ANTIOXIDANTS & REDOX SIGNALING
Volume 4, Number 1, 2002


# Mini Forum Review

# Transcription Factors Regulating the Response to Oxidative Stress in Yeast

W. SCOTT MOYE-ROWLEY

## ABSTRACT

**A main avenue of defense against fungal infection uses oxidative killing of these and other microorganisms. Consequently, the ability of fungi to withstand an oxidative challenge has important implications for their ultimate pathogenicity in a host organism. Fungi also serve as an excellent model system for handling of reactive oxygen species in eukaryotic cells. For these reasons, a great deal of work has been invested in analyzing pathways involved in and the mechanisms regulating oxidative stress tolerance in fungi. The goal of this review is to discuss the current state of knowledge underlying the ability of fungal cells to mount a response to oxidative stress via activation of transcription factors. Studies in *Saccharomyces cerevisiae* have identified multiple transcriptional regulatory proteins that mediate tolerance to oxidative stress. Experiments focused on the fission yeast *Schizosaccharomyces pombe* have led to the discovery of protein kinase cascades highly related to mammalian stress-activated protein kinases. Recent studies on the pathogenic yeast *Candida albicans* have allowed analysis of the role of a critical oxidant-regulated transcription factor in this important human pathogen. Further understanding of oxidative stress resistance pathways in fungi is an important step toward understanding the molecular pathogenesis of these microorganisms.** Antioxid. Redox Signal. 4, 123–140.

## INTRODUCTION

A CENTRAL CHALLENGE FACED BY PATHOGENIC MICROORGANISMS in the animal host is evading cell-mediated killing carried out by macrophages (18). The major route of killing invading microorganisms involves phagocytosis and eventual exposure to a high dose of reactive oxygen species. The ability of pathogenic microbes to tolerate reactive oxygen species challenge is a crucial feature of their ability to cause disease.

Pathogenic fungi illustrate the linkage of antioxidant defense genes and virulence. *Candida albicans* cells engineered to lack an endogenous catalase gene show marked reductions in virulence (112). Loss of normal oxidant-generating capabilities in neutrophils leads to an increase in fungal virulence (13). Understanding of the molecular basis of the oxidative stress response in fungi is a central issue to our understanding of fungal pathogenesis.

The focus of this review will be on the mechanisms of transcriptional control of oxidative stress defense gene induction in yeast cells. Advances in molecular genetic technologies have led to dramatic increases in our understanding of the oxidative stress response in a variety of fungi, but the most complete picture of how a eukaryotic cell responds to changes in the redox potential of its

Department of Physiology and Biophysics, University of Iowa, Iowa City, IA 52242, U.S.A.

environment is still provided by the budding yeast, *Saccharomyces cerevisiae*. The facile genetics available in this organism has led to *S. cerevisiae* serving as a leading model of fungal oxidative stress response. The discussion here will be limited to the participation of *S. cerevisiae* and other yeast transcriptional regulatory proteins in the response to oxidative stress. The many years of study of *S. cerevisiae*, coupled with the ease of genetic analysis in this organism, have provided the most complete description of the transcription factors involved in oxidative stress in any fungus. However, many of these factors are also likely to be involved in similar pathways in *S. pombe* and *C. albicans*, but will not be discussed because direct experimentation confirming their participation in oxidative stress tolerance has not yet been reported.

Although the picture of the molecular basis of and participants in oxidant-responsive gene transcription is most detailed for *S. cerevisiae*, the fission yeast *Schizosaccharomyces pombe* elaborates much better understood signaling pathways that lead to oxidative stress-activated gene expression. Recent progress has permitted the oxidant signaling pathways triggering activation of gene expression to be traced from the plasma membrane to the nucleus of *S. pombe* cells (10). This is in contrast to *S. cerevisiae* in which even the presence of upstream effectors of oxidant inducibility is still uncertain. Strikingly, *S. pombe* expresses a basic region-leucine zipper (bZIP)-containing protein called Atf1 that is a homologe of the mammalian activating transcription factor (ATF)/cyclic AMP responsive element binding protein (CREB) family (92). *S. cerevisiae* also produces ATF/CREB homologues such as Sko1p (64, 100) and Aca1p/Aca2p (26). Whereas Atf1 has a crucial role in oxidative stress tolerance in *S. pombe* (82, 107), none of the *S. cerevisiae* homologues have been found to contribute to this phenotype (26). Clearly, study of these different yeasts will provide insight into the different strategies used by fungi to respond to oxidative challenge.

Study of *S. pombe* and *S. cerevisiae* oxidative stress pathways is greatly facilitated by the ease of genetic analysis in these organisms. However, these species are not typically found associated with fungal infections in clinical settings. Two of the most common opportunistic pathogenic yeasts in humans are the *Candida* species, *Candida albicans* and *Candida glabrata* (108). Major advances in the genetics and molecular biology of these pathogenic organisms have recently provided the first insights into the involvement of oxidative stress tolerance in the virulence of these organisms (11).

The goal of this review will be to summarize current understanding of the transcriptional control pathways leading to oxidative stress-regulated gene expression. The focus here will be on the transcription factors mediating this response (see Table 1), as other reviews have recently considered the genes activated during oxidant challenge (39, 58). Transcription factors that influence oxidant tolerance primarily through their effects on metal homeostasis, like Mac1p (42), will not be considered here. Although similar tran-

TABLE 1. TRANSCRIPTION FACTORS RESPONDING TO REDOX SIGNALS IN FUNGI

| *Protein* | *Factor class* | *Representative target genes* | *Oxidant regulatory input* |
|---|---|---|---|
| *Saccharomyces cerevisiae* | | | |
| Msn2p/Msn4p | Cys2-His2 zinc finger | *CTT1, HSP12* | Nuclear localization |
| Skn7p | Helix–turn–helix | *TRX2, TRR1* | Unknown |
| Hsf1p | Winged helix–turn–helix | *SSA1, CUP1* | Phosphorylation |
| Yap1p | Basic region-leucine zipper | *TRX2, GSH1* | Nuclear localization |
| *Schizosaccharomyces pombe* | | | |
| Pap1 | Basic region-leucine zipper | *ctt1+, apt1+* | Nuclear localization |
| Atf1 | Basic region-leucine zipper | *ctt1+, pyp2+* | Phosphorylation |
| Prr1 | Helix–turn–helix | *ste11+, trr1+* | Unknown |
| *Candida albicans* | | | |
| Cap1p | Basic region-leucine zipper | *CaGLR1, CaMDR1* | Nuclear localization |

scription factors are used to coordinate the oxidative stress response in these different fungi, important differences in the regulation of these factors indicate that study of each system is necessary to unravel fully the pathways that may be used to allow fungal evasion of oxidant-based killing.

## FUNGAL OXIDATIVE STRESS-REGULATED TRANSCRIPTIONAL PATHWAYS

### *Saccharomyces cerevisiae*

#### Msn2p/Msn4p

Some of the earliest work dealing with the molecular basis of oxidative stress regulation in *S. cerevisiae* centered on regulation of the cytosolic catalase gene (*CTT1*). *S. cerevisiae* contains loci encoding two different catalase enzymes, the cytosolic Ctt1p (88) and the peroxisomal Cta1p (12). Analysis of the promoter of *CTT1* identified an element called the stress responsive element (STRE: AGGGG) that was induced by an array of stresses including oxidant challenge (44, 55). Identification of the protein(s) binding to this element led to the determination that the STRE was bound by two homologous transcription factors, Msn2p and Msn4p (56).

*MSN2* and *MSN4* were originally cloned as high-copy-number suppressors of the growth defect on sucrose of a temperature-sensitive *snf1* mutant (21). Early analysis indicated that these factors were capable of activating transcription, but their function remained unknown (21). Experiments aimed at examining the role of these related proteins in the stress response uncovered their importance in this physiological pathway. Loss of both *MSN2* and *MSN4* led to a pronounced loss of viability upon carbon starvation, heat shock, or oxidative challenge by hydrogen peroxide ($H_2O_2$) (56). These factors were also required for induction of an artificial STRE reporter plasmid by various stresses. *CTT1* stress activation was also severely curtailed in the absence of Msn2p/Msn4p. Finally, DNA binding experiments confirmed that both Msn2p and Msn4p were able to bind to the STRE that is found in many genes activated by environmental challenges, including oxidative stress (61).

Although *MSN2* and *MSN4* are clearly involved in a variety of stresses, their specific contribution to oxidant exposure is still unclear. One of the prototypical Msn2p/Msn4p target genes often documented to illustrate the role of these proteins in oxidative stress is the cytosolic catalase gene, *CTT1.* Interestingly, in direct experiments aimed at exploring the role of Ctt1p and the peroxisomal catalase (Cta1p) in $H_2O_2$ tolerance, it was found that these catalases contributed in only minor ways to peroxide resistance in log-phase cells (37). However, loss of *CTT1* and *CTA1* rendered cells extremely sensitive to $H_2O_2$ challenge in stationary-phase cells and eliminated the adaptive response for $H_2O_2$. Comparison of the contribution of *MSN2* and *MSN4* to chronic $H_2O_2$ exposure indicated that these transcription factors had little influence on the observed tolerance of mutant strains (S. Coleman and W.S. Moye-Rowley, unpublished observations). These data, coupled with the large body of evidence demonstrating a role for Msn2p/Msn4p in stress-activated transcription (for review, see 20), argue that these factors are more likely to be involved in the so-called general stress response rather than a specific activation by oxidative stress. Msn2p/Msn4p are activated when cells are subjected to many different stress treatments, and these factors act to arrest growth as well as to allow survival under harsh environmental conditions.

Genetic analysis of the interactions of *MSN2/MSN4* with the protein kinase A (PKA) pathway in *S. cerevisiae* has provided an attractive model for understanding the integration of the stress response of Msn2p/Msn4p with cellular growth control. The presence of at least one gene encoding the catalytic subunit of PKA (*TPK1, TPK2, TPK3*) is required to maintain viability (95). Intriguingly, Garrett and colleagues found that the viability of a triple deletant strain (*tpk1Δ, tpk2Δ, tpk3Δ*) could be restored by removal of both *MSN2* and *MSN4* (84). This led to the important suggestion that a major role for the PKA pathway in transmission of a positive

growth signal is to antagonize the activity, of these transcriptional regulators controlling the stress response. A model consistent with these data is provided by Msn2p/Msn4p being activated by a reduction in PKA activity, which presumably would occur in response to a wide variety of stresses that act to inhibit growth. This could explain the pleiotropic nature of the signals that lead to activation of the Msn proteins. A more thorough consideration of the role of Msn2p and Msn4p in the stress response can be found in a recent review (20).

### Skn7p

A common means of environmental stress sensing in bacterial cells is the use of two-component signal transduction systems (90). These systems consist of a sensor protein, typically associated with the cell membrane, that serves to detect a signal of interest (19). This sensor protein contains an autophosphorylating histidine kinase activity that in turn transfers the phosphate residue from phosphohistidine to the downstream effector or response regulator protein on a conserved aspartate residue (35). The aspartate phosphorylated response regulator is often a transcription factor that requires this phosphorylation event for normal regulation of its activity (35).

In contrast to the prevalence of two-component signaling systems in prokaryotes, there are relatively few examples of this type of regulation in eukaryotic cells. One of the first instances of a eukaryotic two-component regulatory pathway was found in *S. cerevisiae* during analysis of genes that interact with a ubiquitin proteolysis pathway. This gene was shown to encode a sensor kinase called Sln1p (71). Along with this sensor kinase, genetic analysis of loci involved in cell-wall biosynthesis uncovered a response regulator homologue called Skn7p (8). Skn7p possessed two recognizable regions of sequence similarity: a segment homologous to the DNA-binding domain of Hsf1p and a receiver domain containing the conserved aspartate residue found in other response regulators (8).

The first link between Skn7p and oxidative stress came from screens aimed at detecting genes that, when mutated, caused peroxide sensitivity [*POS* loci (45)]. *POS9* was found to encode Skn7p, and the ability of Skn7p to confer normal $H_2O_2$ tolerance was lost if the conserved aspartate residue was replaced by alanine or arginine, but maintained by introduction of a glutamate (46). Later work demonstrated that normal oxidative stress tolerance was maintained if the aspartate residue was replaced by asparagine (60), suggesting that phosphorylation is not obligatorily required for the oxidative stress role of Skn7p. Other functions of Skn7p do require the presence of the conserved aspartate residue, indicating that this regulation is not dispensable for all Skn7p actions (9, 59). Strains lacking the bZIP transcription factor Yap1p were previously known to be hypersensitive to oxidant challenge (48). Genetic analysis of the peroxide tolerance phenotypes of *yap1* and *skn7* mutant strains demonstrated that these two transcription factors appeared to act in the same resistance pathway (46).

Two important target genes mediating the role of Skn7p in oxidant challenge were found to be the thioredoxin-encoding gene *TRX2* and the thioredoxin reductase-encoding locus *TRR1* (60). Both *TRX2* and *TRR1* were strongly induced in response to peroxide challenge in a *SKN7*-dependent manner. Importantly, Yap1p was also required for normal oxidant inducibility of *TRX2* and *TRR1,* suggesting that this convergence of Skn7p and Yap1p on these target promoters could explain the observed lack of increased oxidant sensitivity in a *yap1, skn7* double mutant compared with single-mutant strains lacking these factors individually (46). Loss of either *YAP1* or *SKN7* blocked the oxidant inducibility of *TRX2* and *TRR1,* arguing for a mutual requirement for both Yap1p and Skn7p to ensure oxidative stress response of these redox responsive-loci.

An elusive feature of Skn7p that is under intense investigation is the determination of the binding site for this factor. Gel-shift experiments suggested that a region from −164 to −142 upstream of the *TRX2* translation start codon mediated the interaction of Skn7p with this promoter (60). More recent experiments have shown that Skn7p can interact

with the cell-cycle transcription factor Mbp1p (5) and the heat-shock transcription factor Hsf1p (73). Although a number of Skn7p-responsive genes have been identified (52), no clear consensus sequence has emerged. This may reflect the variety of protein–protein interactions in which Skn7p can participate.

Although the evidence for the role of Skn7p in oxidative stress is very strong, little is known of the regulation of the activity of this factor by oxidants. Analysis of Skn7p localization indicated that the subcellular distribution of this factor does not appear to respond to oxidative stress as Skn7p–green fluorescent protein (GFP) fusions are constitutively localized to the nucleus (73). Recent experiments have identified a nuclear protein designated Fap7p that is required for oxidative stress activation of a Skn7p-dependent reporter gene (41). The precise role of Fap7p remains to be seen, but this protein might participate in communication of oxidative stress to Skn7p.

### Hsf1p

The yeast heat-shock transcription factor (Hsf1p) was first recognized by analogy with related proteins from larger eukaryotes (85, 105). Biochemical purification of *S. cerevisiae* Hsf1p allowed the cloning of its structural gene (87, 106). Availability of the *HSF1* locus led to dissection of the domains required for heat-shock inducibility of the protein (66, 86).

The role of Hsf1p in the heat-shock response is the defining characteristic of this protein, but it is clear that this transcription factor plays roles in response to a much broader range of stresses (for review, see 111). Thorough analyses of the transcriptional control of the copper metallothionein-encoding gene *CUP1* have indicated that Hsf1p-mediated regulation of this locus is important for resistance to the metals copper and cadmium (78, 83). Additionally, expression of Cup1p was found to substitute functionally for the Cu/Zn superoxide dismutase produced by the *SOD1* gene (94). Induction of *CUP1* was correlated with the phosphorylation status of Hsf1p, although different amino acid residues were phosphorylated, depending on the stress used (54).

More recent work has extended the linkage of Hsf1p with oxidative stress tolerance. Hsf1p shares striking sequence similarity with the transcription factor Skn7p (see above) in and around its DNA-binding domain (8). This observation, coupled with previous implications of Hsf1p as being involved in oxidative stress, prompted the investigation of the possible functional interaction between these two regulatory proteins (73).

Several striking findings emerged from this study (73). First, Hsf1p and Skn7p interact both physically and genetically. Coprecipitation studies established that these two transcription factors can associate in cells and loss of the *SKN7* gene exacerbates the peroxide sensitivity of a hypomorphic *HSF1* allele. Second, several heat-shock protein loci require Skn7p for their induction by oxidative stress, but not heat shock. Finally, Skn7p can bind to heat-shock elements that are typically AGAAN as inverted repeats (72).

These data suggest that, at least at some promoters, oxidative stress inducibility is provided by binding of a Skn7p/Hsf1p heteromer. Perhaps the differential Hsf1p phosphorylation seen during oxidative stress requires this protein to interact with Skn7p under these stress conditions. The altered Hsf1p phosphorylation profile during heat shock could remove any requirement for Skn7p and permit Hsf1p to activate transcription from heat-shock elements as a homo-oligomer.

### Yap1p

Arguably the central determinant for oxidative stress tolerance in *S. cerevisiae* is the *YAP1* locus. The protein encoded by this gene (Yap1p) was first identified as a DNA-binding activity present in *S. cerevisiae* nuclear extracts that bound the SV-40 early enhancer in a biochemical manner closely resembling the mammalian activator protein-1 (AP-1) transcription factor (32). A similar activity was found in the fission yeast *Schizosaccharomyces pombe* (40, 96). Production of monoclonal antibodies against the purified *S. cerevisiae* protein allowed the isolation of the structural gene and served to initiate studies directed

toward illuminating the biology in which Yap1p participated (62).

Although the biochemical properties of Yap1p facilitated the isolation of the corresponding structural gene, essentially no information was available concerning the physiological function of this protein. Studies using an artificial AP-1 recognition element (ARE) from the SV-40 early enhancer demonstrated that Yap1p was capable of activating transcription from this viral DNA element in *S. cerevisiae* (32). Several laboratories then cloned genes influencing different resistance phenotypes that were later found to be allelic to *YAP1*. Working in the same institution, two different groups found genes influencing resistance to 1,10-phenanthroline (*PAR1*) or 4-nitroquinoline-*N*-oxide (*SNQ3*) (33, 76) that were allelic to each other and *YAP1* (77). A high copy screen searching for loci elevating resistance to the drugs cycloheximide and sulfometuron methyl recovered *YAP1* and an ATP-binding cassette transporter-encoding gene, *PDR5* (53). Genetic analysis indicated that *YAP1* and *PDR5* define two separate pathways for drug resistance (17).

One important feature of many of the drug hyperresistant phenotypes seen when Yap1p was overproduced was the lack of hypersensitivity seen when the *YAP1* gene was deleted from cells (53, 110). Tolerance to 1,10-phenanthroline, cycloheximide, and sulfometuron methyl was not reduced upon loss of the *YAP1* locus, although 4-nitroquinoline-*N*-oxide resistance was decreased (33, 53, 76, 110). Several important early observations suggested that the response to oxidative stress was a key role for Yap1p expressed at physiological levels. Schnell *et al.* (77) demonstrated that cells lacking Yap1p were hypersensitive to a range of different oxidants and even elevated levels of $O_2$. Several groups found that mutants lacking the *YAP1* structural gene were sensitive to cadmium (6, 34, 110). Cadmium is thought to attribute part of its extreme toxicity to the ability to react with sulfhydryl compounds in the cell and cause oxidative stress (91). Structure/function studies determined that Yap1p contained two separable transactivation domains, at least one of which was required for normal cadmium tolerance (102). Later, Kuge and Jones demonstrated that expression of the thioredoxin-encoding *TRX2* gene was induced by oxidants in a *YAP1*-dependent fashion (48). Other studies found that Yap1p regulated expression of the gene encoding the rate-limiting enzyme in glutathione biosynthesis, *GSH1* (109), and an ABC transporter gene (*YCF1*) producing a vacuolar membrane protein critical for cadmium tolerance (101). Together, these data suggested that oxidative stress would cause induction of Yap1p target genes that, in turn, would lead to buffering of the potentially toxic change in intracellular redox balance.

The finding that Yap1p-dependent transcriptional activation of several target genes was increased by oxidants raised the question of the molecular basis of this induction. A likely site for redox regulation of Yap1p was noted by Toda *et al.* (96) as a cluster of conserved cysteine residues present in the C-terminus of this protein and conserved in an *S. pombe* homologue. Cysteine residues are sensitive to redox potential and have been found to be involved in oxidative regulation of other transcription factors such as c-Jun (1) and OxyR (115). Two complementary approaches were used to provide insight into the modulation of Yap1p during oxidant challenge. Deletion mutants were constructed in the *YAP1* gene and the altered proteins evaluated for their ability to respond to oxidative stress (103). Independently, a GFP–Yap1p fusion was used to assay the subcellular distribution of the protein during oxidant challenge (49).

These two approaches yielded intriguing insight into oxidative stress control of Yap1p activity. Use of a polyclonal anti-Yap1p antiserum demonstrated that steady-state levels of Yap1p did not change during oxidative challenge (103). The GFP–Yap1p fusion protein was found to be primarily cytoplasmic in unstressed cells, but to recruit to the nucleus upon oxidant exposure (49). Gene fusion experiments indicated that the C-terminal region of Yap1p was sufficient to confer oxidative stress-dependent nuclear localization on a heterologous GFP reporter protein (49). Mutational analyses indicated that the cysteine residues in the Yap1p C-terminus were required for normal function of the protein (49,

93, 103). Importantly, Yap1p contains six total cysteine residues present as two clusters of three cysteines each. Originally, the cysteine-rich C-terminal domain was designated the CRD (49). In recognition of the role played by both cysteine-containing domains in protein regulation, we now refer to the originally defined domain as the C-terminal CRD (c-CRD) and the N-terminally located domain as the n-CRD (14).

An important outcome of these studies was the finding that Yap1p exhibited an oxidant-specific stress response. Mutations that removed large internal segments of Yap1p were still able to confer normal or even elevated tolerance to the thiol oxidant diamide, but were unable to complement the $H_2O_2$ hypersensitivity of a *Δyap1* strain (103). Additionally, C-terminal truncation mutants of Yap1p were also hyperresistant to diamide and hypersensitive to $H_2O_2$ (49, 93, 103). The clear separability of these two different resistance phenotypes strongly argued that the response of Yap1p varied depending on the nature of the oxidative stress experienced by the cell.

A molecular explanation for the differential response of Yap1p to oxidants was provided by analysis of regulation of the *TRX2* gene. *TRX2* is required for normal $H_2O_2$ tolerance (48), but interestingly acts to inhibit diamide resistance (63). Mutant forms of Yap1p that produced hyperresistance to diamide, but hypersensitivity to $H_2O_2$, were found to uniformly fail to provide normal induction of *TRX2* during $H_2O_2$ challenge (14). Gene fusion experiments suggested that this failure to normally elevate *TRX2* expression was due to an inability to properly act at this promoter rather than a global defect in Yap1p-mediated regulation. An isolated *TRX2* Yap1p response element (YRE) placed upstream of a heterologous promoter became strongly responsive to hyperactive forms of Yap1p, whereas in its normal *TRX2* setting it was not (14). These data are consistent with Yap1p participating in context-sensitive promoter interactions (for review, see 24) that vary in response to different oxidants.

Other recent experimental progress has focused on the mechanisms underlying control of Yap1p localization by oxidative stress. Two groups determined that a key modulator of subcellular distribution of Yap1p was the nuclear export regulator Crm1p (50, 113). Crm1p was first identified in *S. pombe* as a determinant of chromatin structure (2). Later Crm1p was implicated as a negative regulator of the activity of the *S. pombe* Yap1p homologue, Pap1 (97). Similarly, strains bearing mutant forms of the *S. cerevisiae* Crm1p were found to accumulate Yap1p in their nucleus (113). Biochemical experiments demonstrated that Yap1p–Crm1p interaction is decreased by oxidative stress or by mutations in the CRD region of the factor (50, 113). These findings led to the current model that entry of Yap1p into the nucleus is likely to be constitutive, but its export is regulated in a manner requiring the C-terminus. A model summarizing key features of control of Yap1p subcellular distribution by Crm1p is shown in Fig. 1.

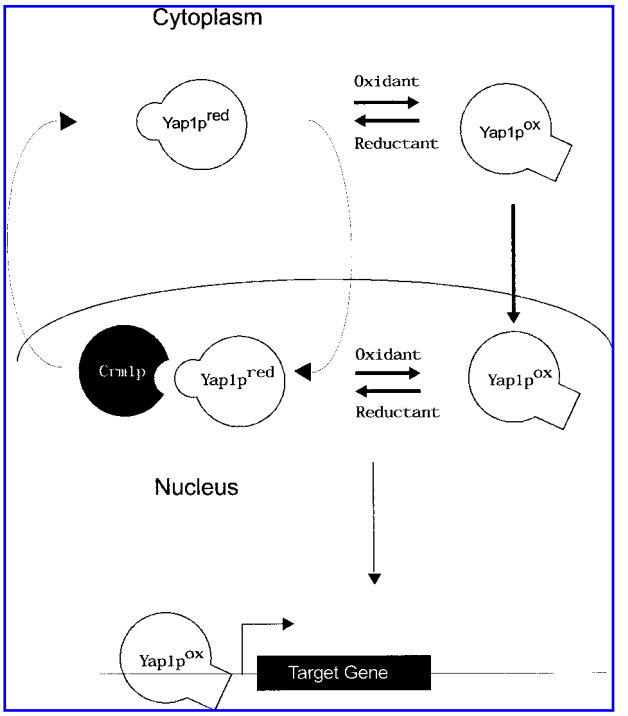


**FIG. 1. Regulation of Yap1p in *S. cerevisiae*.** Under normal redox conditions, Yap1p is enriched in the cytoplasmic compartment due to its high rate of Crm1p-catalyzed nuclear export. Upon oxidant challenge, structural alterations in Yap1p are believed to reduce its ability to interact with Crm1p, and the factor accumulates in the nucleus. Yap1p can then bind to target genes and stimulate transcription. The interconversion of the oxidized and reduced forms of Yap1p could occur in either the nucleus, cytosol, or both. $Yap1p^{red,}$ reduced Yap1p; $Yap1p^{ox,}$ oxidized Yap1p.

Further analysis of mutant variants of Yap1p has argued for a more complex control of localization of this factor. Mutagenesis of a second cluster of cysteine residues (positions 303, 310, and 315) located in an N-terminal segment of the protein (n-CRD) has shown that at least one of these cysteines is critical for normal $H_2O_2$ regulation (14, 16). Biochemical experiments aimed at determining the nature of the modification of Yap1p upon oxidant exposure have suggested that a key intramolecular disulfide bond must form involving cysteines 303 and 598 (in the c-CRD) if Yap1p is to localize to the nucleus and activate target gene expression (16). The formation of this putative disulfide bond was detected by a reductant-sensitive shift in molecular mass of an epitope-tagged form of Yap1p. Interestingly, *S. cerevisiae* thioredoxin proteins have been implicated both in the reversal of this disulfide bond and in determining the level of Yap1p that is localized to the nucleus (38). Further work is required to clarify if the *TRX1*- and/or *TRX2*-encoded thioredoxin proteins are the key, direct reductants that return Yap1p to its cytoplasmic residence following the oxidative stress response.

*Candida albicans*

**Cap1p**

The major human fungal pathogen is the yeast *Candida albicans* (22). This opportunistic organism is associated with ~70% of all fungal infections and poses a significant clinical risk to immunocompromised patients (22). The ability of this organism to tolerate oxidative stress is likely to have important implications for its ultimate pathogenicity because, as mentioned above, this is a major route for elimination of invading microorganisms as indicated by the prevalence of candidemia in patients with neutropenia (99). Although a detailed understanding of the oxidative stress response of *C. albicans* represents an important experimental goal, the current picture of how this yeast deals with oxidants is quite limited. The most available data have focused on a *C. albicans* homologue of *S. cerevisiae* Yap1p. This *C. albicans* protein was designated Cap1p.

Cap1p was originally isolated by virtue of high-copy-number plasmids carrying the *C. albicans CAP1* gene leading to high-level resistance to the antifungal azole drug fluconazole in *S. cerevisiae* (4). The initial isolate of *CAP1* corresponded to a truncated allele expressing only 334 amino acids out of a total of 499. This N-terminal fragment of Cap1p was able to confer high-level tolerance of fluconazole, cycloheximide, and 4-nitroquinoline-*N*-oxide when produced from a high-copy-number plasmid in *S. cerevisiae.* However, the truncated factor failed to confer enhanced tolerance to cadmium or $H_2O_2$ in *S. cerevisiae*. This work also led to the identification of a new target gene for Yap1p in *S. cerevisiae,* the major facilitator superfamily member *FLR1* (4). *FLR1* was identified based on its strong sequence similarity with a known mediator of fluconazole resistance *C. albicans, CaMDR1* (75).

These first experiments on Cap1p were performed exclusively in the heterologous host, *S. cerevisiae*. Later, a homozygous disruption strain of *C. albicans* was constructed and used as a host to evaluate the contribution of both wild-type and the truncated *CAP1* locus to a wide range of resistance phenotypes (3). Expression of the truncated Cap1p in *C. albicans* led to a dramatic increase in fluconazole resistance with an associated elevation in *CaMDR1* mRNA levels. However, deletion of the *CAP1* locus from a fluconazole hyperresistant strain also led to an increase in *CaMDR1* mRNA, making the precise role of Cap1p in *CaMDR1* expression somewhat mystifying.

More recent data focused on the regulation of Cap1p during oxidative stress in *C. albicans* (114). One of the striking features of the Cap1p amino-acid sequence was the conservation of the c-CRD of Yap1p in the *C. albicans* protein (4). All the cysteine residues present in the c-CRD of Yap1p are maintained in the analogous domain in Cap1p. This observation, coupled with previous data demonstrating a role for *CAP1* in tolerance to both diamide and $H_2O_2$ (3), suggested that this

transcription factor might be regulated by oxidative stress in *C. albicans* as Yap1p is in *S. cerevisiae*. Exploration of the redox regulation of Cap1p was facilitated by identification of the *CaGLR1* locus, encoding the *C. albicans* glutathione reductase protein. *GLR1* in *S. cerevisiae* is known to be regulated by Yap1p during oxidative stress (29), and *CaGLR1* contains two potential YREs in its promoter (114).

*CaGLR1* was induced by treatment with either diamide or $H_2O_2$, and this induction required the presence of *CAP1* (114). Western blot analysis demonstrated that although *CaGLR1* expression increased, Cap1p levels remained constant during the course of the oxidant exposure. Finally, use of a Cap1p–GFP fusion gene provided evidence that nuclear localization of Cap1p was increased by oxidant exposure.

These data provide a compelling case for the mechanistically similar regulation of Cap1p and Yap1p by oxidative stress. To determine if similar structural features of Cap1p were required for oxidant regulation, a single amino acid substitution was prepared in *CAP1* that led to the ultimate cysteine residue (C477) being replaced by an alanine. This cysteine residue in Cap1p is analogous to C629 in Yap1p, a critical determinant of the functionality of the *S. cerevisiae* factor (14, 49). Analysis of the C477A form of Cap1p indicated that this protein behaved in a very similar fashion to that of C629A Yap1p. Both mutant proteins were constitutively localized to the nucleus, supported high-level diamide resistance, but were defective in allowing growth on $H_2O_2$-containing medium. Together, this information is most consistent with Cap1p and Yap1p being regulated by similar mechanisms in these two organisms.

Although both Cap1p and Yap1p are regulated at the level of nuclear localization during oxidative stress, there are species-specific requirements for this modulation. Heterologous expression of Cap1p in a *Δyap1* background complemented the cadmium hypersensitivity of this strain, but failed to correct the oxidative stress-sensitive phenotypes (114). Additionally, heterologous expression of Cap1p failed to produce oxidant inducible expression of a YRE-containing reporter plasmid, although Cap1p was capable of activating this gene at a constitutive level. These data indicate that although Cap1p can function as a transcriptional regulator in *S. cerevisiae*, its normal redox control cannot be recapitulated in this foreign environment.

### *Schizosaccharomyces pombe*

#### Pap1p

The first Yap1p homologue identified in any yeast was Pap1p from *S. pombe,* which was isolated as a determinant conferring resistance to the protein kinase inhibitor staurosporine (96). A striking feature of the amino acid sequence of Pap1p was the presence of two regions sharing high sequence identity with Yap1p. The first region was in the N-terminal segment of the proteins and corresponded to the DNA-binding domain, whereas the second was in the extreme C-terminus of the protein in a region of previously undescribed function. This second region of similarity was later found to correspond to the c-CRD domain of Yap1p and was demonstrated to be necessary and sufficient for oxidant-regulated nuclear export of Pap1 (47).

An important early link connecting Pap1 with nuclear export, which also influenced studies in *S. cerevisiae,* came from the observation that overproduction of Pap1 or use of the cold-sensitive *crm1* mutant led to staurosporine resistance (97). The isolation of the *crm1* mutant came from a microscopic screen of *S. pombe* cells for cold-sensitive cells that exhibited abnormal chromosome structure (2). Mutant forms of Crm1 were also found that conferred resistance to the antifungal agent leptomycin B (67). Work in animal and yeast cells then showed that leptomycin B binds to Crm1 and eliminates the ability of the resulting complex to export proteins from the nucleus (23, 25, 70, 89). Search for a Pap1 recognition element in a *S. pombe* database of genomic sequence led to the identification of a Pap1-regulated gene called *apt1+* encoding a protein of 25 kDa designated p25 (97). Expression of the *apt1+* gene was found to be el-

evated in response to overproduction of Pap1 or the presence of a mutant form of Crm1. Interestingly, introduction of a *pap1Δ* allele into the cold-sensitive *crm1* mutant background led to a rescue of the temperature-sensitive growth of the *crm1* strain.

Later experiments showed that the c-CRD of Pap1 was also required for normal function of the protein by ensuring its proper stress-regulated subcellular distribution (47). Strikingly, the c-CRD of Pap1 was found to function in animal cells (47), but not *S. cerevisiae* (50), as an oxidant-responsive nuclear export signal.

Along with the implication of Crm1 in control of Pap1 function, experiments in *S. pombe* have been able to link mitogen-activated protein kinase (MAPK) cascades with the regulation of Pap1 activity. Control of c-Jun by stress-activated protein kinase (SAPK) signaling is an important feature of the regulation of this protooncoprotein (for review, see 104). A homologue of SAPK called Sty1 or Spc1 was found to be required for normal oxidative stress tolerance in *S. pombe* (57, 80). Sty1/Spc1 functions in a MAPK cascade in *S. pombe* and becomes phosphorylated via action of the MAPK kinase (MAPKK) Wis1 when activated by oxidative or other stress regimens (57, 81) (Fig. 2). Mutant strains lacking Sty1/Spc1 were sensitive to a range of chemicals, including several oxidants, that resembled the phenotypic effect of loss of *pap1+* (15). Elimination of Sty1/Spc1 inhibited Pap1-dependent activation of gene expression. Oxidant-dependent nuclear recruitment of Pap1 was found to be inhibited in the absence of Sty1/Spc1, and overexpression of the MAPKK Wis1 led to accelerated oxidant-dependent nuclear localization of Pap1 (98). These data were taken to indicate that Sty1/Spc1 was required for Pap1 oxidative stress-regulated nuclear localization and transcriptional activation; although no evidence has been obtained to indicate that Pap1 can be phosphorylated by Sty1/Spc1. The model placing Pap1 at the bottom of a MAPK cascade was attractive because this would mimic the relationship of c-Jun with SAPK/JNK (for review, see 51).

However, later experiments cast doubt on the direct link between Sty1/Spc1 and Pap1.

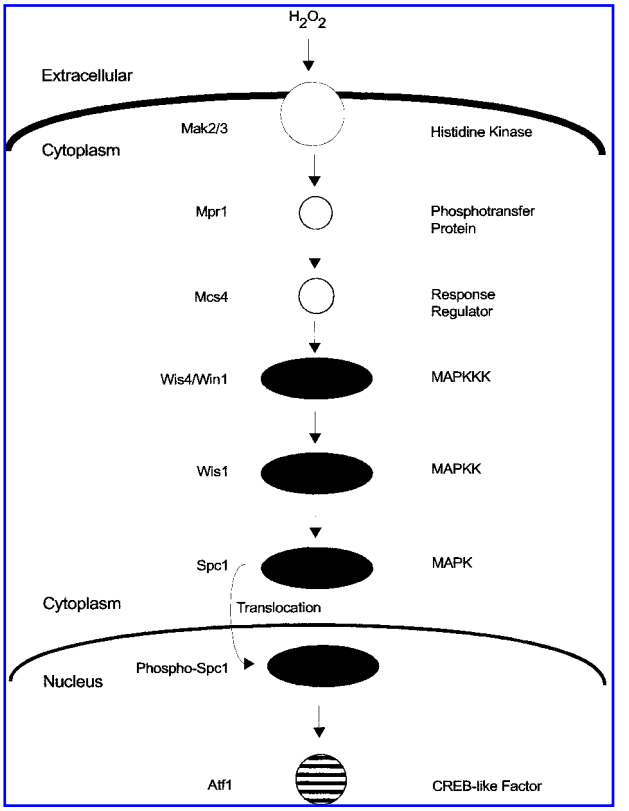


**FIG. 2. SAPK cascade regulating oxidative stress in *S. pombe*.** $H_2O_2$ challenge of *S. pombe* cells is thought to activate the histidine kinases encoded by the *mak2+* and *mak3+* genes. These gene products then transfer a phosphate moiety to the Mpr1 phosphotransferase, which in turn delivers this phosphate to the Mcs4 response regulator protein. Phosphorylated Mcs4 then binds to and activates the Wak1 MAPKKK. Win1 is a functionally related MAPKKK that appears to act in parallel with Wak1 (aka Wis4). Wak1 then activates the MAPKK Wis1, which then phosphorylates the MAPK Spc1. Phosphorylated Spc1 moves to the nucleus, then phosphorylates and activates the CREB-like transcription factor Atf1, rendering it competent to activate gene expression.

A strain containing a Sty1/Spc1 derivative that possessed noninducible kinase activity was found to support Pap1-dependent activation of the catalase-encoding *ctt1+* gene nearly as well as wild-type Sty1/Spc1 (65). This finding led to the hypothesis that the loss of Sty1/Spc1 signaling might be indirectly inhibiting activation of *ctt1+* due to the action of this MAPK on another transcription factor, Atf1. Atf1 is a bZIP transcription factor with strong sequence similarity to the mammalian CREB (28) and ATF family (31). Atf1 is a known substrate for Sty1/Spc1 and is required for normal oxidative stress tolerance (see below for details). As Sty1/Spc1 is re-

quired for activation of Atf1, loss of this MAPK could convert Atf1 into a repressor protein that might block the ability of Pap1 to normally stimulate *ctt1+* expression on oxidant challenge.

To test this idea, the ability to respond to $H_2O_2$ challenge of a doubly mutant strain lacking both Sty1/Spc1 and Atf1 was evaluated (65). This strain was found to mount a robust induction of *ctt1+*, whereas the isogenic single mutant lacking only Sty1/Spc1 was unable to elevate *ctt1+* expression, supporting the idea that lack of MAPK activation causes Atf1 to behave as a repressor protein. Together, these data are most consistent with Atf1 lying at the end of the Wis1–Sty1/Spc1 MAPK cascade and Pap1 being regulated by a separate mechanism. As suggested (47), it seems reasonable to expect that *S. pombe* Pap1 may directly sense oxidative stress and respond in a manner similar to that of Yap1p in *S. cerevisiae*.

The involvement of the Sty1/Spc1 MAPK in *S. pombe* oxidative stress tolerance illustrates a difference in the oxidant response of fission yeast and the budding yeast *S. cerevisiae*. The kinase sharing the most sequence similarity with Sty1/Spc1 in *S. cerevisiae* is the osmotic stress-responsive MAPK Hog1p (82, 107). Disruptions of *HOG1* have been found to have no significant defects in oxidative stress response in *S. cerevisiae* (S. Coleman, unpublished observations). Additionally, although *S. cerevisiae* has Atf1 homologues, these proteins have been found to have no apparent role in the stress response (26). These data suggest that *S. pombe* may have a greater reliance on MAPK cascade control of bZIP factor function as in mammalian cells, whereas *S. cerevisiae* seems to rely on direct modulation of bZIP protein activity in its oxidative-stress response.

### Atf1

Isolation of the *atf1+* gene was accomplished by the serendipitous observation of an open reading frame exhibiting strong sequence similarity with mammalian ATF2 (92). The Atf1 factor was able to recognize ATF/CREB sites and activate expression from a reporter gene containing mammalian versions of these DNA elements in fission yeast. An important observation made in the early characterization of *atf1Δ* cells was the finding that these mutants were sterile, and further genetic analysis indicated that Atf1 appeared to positively regulate entry into the stationary phase.

The *atf1+* gene was also cloned as a high-copy-number suppressor of the mating defect of a strain lacking the Sty1/Spc1 MAPK (82). Sty1/Spc1 was found to serve as an environmental sensor and is activated in response to a number of changes in the extracellular milieu, including osmotic or oxidative stress (43, 57, 80). Sty1/Spc1 is capable of phosphorylating Atf1 both *in vivo* and *in vitro* (82, 107). Activation of Sty1/Spc1 was found to require the action of the MAPKK protein Wis1 and the MAPKK kinase (MAPKKK) proteins Wis4 and Win1 (15, 57, 74, 79). These data indicate that, as for the SAPK or Jun kinase pathway in animal cells, a MAPK cascade regulates oxidative stress in *S. pombe*. This is different from *S. cerevisiae* where the MAPK sharing the most sequence similarity with Sty1/Spc1 [Hog1p (7)] is activated in response to osmotic stress, but not oxidative challenge (30). Likewise, although there are ATF/CREB homologues in *S. cerevisiae,* there is no evidence that these proteins contribute to oxidative-stress resistance (26).

Recent work has provided more detail concerning the likely direct sensors for oxidative stress in *S. pombe* that interface with the Sty1/Spc1 MAPK pathway. A response regulator protein, Mcs4p, was found that directly signals to the two MAPKKK proteins lying upstream of Wis1 (Wis4 and Win1). As response regulator proteins are invariably associated with histidine kinase upstream regulators, degenerate PCR was performed to identify histidine kinase proteins from *S. pombe*. This strategy allowed the isolation of three different genes designated Mcs4p-associated kinase (Mak1, Mak2, Mak3) (10). Mutant strains lacking Mak2 and Mak3 are defective in the ability to activate the Sty1/Spc1 MAPK pathway, whereas a *mak1* mutant cell can still signal via this MAPK pathway. Strikingly, Mak1 appears to signal via the re-

sponse regulator Prr1 (see below) with this pathway required for normal oxidant tolerance. Introduction of a *prr1* mutation into a *mak2*, *mak3* double-mutant strain causes an additive oxidative stress hypersensitivity (10). This is consistent with the idea that Atf1 and Prr1 define two separate and required pathways for normal oxidant tolerance that are regulated by Mak2/Mak3 or Mak1, respectively. This arrangement again contrasts with *S. cerevisiae* in which a single histidine kinase-encoding gene is present (*SLN1*). Sln1p can elicit the phosphorylation of the Skn7p response regulator, but this phosphorylation event does not seem to provide a major contribution to the role of this factor in the oxidative stress response (60).

### Prr1

The *S. pombe* homologue of *S. cerevisiae* Skn7p is designated Prr1. Prr1 was originally detected by inspection of the *S. pombe* genomic DNA sequence via its sequence homology with response regulator proteins like Skn7p (68). Disruption of *prr1+* produced a cell that was hypersensitive to a variety of stress conditions, including oxidant challenge. The likely explanation of this defect was the failure to induce genes involved in the oxidative stress response like *trr1+* and *ctt1+* (68). More detailed comparisons of the oxidant phenotype of *prr1Δ* and *pap1Δ* strains indicated that loss of either gene produced a peroxide-sensitive phenotype, but only the *pap1Δ* strain was sensitive to the thiol oxidant diamide (68). As seen for Skn7p (60), the conserved aspartate residue required for phosphotransfer function of response regulator proteins (35) is not necessary for the ability of Prr1 to mediate oxidative stress tolerance. These data support the notion that Prr1 acts in a fashion analogous to Skn7p in the oxidative stress response of *S. pombe*.

Prr1 in *S. pombe* clearly has roles in addition to activation of oxidant tolerance genes. Strains lacking *prr1+* are sterile due to a failure to express the *ste11+* gene (69). This defect in *ste11+* expression is shared with strains lacking Atf1 and further illustrates the interaction between these two oxidant-responsive transcription factors. It is important to note that whereas Prr1 and *S. cerevisiae* Skn7p are homologues, *skn7* mutants are not sterile (9, 59). These proteins share a common structure, but their precise function in these two yeasts is not identical.

## CONCLUSIONS

As befits the central role of oxidants in cellular defense, fungi have several different genetic pathways that mediate their response to oxidant challenge. These specific pathways are interdigitated with the more general stress-responsive factors like Msn2p/Msn4p and Hsf1p in *S. cerevisiae,* which are triggered by many stresses, including oxidant challenge. It is the combined reprogramming of the transcriptional profile of oxidatively challenged cells that allows their survival in times of oxidant exposure. Direct evaluation of the global gene expression profile during oxidative stress by DNA microarray (27) has provided a complete list of loci that respond transcriptionally to this environmental challenge. Characterization of the transcriptional regulatory pathways that lead to the observed changes in gene expression will provide insight into the molecular logic behind response of fungi to oxidant challenge. Analysis of the precise role of the regulated gene products in reversing the potentially toxic alteration in redox potential will also shed new light on how eukaryotic cells maintain redox balance.

A striking feature that emerges from the comparison of oxidatively regulated transcription factors in the yeasts studied to date is the range of regulatory mechanisms used to mount an oxidative stress response. Activation of Yap1p and related proteins involves a significant contribution from changes in subcellular localization of the factor that appear likely to be directly mediated by oxidation of key cysteine residues in these transcriptional regulators. This contrasts with activation of *S. pombe* Atf1, which is constitutively nuclear and is stimulated upon recruitment of the MAPK Sty1/Spc1 into the nucleus upon oxi-

dant challenge. *S. pombe* also expresses Pap1, a Yap1p homologue important in oxidant resistance, that is regulated in a fashion analogous to *S. cerevisiae* Yap1p. Perhaps the greater range of oxidative stress-regulated factors in *S. pombe* reflects a greater need for this yeast to deal with oxidant exposure. Pap1 and Atf1 target genes also seem to be somewhat different from the genes controlled by *S. cerevisiae* Yap1p. An interesting example of these differences is the strong dependence of the *ctt1+* gene in *S. pombe* on Pap1 and Atf1 for its expression, whereas *CTT1* in *S. cerevisiae* does not exhibit this dependence (S. Coleman and W.S. Moye-Rowley, unpublished observations).

Although our understanding of the mechanisms underlying oxidative stress regulation of gene expression has been greatly advanced by work over the past decade, a number of important challenges remain. How do changes in these redox-regulated transcription factors communicate with RNA polymerase II to lead to enhanced gene transcription? Study of Atf1 will provide a genetically tractable model for MAPK regulation of transcription factor function analogous to oxidant signaling to c-Jun via the JNK/SAPK pathway (for review, see 36). What is the precise nature of the biochemical alterations that activate these oxidant-regulated signal transduction pathways? Direct oxidation of cysteine residues in Yap1p and its homologues presents an attractive model for understanding activation of this class of factor, but this remains to be conclusively shown. Why does activation of certain genes require the presence of two oxidant-responsive factors, whereas others are controlled by only one? Answers to these and related questions are sure to be provided by the continued analysis of redox-regulated control of gene transcription in fungi.

## ACKNOWLEDGMENTS

Work on oxidative stress in my laboratory is supported by NIH GM57007. I thank Sherry Rovinsky and Dr. Gisela Storz for providing critical reviews of the manuscript.

## ABREVIATIONS

Aca1p/Aca2p, CREB homologue in *S. cerevisiae*; AP-1, mammalian activator protein-1; *apt1+*, encodes p25 in *S. pombe*, target of Pap1 regulation; ARE, AP-1 recognition element from SV-40 enhancer; ATF, activating transcription factor; Atf1, activating transcription factor homologue in *S. pombe*; bZIP, basic region-leucine zipper; c-Jun, mammalian protooncoprotein transcription factor; CaGLR1, *C. albicans* gene for glutathione reductase; CaMDR1, *C. albicans* gene for membrane drug transporter; Cap1p, *C. albicans* Yap1p homologue; CRD, cysteine-rich domain; CREB, cyclic AMP response element binding protein; Crm1p, protein required for nuclear export; CTA1, gene encoding peroxisomal catalase in *S. cerevisiae*; CTT1, gene encoding cytosolic catalase in *S. cerevisiae*; CUP1, *S. cerevisiae* gene encoding copper metallothionein; Fap7p, *S. cerevisiae* nuclear protein required for activation of Skn7p by oxidative stress; FLR1, *S. cerevisiae* gene required for fluconazole tolerance; GFP, green fluorescent protein; GSH1, *S. cerevisiae* gene encoding first step of glutathione biosynthetic pathway, Yap1p target; $H_2O_2$, hydrogen peroxide; Hog1p, SAPK homologue in *S. cerevisiae*; Hsf1p, Heat-shock transcription factor in *S. cerevisiae*; HSP12, stress-inducible small heat shock protein in *S. cerevisiae*; JNK, Jun N-terminal kinase; Mac1p, copper responsive transcription factor in *S. cerevisiae*; *Mak1, Mak2,* and *Mak3,* three histidine kinase genes regulating Mcs4 in *S. pombe*; MAPK, mitogen-activated protein kinase; MAPKK, MAPK kinase; MAPKKK, MAPKK kinase; Mbp1p, transcriptional regulator of cell cycle in *S. cerevisiae*; Mcs4p, response regulator protein in *S. pombe*; Mpr1, phosphotransfer protein in *S. pombe;* Msn2p/Msn4p, general stress responsive transcription factor in *S. cerevisiae*; OxyR, *E. coli* transcription factor required for $H_2O_2$ tolerance; Pap1p, *S. pombe* Yap1p homologue; PAR1, allelic with *YAP1*; PDR5, *S. cerevisiae* gene encoding ATP-binding cassette transporter protein; PKA, protein kinase A; POS9, allelic with *SKN7*; Prr1, Skn7p homologue in *S. pombe*; *pyp2+*, protein tyrosine phosphatase gene in *S. pombe;* SAPK, stress-activated pro-

tein kinase; Skn7p, homologue of Hsf1p required for oxidative stress tolerance i n *S. cerevisiae*; Sko1p, CREB homologue in *S. cerevisiae*; Sln1p, histidine kinase in *S. cerevisiae*; Snf1p, protein kinase regulating some aspects of *S. cerevisiae* stress response; SNQ3, allelic with *YAP1*; SOD1, *S. cerevisiae* gene encoding cytosolic superoxide dismutase; *SSA1*, Hsp70 gene in *S. cerevisiae*; ste11, Prr1 target gene in *S. pombe* required for mating; STRE: AGGGG, stress responsive element bound by Msn2p/Msn4p in *S. cerevisiae*; Sty1/Spc1, SAPK homologue in *S. pombe*; *TPK1, TPK2,* and *TPK3*, three structural genes for catalytic subunit of PKA in *S. cerevisiae*; TRR1, thioredoxin reductase gene in *S. cerevisiae*; TRX2, gene encoding a thioredoxin in *S. cerevisiae,* Yap1p target; Wak1, MAPKKK aka Wis4 in *S. pombe;* Wis1, MAPKK upstream of Sty1/Spc1 in *S. pombe*; Wis4 and Win1, two MAPKKKs that regulate Wis1 MAPKK in *S. pombe*; Yap1p, transcriptional regulator of oxidative stress resistance in *S. cerevisiae,* bZIP protein; YCF1, *S. cerevisiae* gene required for cadmium tolerance, Yap1p target; YRE, Yap1p response element.

## REFERENCES


1. Abate C, Patel L, Rauscher FJ 3rd, and Curran T. Redox regulation of Fos and Jun DNA-binding activity in vitro. *Science* 249: 1157–1161, 1990.
2. Adachi Y and Yanagida M. Higher order chromosome structure is affected by cold-sensitive mutations in a *Schizosaccharomyces pombe* gene *crm1+* which encodes a 115-kDa protein preferentially localized in the nucleus and its periphery. *J Cell Biol* 108: 1195–1207, 1989.
3. Alarco AM and Raymond M. The bZip transcription factor Cap1p is involved in multidrug resistance and oxidative stress response in *Candida albicans. J Bacteriol* 181: 700–708, 1999.
4. Alarco AM, Balan I, Talibi D, Mainville N, and Raymond M. AP-1-mediated multidrug resistance in *Saccharomyces cerevisiae* requires *FLR1* encoding a transporter of the major facilitator superfamily. *J Biol Chem* 272: 19304–19313, 1997.
5. Boquin N, Johnson AL, Morgan BA, and Johnston LH. Association of the cell cycle transcription factor Mbp1 with the Skn7 response regulator in budding yeast. *Mol Biol Cell* 10: 3389–3400, 1999.
6. Bossier P, Fernandes L, Rocha D, and Rodrigues-Pousada C. Overexpression of YAP2, coding for a new yAP protein, and YAP1 in *Saccharomyces cerevisiae* alleviates growth inhibition caused by 1,10-phenanthroline. *J Biol Chem* 268: 23640–23645, 1993.
7. Brewster JL, de Valoir T, Dwyer ND, Winter E, and Gustin MC. An osmosensing signal transduction pathway in yeast. *Science* 259: 1760–1763, 1993.
8. Brown JL, North S, and Bussey H. *SKN7,* a yeast multicopy suppressor of a mutation affecting cell wall beta-glucan assembly, encodes a product with domains homologous to prokaryotic two-component regulators and to heat shock transcription factors. *J Bacteriol* 175: 6908–6915, 1993.
9. Brown JL, Bussey H, and Steward RC. Yeast Skn7p functions in a eukaryotic two-component regulatory pathway. *EMBO J* 13: 5186–5194, 1994.
10. Buck V, Quinn J, Soto Pino T, Martin H, Saldanha J, Makino K, Morgan BA, and Millar JBA. Peroxide sensors for the fission yeast stress-activated mitogen-activated protein kinase pathway. *Mol Biol Cell* 12: 407–419, 2001.
11. Calera JA, Zhao XJ, and Calderone R. Defective hyphal development and avirulence caused by a deletion of the *SSK1* response regulator gene in *Candida albicans. Infect Immun* 68: 518–525, 2000.
12. Cohen G, Fessl F, Traczyk A, Tytka J, and Ruis H. Isolation of the catalase A gene of *Saccharomyces cerevisiae* by complementation of the *cta1* mutation. *Mol Gen Genet* 200: 74–79, 1985.
13. Cohen MS, Isturiz RE, Malech HL, Root RK, Wiolfert CM, Gutman L, and Buckley RH. Fungal infection in chronic granulomatous disease—the importance of the phagocyte in defense against fungi. *Am J Med* 71: 59–66, 1981.
14. Coleman ST, Epping EA, Steggerda SM, and Moye-Rowley WS. Yap1p activates gene transcription in an oxidant-specific fashion. *Mol Cell Biol* 19: 8302–8313, 1999.
15. Degols G, Shiozaki K, and Russell P. Activation and regulation of the Spc1 stress-activated protein kinase in *Schizosaccharomyces pombe. Mol Cell Biol* 16: 2870–2877, 1996.
16. Delaunay A, Isnard AD, and Toledano MB. $H_2O_2$ sensing through oxidation of the Yap1 transcription factor. *EMBO J* 19: 5157–5166, 2000.
17. Dexter D, Moye-Rowley WS, Wu A-L, and Golin J. Mutations in the yeast *PDR3, PDR4, PDR7* and *PDR9* pleiotropic drug resistance loci affect the transcript level of an ATP binding cassette transporter encoding gene, *PDR5. Genetics* 136: 505–515, 1994.
18. Domer JE and Lehrer RI. Introduction to *Candida:* systemic candidiasis. In: *Fungal Infections and Immune Responses,* edited by Murphy JW, Friedman H, and Bendinelli M. New York: Plenum Press, 1993, pp. 49–116.
19. Dutta R, Qin L, and Inouye M. Histidine kinases: diversity of domin organisation. *Mol Microbiol* 34: 633:640, 1999.
20. Estruch F. Stress-controlled transcription factors, stress-induced genes and stress tolerance in budding yeast. *FEMS Microbiol Rev* 24: 469–486, 2000.

21. Estruch F and Carlson M. Two homologous zinc finger genes identified by multicopy suppression in a *SNF1* protein kinase mutant of *Saccharomyces cerevisiae*. *Mol Cell Biol* 13: 3872–3881, 1993.
22. Fidel PL Jr, Vazquez JA, and Sobel JD. *Candida glabrata:* review of epidemiology, pathogenesis and clinical disease with comparison to *C. albicans. Clin Microbiol Rev* 12: 80–96, 1999.
23. Fornerod M, Ohno M, Yoshida M, and Mattaj IW. CRM1 is an export receptor for leucine-rich nuclear export signals. *Cell* 90: 1051–1060, 1997.
24. Fry CJ and Farnham PJ.Context-dependent transcriptional regulation. *J Biol Chem* 274: 29583–29586, 1999.
25. Fukuda M, Asano S, Nakamura T, Adachi M, Yoshida M, Yanagida M, and Nishida E. CRM1 is responsible for intracellular transport mediated by the nuclear export signal. *Nature* 390: 308–311, 1997.
26. Garcia-Gimeno MA and Struhl K. Aca1 and Aca2, ATF/CREB activators in *Saccharomyces cerevisiae,* are important for carbon source utilization but not the response to stress. *Mol Cell Biol* 20: 4340–4349, 2000.
27. Gasch AP, Spellman PT, Kao CM, Carmel-Harel O, Eisen MB, Storz G, Botstein D, and Brown PO. Genomic expression programs in the response of yeast cells to environmental changes. *Mol Biol Cell* 11: 4241–4257, 2000.
28. Gonzalez GA, Yamamoto KK, Fischer WH, Karr D, Menzel P, Biggs W 3rd, Vale WW, and Montminy MR. A cluster of phosphorylation sites on the cyclic AMP-regulated nuclear factor CREB predicted by its sequence. *Nature* 337: 749–752, 1989.
29. Grant CM, Collinson LP, Roe J-H, and Dawes IW. Yeast glutathione reductase is required for protection against oxidative stress and is a target gene for yAP-1 transcriptional regulation. *Mol Microbiol* 21: 739–746, 1996.
30. Gustin MC, Albertyn J, Alexander M, and Davenport K. MAP kinase pathways in the yeast *Saccharomyces cerevisiae. Microbiol Mol Biol Rev* 62: 1264–1300, 1998.
31. Hai TW, Liu F, Coukos WJ, and Green MR. Transcription factor ATF cDNA clones: an extensive family of leucine zipper proteins able to selectively form DNA-binding heterodimers. *Genes Dev* 3: 2083–2090, 1989.
32. Harshman KD, Moye-Rowley WS, and Parker CS. Transcriptional activation by the SV40 AP-1 recognition element in yeast is mediated by a factor similar to AP-1 that is distinct from GCN4. *Cell* 53: 321–330, 1988.
33. Hertle K, Haase E, and Brendel M. The *SNQ3* gene of *Saccharomyces cerevisiae* confers hyper-resistance to several functionally unrelated chemicals. *Curr Genet* 19: 429–433, 1991.
34. Hirata D, Yano K, and Miyakawa T. Stress-induced transcriptional activation mediated by *YAP1* and *YAP2* genes that encode the Jun family of transcriptional activators in *Saccharomyces cerevisiae. Mol Gen Genet* 242: 250–256, 1994.
35. Hoch JA. Two-component and phosphorelay signal transduction. *Curr Opin Microbiol* 3: 165–170, 2000.
36. Ip YT and Davis RJ. Signal transduction by the c-Jun N-terminal kinase (JNK)—from inflammation to development. *Curr Opin Cell Biol* 10: 205–219, 1998.
37. Izawa S, Inoue Y, and Kimura A. Importance of catalase in the adaptive response to hydrogen peroxide: analysis of acatalasaemic *Saccharomyces cerevisiae. Biochem J* 320: 61–67, 1996.
38. Izawa S, Maeda K, Sugiyama K, Mano J, Inoue Y, and Kimura A. Thioredoxin deficiency causes the constitutive activation of Yap1, an AP-1-like transcription factor in *Saccharomyces cerevisiae. J Biol Chem* 274: 28459–28465, 1999.
39. Jamieson DJ. Oxidative stress responses of the yeast *Saccharomyces cerevisiae. Yeast* 14: 1511–1527, 1998.
40. Jones RH, Moreno S, Nurse P, and Jones NC. Expression of the SV40 promoter in fission yeast: identification of an AP-1-like factor. *Cell* 53: 659–667, 1988.
41. Juhnke H, Charizanis C, Latifi F, and Krems B. The essential protein fap7 is involved in the oxidative stress response of *Saccharomyces cerevisiae. Mol Microbiol* 35: 936–948, 2000.
42. Jungmann J, Reins H-A, Lee J, Romeo A, Hassett R, Kosman D, and Jentsch S. MAC1, a nuclear regulatory protein related to Cu-dependent transcription factors, is involved in Cu/Fe utilization and stress resistance in yeast. *EMBO J* 12: 5051–5056, 1993.
43. Kato T Jr, Okazaki K, Murakami H, Stettler S, Fantes PA, and Okayama H. Stress signal, mediated by a Hog1-like MAP kinase, controls sexual differentiation in fission yeast. *FEBS Lett* 378: 207–212, 1996.
44. Kobayashi N, McEntee K. Identification of cis and trans components of a novel heat shock stress regulatory pathway in *Saccharomyces cerevisiae. Mol Cell Biol* 13: 248–256, 1993.
45. Krems B, Charizanis C, and Entian K-D. Mutants of *Saccharomyces cerevisiae* sensitive to oxidative and osmotic stress. *Curr Genet* 27: 427–434, 1995.
46. Krems B, Charizanis C, and Entian K-D. The response regulator-like protein Pos9/Skn7 of *Saccharomyces cerevisiae* is involved in oxidative stress resistance. *Curr Genet* 29: 327–334, 1996.
47. Kudo N, Taoka H, Toda T, Yoshida M, and Horinouchi S. A novel nuclear export signal sensitive to oxidative stress in the fission yeast transcription factor Pap1. *J Biol Chem* 274: 15151–15158, 1999.
48. Kuge S and Jones N. *YAP1*-dependent activation of *TRX2* is essential for the response of *S. cerevisiae* to oxidative stress by hydroperoxides. *EMBO J* 13: 655–664, 1994.
49. Kuge S, Jones N, and Nomoto A. Regulation of yAP-1 nuclear localization in response to oxidative stress. *EMBO J* 16: 1710–1720, 1997.
50. Kuge S, Toda T, Iizuka N, and Nomoto A. Crm1 (Xpo1) dependent nuclear export of the budding yeast transcription factor yAP-1 is sensitive to oxidative stress. *Genes Cells* 3: 521–532, 1998.
51. Kyriakis JM and Avruch J. Protein kinase cascades activated by stress and inflammatory cytokines. *Bioassays* 18: 567–577, 1996.

52. Lee J, Godon C, Lagniel G, Spector D, Garin J, Labarre J, and Toledano MB. Yap1 and Skn7 control two specialized oxidative stress response regulons in yeast. *J Biol Chem* 181: 16040–16046, 1999.
53. Leppert G, McDevitt R, Falco SC, Van Dyk TK, Ficke MB, and Golin J. Cloning by gene amplification of two loci conferring multiple drug resistance in *Saccharomyces*. *Genetics* 125: 13–20, 1990.
54. Liu X-D and Thiele DJ. Oxidative stress induces heat shock factor phosphorylation and HSF-dependent activation of yeast metallothionein gene transcription. *Genes Dev* 10: 592–603, 1996.
55. Marchler G, Schuller C, Adam G, and Ruis H. A *Saccharomyces cerevisiae* UAS element controlled by protein kinase A activates transcription in response to a variety of stress conditions. *EMBO J* 12: 1997–2003, 1993.
56. Martinez-Pastor MT, Marchler G, Schuller C, Marchler-Bauer A, Ruis H, and Estruch F. The *Saccharomyces cerevisiae* zinc finger proteins Msn2p and Msn4p are required for transcriptional induction through the stress-response element (STRE). *EMBO J* 15: 2227–2235, 1996.
57. Millar JB, Buck V, and Wilkinson MG. Pyp1 and Pyp2 PTPases dephosphorylate an osmosensing MAP kinase controlling cell size at division in fission yeast. *Genes Dev* 9: 2117–2130, 1995.
58. Moradas-Ferreira P and Costa V. Adaptive response of the yeast *Saccharomyces cerevisiae* to reactive oxygen species: defenses, damage and death. *Redox Rep* 5: 277–285, 2000.
59. Morgan BA, Bouquin N, Merrill GF, and Johnston LH. A yeast transcription factor bypassing the requirement for SBF and DSC1/MBF in budding yeast has homology to bacterial signal transduction proteins. *EMBO J* 14: 5679–5689, 1995.
60. Morgan BA, Banks GR, Toone WM, Raitt D, Kuge S, and Johnston LH. The Skn7 response regulator controls gene expression in the oxidative stress response of the budding yeast *Saccharomyces cerevisiae*. *EMBO J* 16: 1035–1044, 1997.
61. Moskvina E, Schuller C, Maurer CT, Mager WH, and Ruis H. A search in the genome of *Saccharomyces cerevisiae* for genes regulated via stress response elements. *Yeast* 14: 1041–1050, 1998.
62. Moye-Rowley WS, Harshman KD, and Parker CS. Yeast *YAP1* encodes a novel form of the jun family of transcriptional activator proteins. *Genes Dev* 3: 283–292, 1989.
63. Muller EGD. A glutathione reductase mutant of yeast accumulates high levels of oxidized glutathione and requires thioredoxin for growth. *Mol Biol Cell* 7: 1805–1813, 1996.
64. Nehlin JO, Carlberg M, and Ronne H. Yeast *SKO1* gene encodes a bZIP protein that binds to the CRE motif and acts as a repressor of transcription. *Nucleic Acids Res* 20: 5271–5278, 1992.
65. Nguyen AN, Lee A, Place W, and Shiozaki K. Multistep phosphorelay proteins transmit oxidative stress signals to the fission yeast stress-activated protein kinase. *Mol Biol Cell* 11: 1169–1181, 2000.
66. Nieto-Sotelo J, Weiderrecht G, Okuda A, and Parker C. The yeast heat shock transcription factor contains a transcriptional activation domain whose activity is repressed under nonshock conditions. *Cell* 62: 807–817, 1990.
67. Nishi K, Yoshida M, Fujiwara D, Nishikawa M, Norinouchi S, and Beppu T. Leptomycin B targets a regulatory cascade of Crm1, a fission yeast nuclear protein, involved in control of higher order chromosome structure and gene expression. *J Biol Chem* 269: 6320–6324,1994.
68. Ohmiya R, Kato C, Yamada H, Aiba H, and Mizuno T. A fission yeast gene (*prr1+*) that encodes a response regulator implicated in oxidative stress response. *J Biochem (Tokyo)* 125: 1061–1066, 1999.
69. Ohmiya R, Yamada H, Kato C, Aiba H, and Mizuno T. The Prr1 response regulator is essential for transcription of *ste11+* and for sexual development in fission yeast. *Mol Gen Genet* 264: 441–451, 2000.
70. Ossareh-Nazari B, Bachelerie F, and Dargemont C. Evidence for a role of CRM1 in signal-mediated nuclear export. *Science* 278: 141–144, 1997.
71. Ota IM and Varshavsky A. A yeast protein similar to bacterial two-component regulators. *Science* 262: 566–569, 1992.
72. Pelham H. Activation of heat shock genes in eukaryotes. *Trends Genet* 1: 31–35, 1984.
73. Raitt DC, Johnson AL, Erkine AM, Makino K, Morgan BA, Gross DS, and Johnston LH. The Skn7 response regulator of *Saccharomyces cerevisiae* interacts with Hsf1 in vivo and is required for the induction of heat shock genes by oxidative stress. *Mol Biol Cell* 11: 2335–2347, 2000.
74. Samejima I, Mackie S, and Fantes PA. Multiple modes of activation of the stress-responsive MAP kinase pathway in fission yeast. *EMBO J* 16: 6162–6170, 1997.
75. Sanglard D, Ischer F, Monod M, and Bille J. Cloning of *Candida albicans* genes conferring resistance to azole antifungal agents: characterization of *CDR2*, a new multidrug ABC transporter gene. *Microbiology* 143: 405–416, 1997.
76. Schnell N and Entian K-D. Identification and characterization of a *Saccharomyces cerevisiae* gene (*PAR1*) conferring resistance to iron chelators. *Eur J Biochem* 200: 487–493, 1991.
77. Schnell N, Krems B, and Entian K-D. The *PAR1* (*YAP1/SNQ3*) gene of *Saccharomyces cerevisiae*, a c-jun homolog, is involved in oxygen metabolism. *Curr Genet* 21: 269–273, 1992.
78. Sewell AK, Yokoya F, Yu W, Miyagawa T, Murayama T, and Winge DR. Mutated yeast heat shock transcription factor exhibits elevated basal transcriptional activation and confers metal resistance. *J Biol Chem* 270: 25079–25086, 1995.
79. Shieh JC, Wilkinson MG, and Millar JB. The Win1 mitotic regulator is a component of the fission yeast

stress-activated Sty1 MAPK pathway. *Mol Biol Cell* 9: 311–322, 1998.
80. Shiozaki K and Russell P. Cell cycle control linked to extracellular environment by MAP kinase pathway in fission yeast. *Nature* 378: 739–743, 1995.
81. Shiozaki K and Russell P. Counteractive roles of protein phosphatase 2C (PP2C) and a MAP kinase kinase homolog in the osmoregulation of fission yeast. *EMBO J* 14: 492–502, 1995.
82. Shiozaki K and Russell P. Conjugation, meiosis, and the osmotic stress response are regulated by Spc1 through Atf1 transcription factor in fission yeast. *Genes Dev* 10: 2276–2288, 1996.
83. Silar P, Butler G, and Thiele DJ. Heat shock transcription factor activates expression of the yeast metallothionein gene. *Mol Cell Biol* 11: 1232–1238, 1991.
84. Smith A, Ward MP, and Garrett S. Yeast PKA represses Msn2p/Msn4p-dependent gene expression to regulate growth, stress response and glycogen accumulation. *EMBO J* 17: 3556–3564, 1998.
85. Sorger P, Lewis M, and Pelham H. Heat shock factor is regulated differently in yeast and HeLa cells. *Nature* 329: 81–84, 1987.
86. Sorger PK. Yeast heat shock factor contains separable transient and sustained response transcriptional activators. *Cell* 62: 793–805, 1990.
87. Sorger PK and Pelham HR. Yeast heat shock factor is an essential DNA-binding protein that exhibits temperature-dependent phosphorylation. *Cell* 54: 855–864, 1988.
88. Spevak W, Fessl F, Rytka J, Traczyk A, Skoneczny M, and Ruis H. Isolation of the catalase T structural gene of *Saccharomyces cerevisiae* by functional complementation. *Mol Cell Biol* 3: 1545–1551, 1983.
89. Stade K, Ford CS, Guthrie C, and Weis K. Exportin 1 (Crm1p) is an essential nuclear export factor. *Cell* 90: 1041–1050, 1997.
90. Stock AM, Robinson VL, and Goudreau PN. Two-component signal transduction. *Annu Rev Biochem* 69: 183–215, 2000.
91. Stohs SJ and Bagchi D. Oxidative mechanisms in the toxicity of metal ions. *Free Radic Biol Med* 18: 321–336, 1995.
92. Takeda T, Toda T, Kominami K, Kohnosu A, Yanagida M, and Jones N. *Schizosaccharomyces pombe atf1+* encodes a transcription factor required for sexual development and entry into stationary phase. *EMBO J* 14: 6193–6208, 1995.
93. Takeuchi T, Miyahara K, Hirata D, and Miyakawa T. Mutational analysis of Yap1 protein, an AP-1-like transcriptional activator of *Saccharomyces cerevisiae*. *FEBS Lett* 416: 339–343, 1997.
94. Tamai KT, Gralla EB, Ellerby LM, Valentine JS, and Thiele DJ. Yeast and mammalian metallothioneins functionally substitute for yeast copper-zinc superoxide dismutase. *Proc Natl Acad Sci U S A* 90: 8013–8017, 1993.
95. Toda T, Cameron S, Sass P, Zoller M, and Wigler M. Three different genes in *S. cerevisiae* encode the catalytic subunits of the cAMP-dependent protein kinase. *Cell* 50: 277–287, 1987.
96. Toda T, Shimanuki M, and Yanagida M. Fission yeast genes that confer resistance to staurosporine encode an AP-1-like transcription factor and a protein kinase related to the mammalian ERK1/MAP2 and budding yeast FUS3 and KSS1 kinases. *Genes Dev* 5: 60–73, 1991.
97. Toda T, Shimanuki M, Saka Y, Yamano H, Adachi Y, Shirikawa M, Kyogoku Y, and Yanagida M. Fission yeast pap1-dependent transcription is negatively regulated by an essential nuclear protein, crm1. *Mol Cell Biol* 12: 5474–5484, 1992.
98. Toone WM, Kuge S, Samuels M, Morgan BA, Toda T, and Jones N. Regulation of the fission yeast transcription factor Pap1 by oxidative stress: requirement for the nuclear export factor Crm1 (Exportin) and the stress-activated MAP kinase Sty1/Spc1. *Genes Dev* 12: 1453–1463, 1998.
99. Uzun AEJ. Predictors of outcome in cancer patients with candidemia. *Ann Oncol* 11: 1517–1521, 2000.
100. Vincent AC and Struhl K. ACR1, a yeast ATF/CREB repressor. *Mol Cell Biol* 12: 5394–5405, 1992.
101. Wemmie JA, Szczypka MS, Thiele DJ, and Moye-Rowley WS. Cadmium tolerance mediated by the yeast AP-1 protein requires the presence of an ATP-binding cassette transporter-encoding gene, YCF1. *J Biol Chem* 269: 32592–32597, 1994.
102. Wemmie JA, Wu A-L, Harshman KD, Parker CS, and Moye-Rowley WS. Transcriptional activation mediated by the yeast AP-1 protein is required for normal cadmium tolerance. *J Biol Chem* 269: 14690–14697, 1994.
103. Wemmie JA, Steggerda SM, and Moye-Rowley WS. The *Saccharomyces cerevisiae* AP-1 protein discriminates between oxidative stress elicited by the oxidants $H_2O_2$ and diamide. *J Biol Chem* 272: 7908–7914, 1997.
104. Whitmarsh AJ and Davis RJ. Transcription factor AP-1 regulation by mitogen-activated protein kinase signal transduction pathways. *J Mol Med* 74: 589–607, 1996.
105. Wiederrecht G, Shuey DJ, Kibbe WA, and Parker CS. The *Saccharomyces* and *Drosophila* heat shock transcription factors are identical in size and DNA binding properties. *Cell* 48: 507–515, 1987.
106. Wiederrecht G, Seto D, and Parker CS. Isolation of the gene encoding the *Saccharomyces cerevisiae* heat shock transcription factor. *Cell* 54: 841–853, 1988.
107. Wilkinson MG, Samuels M, Takeda T, Toon WM, Shieh J-C, Toda T, Millar JBA, and Jones N. The Atf1 transcription factor is a target for the Sty1 stress-activated MAP kinase pathway in fission yeast. *Genes Dev* 10: 2289–2301, 1996.
108. Wingard JR. Importance of *Candida* species other than *C. albicans* as pathogens in oncology patients. *Clin Infect Dis* 20: 115–125, 1995.
109. Wu A and Moye-Rowley WS. *GSH1,* which encodes γ-glutamylcysteine synthetase, is a target gene for

yAP-1 transcriptional regulation. *Mol Cell Biol* 14: 5832–5839, 1994.
110. Wu A, Wemmie JA, Edgington NP, Goebl M, Guevara JL, and Moye-Rowley WS. Yeast bZIP proteins mediate pleiotropic drug and metal resistance. *J Biol Chem* 268: 18850–18858, 1993.
111. Wu C. Heat shock transcription factors: structure and regulation. *Annu Rev Cell Dev Biol* 11: 441–469, 1995.
112. Wysong DR, Christin L, Sugar AM, Robbins PW, and Diamond RD. Cloning and sequencing of a *Candida albicans* catalase gene and effects of the disruption of this gene. *Infect Immun* 66: 1953–1961, 1998.
113. Yan C, Lee LH, and Davis LI. Crm1p mediates regulated nuclear export of a yeast AP-1-like transcription factor. *EMBO J* 17: 7416–7429, 1998.
114. Zhang X, De Micheli M, Coleman ST, Sanglard D, and Moye-Rowley WS. Analysis of the oxidative stress regulation of the *Candida albicans* transcription factor, Cap1p. *Mol Microbiol* 36: 618–629, 2000.
115. Zheng M, Aslund F, and Storz G. Activation of the OxyR transcription factor by reversible disulfide bond formation. *Science* 279: 1718–1721, 1998.

Address reprint requests to:
*Dr. W. Scott Moye-Rowley*
*6-530 Bowen Science Building*
*Department of Physiology and Biophysics*
*University of Iowa*
*Iowa City, IA 52242 U.S.A.*

*E-mail:* moyerowl@blue.weeg.uiowa.edu

Received for publication May 24, 2001; accepted November 3, 2001.

**This article has been cited by:**


1. M. Zhang, C. Zhang, J. Li, M. Hanna, X. Zhang, H. Dai, W. Xiao. 2011. Inactivation of YAP1 Enhances Sensitivity of the Yeast RNR3-lacZ Genotoxicity Testing System to a Broad Range of DNA-Damaging Agents. *Toxicological Sciences* **120**:2, 310-321. [CrossRef]
2. Claudia-Valentina Popa, Ioana Dumitru, Lavinia L. Ruta, Andrei F. Danet, Ileana C. Farcasanu. 2010. Exogenous oxidative stress induces Ca2+ release in the yeast Saccharomyces cerevisiae. *FEBS Journal* **277**:19, 4027-4038. [CrossRef]
3. Rebeca Alonso-Monge, Elvira Román, David M. Arana, Daniel Prieto, Verónica Urrialde, César Nombela, Jesús Pla. 2010. The Sko1 protein represses the yeast-to-hypha transition and regulates the oxidative stress response in Candida albicans. *Fungal Genetics and Biology* **47**:7, 587-601. [CrossRef]
4. E HERRERO, J ROS, G BELLI, E CABISCOL. 2008. Redox control and oxidative stress in yeast cells. *Biochimica et Biophysica Acta (BBA) - General Subjects* **1780**:11, 1217-1235. [CrossRef]
5. Chong-Han Ng, Shi-Xiong Tan, Gabriel G. Perrone, Geoffrey W. Thorpe, Vincent J. Higgins, Ian W. Dawes. 2008. Adaptation to hydrogen peroxide in Saccharomyces cerevisiae: The role of NADPH-generating systems and the SKN7 transcription factor. *Free Radical Biology and Medicine* **44**:6, 1131-1145. [CrossRef]
6. Katrin Brombacher, Beat B. Fischer, Karin Rüfenacht, Rik I. L. Eggen. 2006. The role of Yap1p and Skn7p-mediated oxidative stress response in the defence ofSaccharomyces cerevisiae against singlet oxygen. *Yeast* **23**:10, 741-750. [CrossRef]
7. Neeraj Chauhan, Jean-Paul Latge, Richard Calderone. 2006. Signalling and oxidant adaptation in Candida albicans and Aspergillus fumigatus. *Nature Reviews Microbiology* **4**:6, 435-444. [CrossRef]
8. Ingeborg Hanbauer, Jackob Moskovitz. 2006. The yeast cytosolic thioredoxins are involved in the regulation of methionine sulfoxide reductase A. *Free Radical Biology and Medicine* **40**:8, 1391-1396. [CrossRef]
9. Yan Wang, Ying-Ying Cao, Xin-Ming Jia, Yong-Bing Cao, Ping-Hui Gao, Xu-Ping Fu, Kang Ying, Wan-Sheng Chen, Yuan-Ying Jiang. 2006. Cap1p is involved in multiple pathways of oxidative stress response in Candida albicans. *Free Radical Biology and Medicine* **40**:7, 1201-1209. [CrossRef]
10. Ana P. D. Demasi, Goncalo A. G. Pereira, Luis E. S. Netto. 2006. Yeast oxidative stress response. Influences of cytosolic thioredoxin peroxidase I and of the mitochondrial functional state. *FEBS Journal* **273**:4, 805-816. [CrossRef]
11. Mark D. Temple, Gabriel G. Perrone, Ian W. Dawes. 2005. Complex cellular responses to reactive oxygen species. *Trends in Cell Biology* **15**:6, 319-326. [CrossRef]
12. Kazuhiro Maeta, Kaoru Mori, Yoshifumi Takatsume, Shingo Izawa, Yoshiharu Inoue. 2005. Diagnosis of cell death induced by methylglyoxal, a metabolite derived from glycolysis, in Saccharomyces cerevisiae. *FEMS Microbiology Letters* **243**:1, 87-92. [CrossRef]
13. Eric S. Bensen, Samuel J. Martin, Mingchun Li, Judith Berman, Dana A. Davis. 2004. Transcriptional profiling in Candida albicans reveals new adaptive responses to extracellular pH and functions for Rim101p. *Molecular Microbiology* **54**:5, 1335-1351. [CrossRef]
14. Yoon-Dong Park, Won-Hwa Kang, Wan-Soo Yang, Kwang-Soo Shin, Kyung Sook Bae, Hee-Moon Park. 2003. LAMMER kinase homolog, Lkh1, is involved in oxidative-stress response of fission yeast. *Biochemical and Biophysical Research Communications* **311**:4, 1078-1083. [CrossRef]
15. I. Hanbauer. 2003. A homologue of elongation factor 1 regulates methionine sulfoxide reductase A gene expression in Saccharomyces cerevisiae. *Proceedings of the National Academy of Sciences* **100**:14, 8199-8204. [CrossRef]
16. Paul R Ingram, Natalie Z.M Homer, Rachel A Smith, Andrew R Pitt, Clive G Wilson, Orest Olejnik, Corinne M Spickett. 2003. The interaction of sodium chlorite with phospholipids and glutathione: a comparison of effects in vitro, in mammalian and in microbial cells. *Archives of Biochemistry and Biophysics* **410**:1, 121-133. [CrossRef]

17. W.Scott Moye-RowleyTranscriptional Control of Multidrug Resistance in the Yeast Saccharomyces **73**, 251-279. [CrossRef]