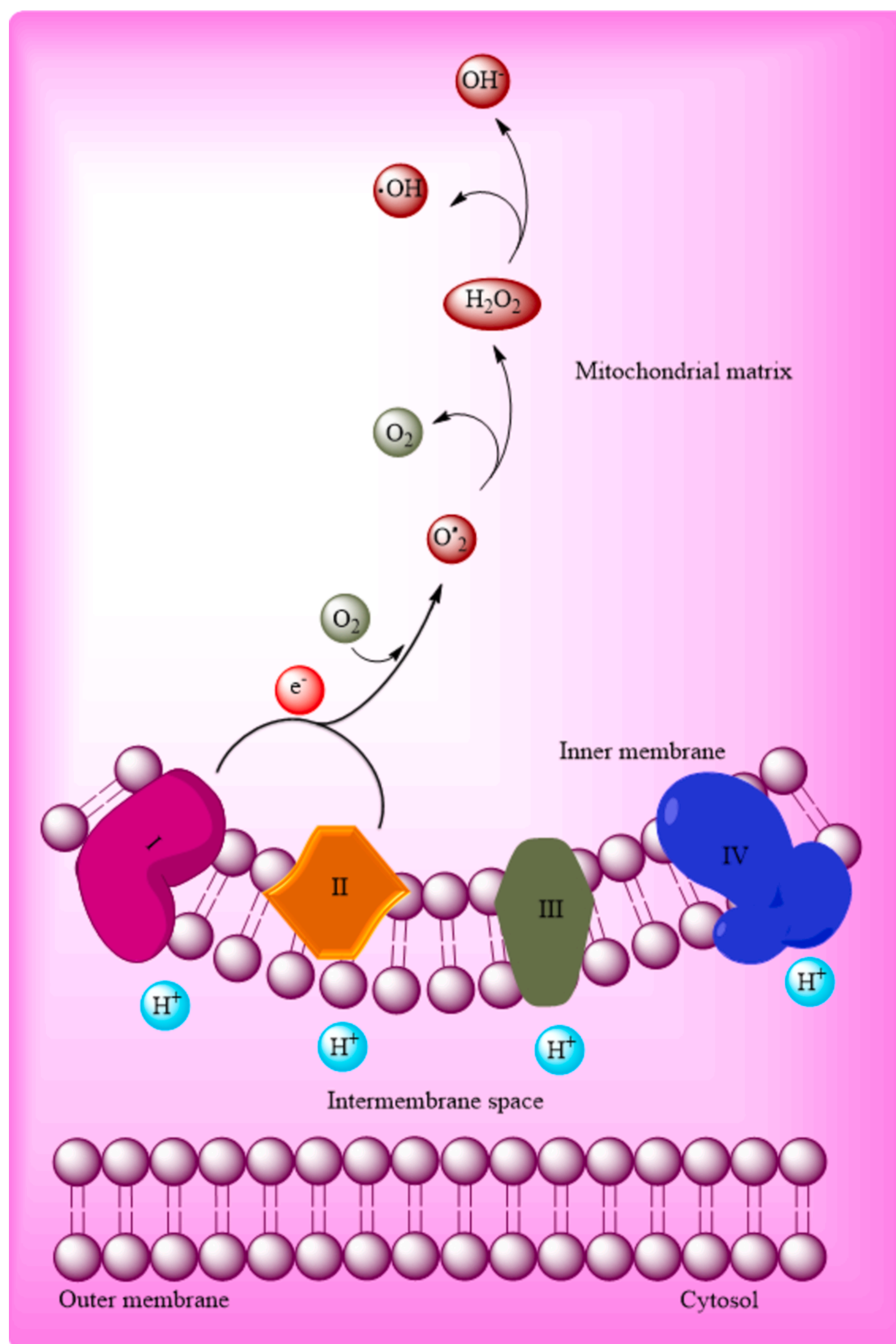

Fig. 2. ROS formation in the mitochondrion (Noreen et al., 2018).

respiratory $FADH_2$ or NADH coincide at the ubiquinone pool. Through the cytochrome bc1 complex (complex III), ubiquinone transfers its electron to cytochrome *c*. Cytochrome c's terminal oxidation is mediated by cytochrome *c* oxidase through molecular oxygen (cox or complex 1V) (Watson and McStay, 2020).

3.2. Endoplasmic reticulum

The endoplasmic reticulum (ER) stands as one of the most extensive membrane-bound organelles, undertaking a diverse range of functions that include protein and lipid synthesis, folding, calcium storage and release, ER maturation, and protein secretory pathways (Schwarz and Blower, 2016).

The functioning of the protein disulfide bond-forming machinery (PDBFM) entails several components, including multiple proteins such as protein disulfide isomerase pdi1p, flavin-containing oxidoreductase, Ero1p, Eug1p, and Mdi1p. These components collaboratively participate in the process of protein folding in the ER under aerobic circumstances (Narayan, 2020). In aerobic environments, two electrons transfer to Ero1p/Pdi1p, where oxygen acts as a terminal electron acceptor, as a consequence of correct disulfide bond formation, which is critical for a protein to achieve its natural shape. (Fu et al., 2020). Fig. 3 shows that PDBFM produces H_2O_2 as a result of oxidative protein folding in the ER. H_2O_2 is a byproduct of the disulfide bonds formed *in vitro* by thioredoxin oxidation mediated by Ero1p (Peixoto et al., 2018; Mennerich et al., 2019). Consequently, it is anticipated that under normal physiological situations, ER set up a source of ROS in living cells, and the flow of electrons from reduced sulfhydryl to Pdi1p/Ero1p would be reflected in

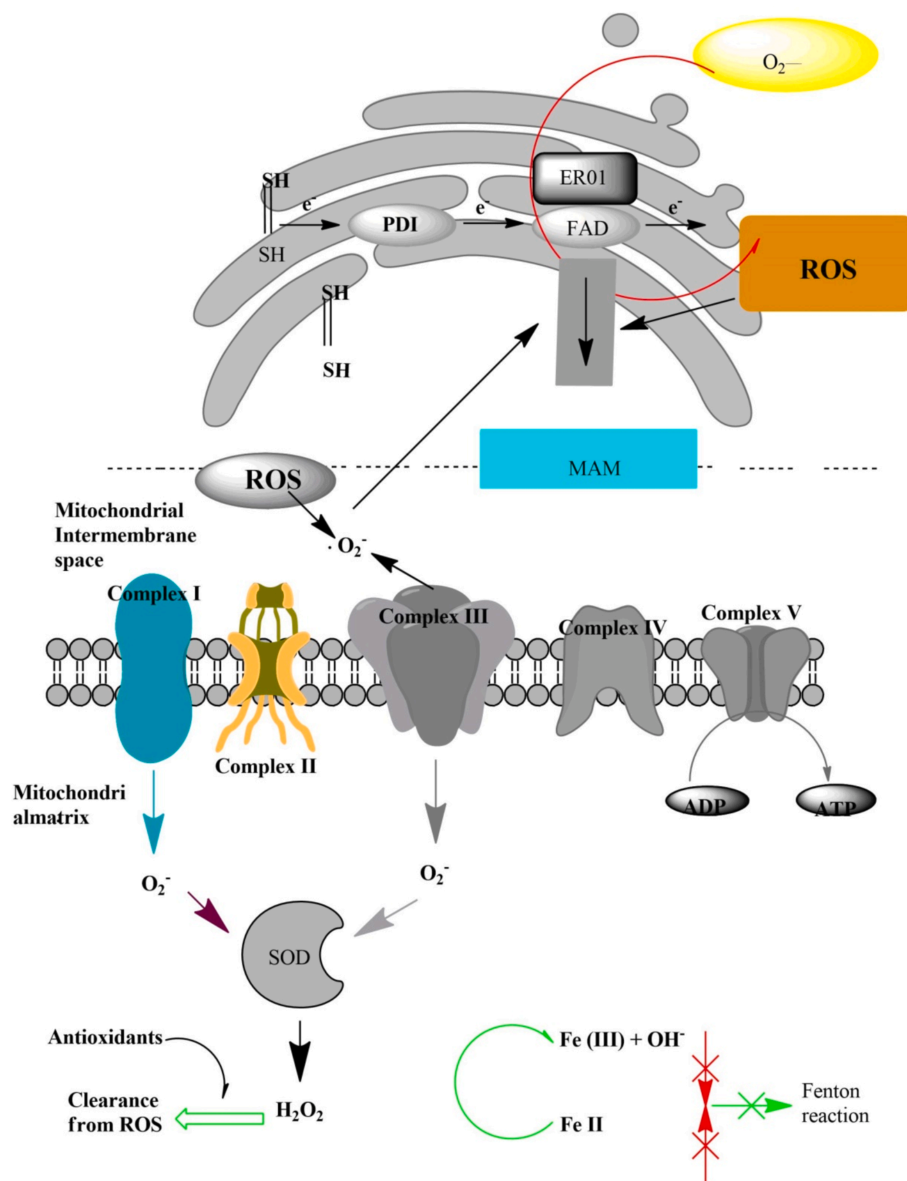

Fig. 3. Generation of reactive oxygen species (ROS) in the ER and mitochondria in response to ER stress (Park et al., 2018).

which the amount of ROS generated (Park et al., 2018) (Fig. 3).

ETC of mitochondria consists of four protein complexes (1–4) and an ATP synthetase resides inside the inner mitochondrial membrane. The electron transfer from NADH+ and FADH+ to NAD and FAD by complexes 1 and 4 produce O_2^- radicals which are then converted into H_2O_2 enzymatically by the catalytic activity of SOD. To suppress the generation of H_2O_2 various antioxidants such as catalase reacts with them and neutralize their effect. OH^- can react with metals like Fe (already present in the cytosol) to start a chain of oxidation reaction and the subsequent generation of ROS, resulting from the Fenton reaction, leads to cellular damage (Hasan et al., 2024).

3.3. Peroxisomes

Peroxisome, previously known as a microbody, is a membrane-bounded organelle that is very important for the metabolism of D-amino acids, methanol, and fatty acids in yeasts. These influence the size, number, and enzyme content of peroxisomes and initiate their biogenesis (Mast et al., 2020). It is reported that a signal called peroxisomal targeting signals (PTS) directs proteins to these microbodies' milieu. On the other hand, independent proteins importing pathways of PTS have also been reported (Kim and Hettema, 2015). The genesis of ROS, in most cases which is H_2O_2, is carried out by various peroxisomal enzymes, for example, the degradation of fatty acid during the participation of acyl-CoA oxidase in the β-oxidation pathway. Subsequently, yeast cells produce large amounts of H_2O_2 when they consume fatty acids, which in turn produce a large amount of catalase (Sen and Heerspink, 2021). Methanol may be chemically converted into formaldehyde and hydrogen peroxide with the help of alcohol oxidase, which is the first enzyme in the methanol metabolism process. H_2O_2 is also generated by urate oxidation to allantoin using urate oxidase (Kurylenko et al., 2019).

4. Types of ROS

4.1. Superoxide anion ($O_2^{\bullet}-$)

ROS produces superoxide anion (O_2-) as its main product. Oxygen is very abundant inside the living cell and relatively stable when there are two electrons in the outermost shell upon losing or reducing by an electron it yields a dangerous byproduct which is a product of oxygen metabolism.

For the most part, it is the result of the withdrawal of electrons from the respiratory chain of mitochondria, which is an end product of aerobic respiration (Wong et al., 2017). It is said to be hew through phagocytes during respiratory burst and microsomal metabolism. The superoxide anion has been reported to be directly involved in the reaction with some proteins but is not potentially reactive (Castro et al., 2019).

4.2. Hydrogen peroxide (H_2O_2)

Enzyme superoxide dismutase (SOD) catalyzes the transformation of superoxide ion into hydrogen peroxide. This conversion of H_2O_2 to water takes place as a result of several peroxidase reactions. The enzyme is a byproduct of fatty acid oxidation in the peroxisome and protein folding in the ER. Yeast produces H_2O_2 as a byproduct of O_2-detoxification and several oxidase processes (Sachdev et al., 2021). H_2O_2 is reasonably unreactive and can eagerly pass through many biological membranes but has a detrimental outcome upon converting into tremendously reactive hydroxyl radical (OH^-). A very reactive hypochlorite (CLO^-) is formed from chloride ions and H_2O_2 through myeloperoxidase action by neutrophils during phagocytosis. CLO^- which is generated through this reaction will now form the chloramines by reacting with free amines, which are extremely toxic to living cells (Maiorino et al., 2018).

4.3. Hydroxyl radical

Hydroxyl radical (OH^-) is found to be very strongest oxidant in nature. H_2O_2 and O_2 are combined in the Fenton and Haber-Weiss reaction, which is catalyzed through transition metal ions like Fe^{2+} which yield hydroxyl radicals (Walter et al., 2020). H_2O_2 upon reacting with Fe^{2+} yields the OH and OH^- and leads to the production of Fe^{3+} which is then degraded again to Fe^{2+} through the action of O^{2-} to relaunch the process. Several metabolites and bio-macromolecules react with this radical and yield secondary radicals (Kim et al., 2019a,b). The homeostasis process involved in Cu and Fe is vital for the cellular defense mechanism through Lassen down the damage spawned by ROS. Unsaturated fatty acids represent a primary target for the protonated O_2-. This interaction leads to the formation of lipid radicals and the subsequent generation of toxic lipid hydroperoxides (Su et al., 2019). Carbonyls and methylglyoxal formed through the breakdown of lipid hydroperoxide and non-enzymatically by glycolysis respectively, which can both lead to the generation of carbonylation of protein and glycation. Several amino acids, predominantly arginine, and proline are attacked with metal-catalyzed forces to yield glutamic semialdehyde, whereas lysine generates aminoadipic semialdehyde (Bellahcène et al., 2018). These changed proteins assemble with chronological age resulting in apoptosis (Arlia Ciommo, 2018).

5. ROS detoxification via enzymes

5.1. Superoxide dismutase

The catalysts for the disproportionation of superoxide ions to hydrogen peroxide in *S. cerevisiae* have been identified as manganese-dependent superoxide dismutase (Mn-SOD) and copper, zinc-dependent superoxide dismutase (Cu, Zn-SOD). The major superoxide scavenger in mitochondria is Mn-SOD, Superoxide dismutase-2 gene encodes it and is responsible for 5–15 % of all SOD activity (Gangwar et al., 2020; Wang et al., 2021). Its activity in fermentative cells is fairly modest and can be increased by respiration, starvation, or ethanol exposure (Bagamery et al., 2020). The gene responsible for superoxide dismutase-1 encodes a SOD which contains copper and zinc. This enzyme is believed to be primarily located in the cytosol, with some presence in the mitochondrial intermembrane gap (Warris and Ballou, 2019). During respiration and fermentation, Cu, Zn-SOD accounts for up to 90 % of total SOD1 activity and around one percent of soluble protein in the cell (Montllor Albalate, 2021). It prevents oxidation of cytosolic and mitochondrial components and ensures their survival for the long term. After heat shock, a defect in cytosolic superoxide dismutase causes a rise in intracellular oxidation and rapid mortality in the stationary phase (Sunthonkun et al., 2019) (Table 1).

S. cerevisiae SOD1 and *SOD2* mutations are oxygen hypersensitive. SOD deficiency results in poor aerobic development, a high amount of mutations, and a high susceptibility to redox-cycling medicines (Lalève et al., 2016; Rosa et al., 2021). *SOD1* mutants have a range of symptoms, including poor respiratory growth, hypersensitivity to exogenous oxidants (like paraquat or menadione), stationary phase instability, and defects in methionine and lysine biosynthesis (Funada et al., 2022). Under internal oxidative stress circumstances, the pentose phosphate pathway is inhibited consequently, the NADPH pool is depleted, which is essential for methionine biosynthesis (Bertels et al., 2021). Lysine auxotrophy might be a result of damaged mitochondria's retrograde reaction, which affects the lysine biosynthesis process (Parkhitko et al., 2019). Even though superoxide dismutase is an important antioxidant enzyme, several studies have found that high dosages of superoxide dismutase promote lipid peroxidation, produce OH, and cause cell death (Fig. 4) (Case, 2017; Palma et al., 2020).

5.2. Chaperone Ccs1

For SOD1 activity the intermolecular disulfide bond is very vital. The copper chaperone Ccs1 is important and its requirement is essential for the maturation of SOD1 and its inter-compartmentalization between mitochondria and cytosol (Barchiesi, 2018; Horn and Wittung-Stafshede, 2021). In addition to assisting in the delivery of copper to superoxide dismutase-1, the principal functions of the Cs1 chaperone include protein maturation and the synthesis of disulfide bonds. The absence of an intermolecular disulfide bond in sod1 facilitates protein aggregation (McAlary et al., 2019; Wright et al., 2019; Cox et al., 2020).

5.3. Catalase

S. cerevisiae has two enzymes and both contain heme. cytosolic catalase T is encoded by CTT1, while peroxisomal catalase is encoded by CTA1 (Dzanaeva et al., 2020; Yuan et al., 2021). Catalase T (CTT1) has been reported non-essential one for yeast in normal conditions perhaps it plays a crucial role in protection during severe stress situations (Guaragnella et al., 2019). CTA1 is proposed to have a function in the process of neutralizing H_2O_2 produced through fatty acid oxidation due to its coordinated regulation with peroxisomal structure and fatty acid metabolism (Deori et al., 2018; Fransen and Lismont, 2019). CTT1 is considered to have a broader function as an antioxidant during oxidative stress, several stresses may trigger its activation, including high temperatures, osmotic stress, hunger, and hydrogen peroxide (Miles et al., 2018). Furthermore, CTT1 lacking yeast strain was susceptible to heat stress and demonstrated low cross-adaption to hydrogen peroxide after mild heat stress (Bayliak et al., 2017; Galkina et al., 2020). The double cta1 ctt1 mutant grew normally under aerobic conditions and was insensitive to H_2O_2 raising issues regarding the actual role of catalases in yeast (Eleutherio et al., 2018). Nevertheless, after being pre-treated with a mild dosage of H_2O_2 and entering the stationary phase, catalase is shown to be important for peroxide resistance acquisition, suggesting its

Table 1
Antioxidant defenses in *Saccharomyces cerevisiae*.

Mechanism	Gene(s)	Target Location*	Role
Metabolites of antioxidants			
Glutathione		General	Redox Aqueous buffer, xenobiotic excretion
Ubiquinone		Mit, ER and Mem	Antioxidant (lipid soluble), Respiratory Chain components
D-erythroascorbate		Cyt?	Antioxidant (water-soluble)
Enzymes			
Catalases	*CTT1*	Cyt	Dis-mutation of H_2O_2 to $H_2O + O_2$
	CTA1	Per	
Superoxide dismutases	*SOD1*	Cyt, Mit, and Nuc?	Dis-mutation of O2− to $H_2O + O_2$
	SOD2	Mit	
SOD chaperone	*CCS1*	Cyt	Needed for stacking copper in toSod1p
Thioredoxins	*TRX1, TRX2*	Cyt	Redox control, sulphate assimilation, Deoxyribonucleotide synthesis, a cofactor for some peroxidase.
Dithiol glutaredoxins	*GRX1, GRX2*	Cyt, Nuc	Enzymatic activities overlap with thioredoxins, and contain glutathione peroxidase activity.
Monothiol glutaredoxins	*GRX3, GRX4, GRX5*	Nuc, Mit, Matrix	Defend cells against redox damage Assembling Fe/S clusters
Peroxiredoxins	*AHP1, PRX1*	Cyt Mit	Reduction of alkyl peroxidase, ROOH + R'SH = R'SSR'+ROH
Thioredoxin peroxidases	*TSA1*	Cyt	H2O2 + RSH = H2O + RSSR peroxiredoxin activity, thioredoxin peroxidase activity Yap1p nuclear localization is also mediated by this protein.
Sulfiredoxin	*SRX1*	Cyt, Nuc	Reduced cysteine sulfinic acid residue in Ahp1p,Tas1p
Glutathione peroxidases	*GPX1, GPX2*	Cyt/Mem	Reduction of oxidized lipid hydroperoxides
Phospholipid hydroperoxide GSH peroxidase	*GPX3/ORP1*	Cyt	Thioredoxin peroxidase activity is present. Yap1p receives a signal from the hydroperoxide receptor
cytochrome *c* peroxidase	*CCP1*	Mit inner membrane space	Hydrogen peroxide reduction in the mitochondrion
Glutathione synthesis	*GSH1, GSH2*	Cyt	GSH synthesis in stages
Glutathione reductase	*GLR1*	Cyt	GSSG to GSH reduction
Pentose phosphate pathway enzymes	*ZWF1, GND1, TAL1, TKL1,2, RPE1,*	Cyt	NADPH is produced in order to recycle oxidized glutathione, glutaredoxins, and thioredoxins
	ALO1, ARA2	Mit Outer mem?	D-erythroascorbate synthesis
Metal-binding proteins	*CUP1, CRS5*	Cyt	Multiple genes at this locus code for a copper-binding protein that also binds Cd^{2+}.
Transcription factors, regulators			
Yap1p	*YAP1*	Cyt/Nuc	oxidative stress, xenobiotic resistance, and cadmium
Skn7p	*SKN7*	Nuc	Auxiliary transcription factor that interacts with Yap1p to help with oxidative stress and also has a role in osmoregulation.
Msn2/4	*MSN2, MSN4*	Cyt/Nuc	Heat, hunger, osmotic, and oxidative stress all cause this transcription factor to react to the PKA pathway.
Yap1-binding protein	*YBP1*	Cyt	Yap1p nuclear localization is mediated in part by a protein.
Haem activated protein	*HAP1*	Nuc	
	HAP2,3,4,5	Nuc	Regulation of respiratory functions
Metal-binding activator	*MAC1*	Nuc	H_2O_2-induction of CTT1 is regulated by a gene that regulates genes involved in copper ion homeostasis
Cup2p	*ACE1/CUP2*	Nuc	CUP1 is activated by a copper-binding transcription factor when copper levels are high.

* ER: endoplasmic reticulum; Per: peroxisome; Nuc: nucleus; Mem: membrane; Cyt: cytoplasm; Mit: mitochondrion; suggests that anything is unknown or uncertain. Where known or suggested in the SGD database, genes encoding the functions are listed with their cellular location. (http://www.yeastgenome.org/).

involvement in the adaptive response (Agashe and Kuzminov, 2021). The double cta1 ctt1 mutant exhibits hypersensitivity to peroxide during the stationary phase, indicating that both catalases work together to defend against external hydrogen peroxide (Xiao et al., 2018). Nonetheless, during oxidative, osmotic carbon deprivation, or freeze-thawing stressors, CTT1 expression is increased (Fig. 5) (Guaragnella et al., 2021).

6. Glutathione pathway

The enzymes γ-glutamyl cysteine synthetase (GSH1) and glutathione synthase (GSH2) in yeast are responsible for producing glutathione (GSH), which is made up of glutamate, cysteine, and glycine (Fig. S1). Two glutaredoxin classes and one glutathione reductase have also been found involved in GSH genesis (Fig. 5). One well-known antioxidant in many species is the tripeptide GSH and is generally available as a most frequent non-protein thiol of low molecular weight and plays a postulated detoxification role for xenobiotics, ROS, and carcinogens (Fig. S2) (Sao Emani et al., 2018).

GSH may be used in yeast *S. cerevisiae* as an endogenous sulfur source (Chen et al., 2018). In the presence of sulfate, much of the sulfur is incorporated into GSH. Under the starved condition, GSH functioned as an endogenous sulfur supply until it reached a crucial residual level of about 10 % of its typical concentration. This led to a rise in GSH turnover and a decrease in γ-glutamyl transpeptidase (γ-GT: GSH + amino acid + H_2O) and 3L γ-glutamyl-amino acid (L-glutamate). A single generation of *S. cerevisiae* on a minimal medium deficient in $(NH_4)_2SO_4$ resulted in an increase in the GSH pool from 7 to 17 nM/mg dry weight (Chen et al., 2021). The yeast cytoplasm contained about 50 % of the GSH while the rest stood up in the central vacuole on nitrogen-sufficient media. The central vacuole accumulates GSH in response to nitrogen deprivation. In eukaryotic cells, in addition to being the major redox buffer, GSH is also an important marker of the redox status of a cell, in which the GSH/GSSG a redox potential couple is also considered. In wild-type *S. cerevisiae* cells, GSH concentration can range from 1–10 nM or even higher (Hasanuzzaman et al., 2019). In the TRX system, a GSH, substrate for GSTs, GRXs, and GPXs is also involved (Lyall et al., 2020). Since mutants devoid of GSH (*gsh1*) or with an altered GSH redox ratio (*glr1*) were susceptible to H_2O_2, GSH is a crucial antioxidant found in yeast cells that plays a vital role in protecting against H_2O_2 damage (Shao et al., 2019; Vázquez et al., 2017). Furthermore, H_2O_2 was discovered to change both the extent of GSH and the redox state in connection with a more oxidized state. As in typical aerobic situations yeast cells in the exponential phase exhibit a high redox ratio (GSH/GSSG), showing that

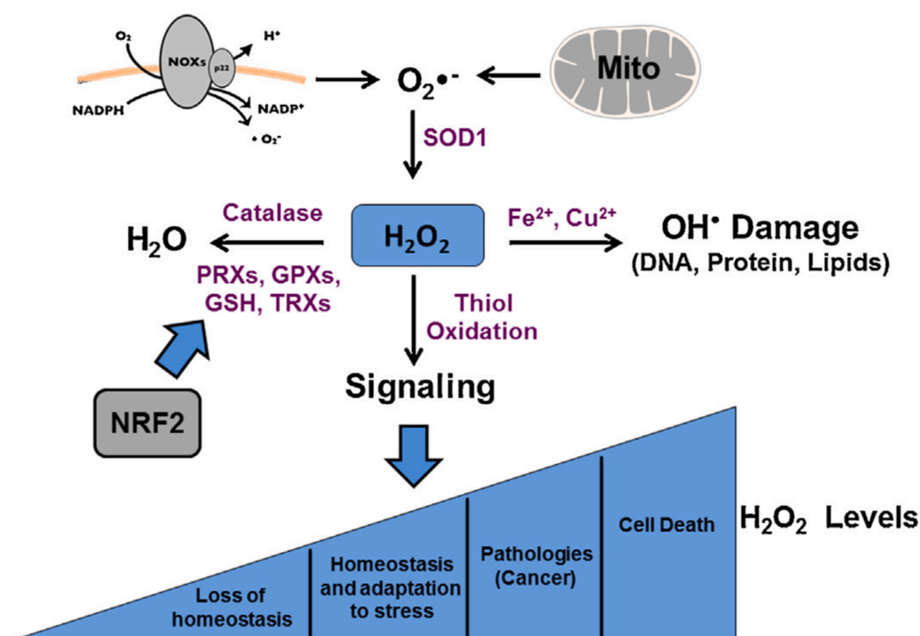

Fig. 4. ROS regulation and cellular effects (Noreen et al., 2018).

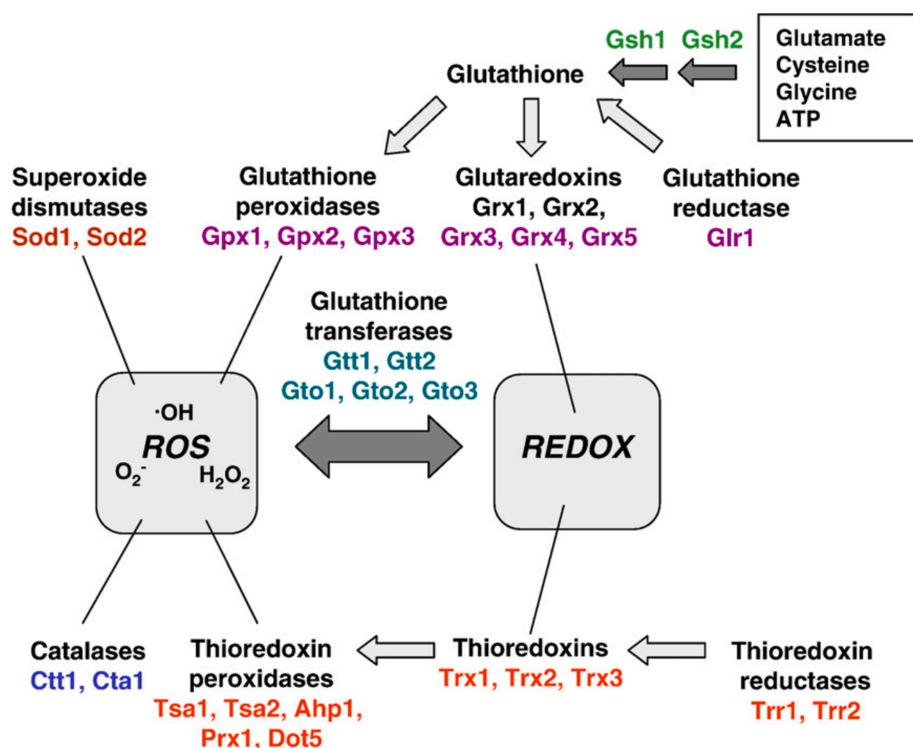

Fig. 5. In S. cerevisiae, the enzyme systems involved in detoxifying reactive oxygen species and controlling the redox state of protein sulphydryl groups and their interrelationships (Herrero et al., 2008).

more than 99.5 % of intracellular GSH is kept in reduced form (Picazo and Molin, 2021).

In eukaryotic cells, GSH is very important, in yeast cells needed as a reductant, which may serve to eliminate endogenously produced toxic metabolites (Cooper and Hanigan, 2018; Fabarius et al., 2021). Toxic lipid peroxidation products and oxidative stress caused by peroxides are problems for yeast strains that are either GSH-deficient or have changes to their GSH redox status. The redox-active sulfhydryl moiety in GSH's cysteine residue performs an inescapable role in its biological importance by acting as a free radical scavenger (Kim et al., 2019a,b). Thorsen et al. (2012) reported that GSH biosynthesis was boosted in *S. cerevisiae* when exposed to arsenite. A 128 % rise in GSH levels and a 66 % rise in the GSH/GSSG ratio were noted. It was also discovered that a 118.6 % rise in non-protein thiols was caused by Cd^{+2} stress (Hasanuzzaman et al., 2017). Furthermore, as reported by Meunier et al. (2004) ROS undergo a crucial oxidative change through the cysteine-to-heme enzyme of reticular membranes, found in the endoplasmic reticulum. One reason yeast cells are more resistant to metal-induced ROS is

because they include cytochrome P450, cytoplasmic GSH, and non-protein thiols (Fig. S2) (Liu and Ma, 2020).

6.1. Monothiol glutaredoxins

In *S. cerevisiae*, monothiol GRX molecules were originally discovered, composed of three monothiol enzymes; Grx3, Grx4, and Grx5. They all have CGFS as their catalytic core (Chi et al., 2018; Mondal et al., 2020; Berndt et al., 2021;). Aft1, a transcription factor that senses iron in the nucleus, interacts with Grx3 and Grx4. In this case, when there is an iron shortage, Aft1 causes the transcription of genes belonging to an iron regulon (Gupta and Outten, 2020; Pujol-Carrion et al., 2021).

Aft1 was constitutively localized in Grx3 and Grx4, iron homeostasis was disrupted, and they became hypersensitive to oxidative stress. It is not known how Grx3 and Grx4 identify iron in yeast cells. The mitochondrial matrix contains Grx5, an enzyme involved in the last stages of iron/sulfur cluster synthesis (Ramos-Alonso et al., 2018; Wang et al., 2019). In eukaryotic cells, Grx5 is an inevitable component of the mitochondrial production of Fe/S clusters (Braymer et al., 2021; Pandey et al., 2019; Tsaousis, 2019). When it is absent, iron builds up and inhibits Fe/S enzymes in the respiratory electron chain. Enhanced sensitivity to oxidants is also shown by Grx5 mutants same as shown by Grx3 and Grx4 (Talib and Outten, 2021). Iron metabolism is regulated by Grx3, Grx4, and Grx5 (Chi et al., 2018; Mühlenhoff et al., 2020) (Fig. 2).

6.2. Dithiol glutaredoxins

The glutaredoxin system consists of glutathione reductase (GR), glutathione peroxidase (GPx), and glutathione-S-transferase (GST), which allows electrons to be transferred from NADPH to glutaredoxin via GSH (Miller et al., 2018; Zuo et al., 2022). Glutaredoxin is a tiny heat-stable oxidoreductase that is well preserved in the active sites during the development period (Kumar et al., 2020). Besides reducing dehydroascorbate and protecting cells from ROS, glutaredoxins are important for protein folding and regulatory activities in sulfur metabolism (Hasanuzzaman et al., 2019; Kim et al., 2020). Glutaredoxin may act as a catalyst for the dissolution of mixed disulfide complexes when exposed to oxidative stress (Fig. S3). Several proteins are rendered inactive by thiol oxidation, which may also restore the functionalities of proteins that have been oxidized (Barinova et al., 2017; Xiao et al., 2019). Glutaredoxin from bacterial and mammalian species share 4–50 % and 61–76 % identity with Grx1 and Grx2, respectively. Both enzymes are found in the cytoplasm, however ATG sites in the frame are responsible for alternative translation initiation, and a portion of Grx2 is also found in the mitochondria (Menon, 2015). The -C-P-Y-C- motif is found in the catalytic core of Grx1 and Grx2 (Liedgens et al., 2020; Roret et al., 2021). There was a concentration-dependent rise in Grx1 expression in response to Cd^{+2} stress. Evidence suggests that *Candida tropicalis* 3Aer Grx/GSH system directly reduces ROS damage caused by Cd^{+2}.

Grx1 protects superoxide anion and hydroperoxide, based on a relevant mutation, but exclusively Grx2 provides hydroperoxide protection suggesting partial overlap functions (Auesukaree, 2017; Ulrich and Jakob, 2019). Although the double mutant strains were viable, they exhibited heat-sensitive oxidoreductase function when L-hydro-oxy-ethylene disulfide was used as the disulfide substrate. Surprisingly, both *Grx1* and *Grx2* have shown 64 % similarity, *Grx1* mutants were not impacted whereas 5 % wild-type activity affected *Grx2* mutants, which indicated that *Grx2* played the leading role. Furthermore, *Grx1* mutants were susceptible to superoxide anion-induced oxidative stress, but *Grx2* mutants were selectively sensitive to H_2O_2, showing that Grx1 and *Grx2* operate differently in a yeast cell. The stress response element (STRE) and Hog1 mitogen-activated protein kinase (MAPK) pathway control Grx1 and Grx2. Unfortunately, we still don't know what these proteins do or what they bind to (Gutin et al., 2015).

6.3. Thioredoxins (Trx) system

Three thioredoxins designated Trx1, Trx2, and Trx3, are found in *S. cerevisiae.* The cytoplasm contains two of them, while the mitochondria house the third (Dickson-Murray et al., 2021). The TRX reductase mutations show that the mitochondrial and cytosolic TRX systems work separately, based on the redox state of the TRX proteins. (Matsuzawa, 2017). *S. cerevisiae's* cytosolic TRX system is crucial for defense against externally introduced hydroperoxides. Individual and double mutant experiments with cytosolic TRXs indicated that their activities do not exactly coincide. Trx2 has been demonstrated to have a more essential function in the defensive system than Trx1 (Meyer et al., 2021). Similarly, when oxidants are supplied externally, Trx2 expresses more induction levels than Trx1. Trx2 metabolizes Tsa1 Trx peroxidase cytosolically, providing protection (Garrigós et al., 2020). It seems that the cytosolic Trx system does not play an important protective function against singlet oxygen (Gutiérrez-Escobedo et al., 2020). A set of proteins i.e., Tsa1, Tsa2, Ahp1, and Prx1, together with Gpx Prx1, belong to a small family of proteins that may hyperoxidize cysteine groups when Trx1 and Trx2 are not present. The involvement of cytoplasmic thioredoxins is vital in safeguarding against hydroperoxides (Curtis, 2019). During reductive stress, Trx2 expression is also increased by dithiothreitol as a disulphide-reducing agent which causes the development of unfolded protein response (UPR) (Zhang, 2019). While this is not due to the activation of UPR, the dithiothreitol is hypersensitive to two Trx1 and Trx2 proteins. The chaperone function of Tsa1 prevents the accumulation of misfolded ribosomal proteins under reductive stress, which occurs when Tsa1 is present in the cytoplasm (Dauplais et al., 2021; Picazo and Molin, 2021) (Fig. 2).

7. Transcription factors and regulators

7.1. Yap1p

Yap1p, a leucine zipper (bZip DNA-binding protein) AP-1 transcriptional component is known to be the foremost designated element of ROS sensing in *S. cerevisiae*, which also acts as a key regulator in response to oxidants. It regulates the production of cellular antioxidants and components involved in thiol reduction (Zhang et al., 2020). Yap1 binds to the Yap1 recognition element (YRE) in different gene promoters. Nevertheless, the discovery of several Yap1 targets that do not include YRE boxes suggests the presence of other recognition sites (Rodrigues-Pousada et al., 2019). Alongside its important part in oxidative stress response, Yap1 is activated by a variety of agents including methyl methane sulphonate, electrophile diethyl maleate, thiol oxidant diamide benomyl, cadmium, mercury, selenite quinone menadione, N-ethylmaleimide, methylglyoxal ionizing radiation, and drugs (Ansarypour and Shahpiri, 2017; Gast et al., 2021; Yilmaz, 2021). Because of its interaction with hydroperoxides and H_2O_2, Yap1p accumulates in the nucleus and influences the transcription of over 70 genes. Thioredoxin reductase, cytosolic superoxide dismutase, cytosolic catalase, and cytochrome *c* peroxidase are all encoded by the same set of genes. GSH metabolism and synthesis genes are also impacted by this process (Dawes and Perrone, 2020; Sen and Imlay, 2021). The C-CRD of Yap1 consists of a leucine-rich export signal (NES) and two cysteine-rich domains (CRD) positioned at the N- and C-termini. All the cysteine residue is provided through N- and C-CRD which is found in the Yap1 sequence and controls the Yap1 function under oxidative stress (Netto and Antunes, 2016; So et al., 2019). Because of the rapid nuclear export set off through nuclear export receptor (Crm1) in unstressed cells, Yap1 constrain in the cytoplasm (Kritsiligkou, 2016). Yap1 nuclear export is inhibited through diamide and hydroperoxides, which impair the connection between Yap1 and Crm1, resulting in Yap1 nuclear accumulation (So et al., 2019). A redox-dependent Yap1 NES, which is activated through two distinct pathways, depends on the kind of oxidant that disrupts the Yap1-Crm1 complex.

The same regulator is triggered YaP2 by two molecular redox centers, each in a different way. The occurrence of a ROS-induced reaction requires the presence of both C- and N-CRD redox centers, involving superoxide anions and hyperoxides. Conversely, a chemical reaction that involves the interaction of thiol groups with divalent heavy metal cations and electrophiles may be achieved only via the presence of C-CRD redox centers. Since an intramolecular disulfide bond forms between the N- and C-terminal CRDs (Cys310-Cys629 and Cys303-Cys598), the higher amounts of reactive oxygen species cause Yap1 to undergo transitory redox-induced conformational changes that hide the NES. As a result, the Yap1-Crms1 connection is disrupted and spurned, resulting in Yap1 nuclear accumulation and activation. The disulfide bond is reduced, causing structural changes that contribute to NES exposure (Mendoza-Martínez et al., 2020). Yap1 does not immediately start the oxidation of hydroperoxides.

The Gpx3 peroxidase, also known as Orp1, acts as H_2O_2 detector and transmits the signal to Yap1. Ybp1 is an essential component that forms a complex with Yap1 by specifically attaching to its C-terminus. It also plays a critical role in the activation of Yap1 caused by H_2O_2 (Yaakoub et al., 2022). Although the specific molecular mechanisms of Ybp1 are not yet fully understood, it is hypothesized that Ybp1 plays a role in relaying signals from Gpx3 to Yap1. The basis for this presumption is the fact that the synthesis of the Gpx3-Yap1 intermediate relies on the existence of Ybp1 (Tomalin, 2015; Curtis, 2019). Sulfonic acid (Cys36-SOH) is produced when peroxides directly oxidize Gpx3′s catalytic Cys36. A temporary Yap1-Gpx3 disulfide intermediate is formed when this sulfonic acid reacts with Yap1 Cys598. The Yap1 intramolecular disulfide bond is formed once this intermediate is resolved. Since Gpx3 is responsible for detecting and relaying an increase in ROS levels to Yap1, Yap1 becomes a vital member of a two-component system. Afterward, Yap1 promotes the activation of genes (Montibus et al., 2015; Mendoza-Martínez et al., 2017).

7.2. *Msn2p and Msn4p and others*

Msn2 and Msn4 (Zn-fingers) have been discovered as transcription factors that mediate various stress responses (Gupta, 2020). As they transition towards diauxic growth, face challenges like high temperature, changes in osmotic pressure, acidity, and exposure to hydrogen peroxide. These stressors attach themselves to the DNA at the CCCCT (a component of the stress response element) (Święciło, 2016). Both compounds endure a reversible translocation into the core as a result of oxidative stress. The molecular mechanisms that regulate this phenomenon, nevertheless, necessitate further explanation. An unexpected finding emerged suggesting that a single instance of the STRE component (CCCCT) was sufficient to increase the expression of a reporter construct in response to thermal stress. On the contrary, the stress-induced expression was significantly enhanced by the additive effect of multiple copies (Alford, 2020). HSP12, TPS2 (GSY2), SOD2, CTT1, and DDR2 are genes identified as being regulated by STRE. SKn7, alternatively referred to as Pos9 (peroxide sensitivity), controls the susceptibility of *S. cerevisiae* to H_2O_2, methyl viologen, and elevated oxygen pressure. Previously, this factor was thought to be insignificant in typical conditions (Ruta et al., 2020). The sequencing of Pos9 has unveiled its association with Skn7. There are notable resemblances between it and a bacterial protein that is linked to the two-component signal transduction system. Skn7 is susceptible to phosphorylation in response to hyperosmotic stress; this modification inhibits the oxidative stress response. Nevertheless, the specific molecular mechanisms that govern their operation continue to be mysterious. Skn7 proteins are implicated in yeast pathogens, including *C. albicans* and *Cryptococcus neoformans*, by constitutively protecting against oxidation, thereby boosting their pathogenic potential (Pais et al., 2016). One protein that helps fission yeast deal with oxidative stress is Prr1, which is similar to Skn7 (Papadakis and Workman, 2015; Shehzad et al., 2024).

CRediT authorship contribution statement

Sidra Gull: Methodology, Investigation. **Chaudhry Ahmed Shabbir:** Methodology, Investigation, Data curation. **Zaman Khan:** Writing – original draft, Investigation. **Dilara A. Bukhari:** Writing – original draft, Supervision, Investigation. **Abdul Rehman:** Writing – review & editing, Supervision, Conceptualization.

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Conflict of interest

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Appendix A. Supplementary data

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