Hydrogen peroxide-induced response in *E. coli* and *S. cerevisiae*: different stages of the flow of the genetic information

Review Article

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Abstract: Adaptation to oxidative stress is a major topic in basic and applied research. Cell response to stressful changes is realized through coordinated reorganization of gene expression. *E. coli* and *S. cerevisiae* are extremely amenable to genetic or molecular biological and biochemical approaches, which make these microorganisms suitable models to study stress response at a molecular level in prokaryotes and eukaryotes, respectively. The main focus of this review is (*i*) to discuss transcriptional control of global response to hydrogen peroxide in *E. coli* and *S. cerevisiae*, (*ii*) to summarize recent literature data on *E. coli* and *S. cerevisiae* adaptive response to oxidative stress at different stages of the flow of the genetic information: from transcription and translation to functionally active proteins and (*iii*) to discuss possible reasons for a lack of correlation between the expression of certain antioxidant genes at different levels of cellular organization.

Keywords: *E. coli* • *S. cerevisiae* • *Hydrogen peroxide* • *mRNA level* • *Protein synthesis* • *Enzyme activity*
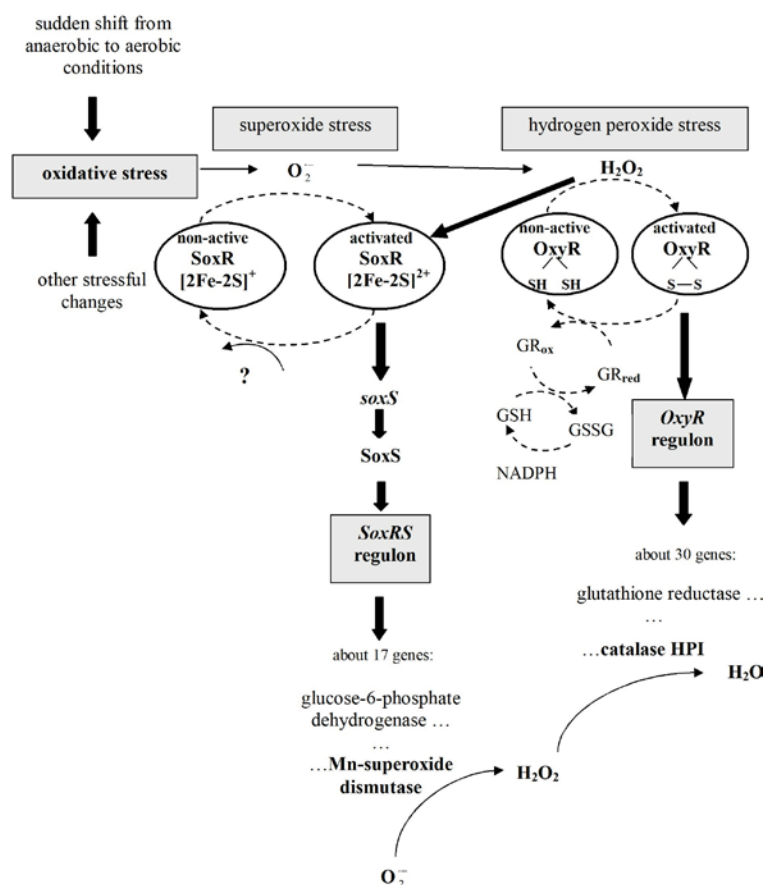
1. Introduction

Most unicellular organisms constantly have to cope with stressful changes in their external surroundings, because natural conditions usually are not optimal. Acid and osmotic stresses, temperature shock, starvation, exposure to oxidants, heavy metal ions and other toxic compounds, and irradiation are the most common stresses experienced by microorganisms in nature. Many of these challenges for aerobic cells are associated with so-called oxidative stress [1-4]. A number of works have been published on oxidative stress in microorganisms. Mostly enterobacteria *Escherichia coli* and budding yeast *Saccharomyces cerevisiae* as prokaryotic and eukaryotic model systems were used for these experiments. There are several advantages for choosing *E. coli* and *S. cerevisiae* to perform research on cellular adaptation to oxidative stress. Since these species are extremely amenable to microbiological, biochemical, genetic and molecular biological manipulations, it is likely that they are the best-characterized among prokaryotes and eukaryotes. The availability of specific mutants that are defective in the respective genes makes it possible to test the functional role of these genes under different circumstances. In addition, researching stress adaptation using these two model systems is not only interesting for basic biology, but is valuable for understanding higher eukaryotes and useful in biotechnology, medicine and other areas.

2. Regulation of global response to hydrogen peroxide in *E. coli* and *S. cerevisiae*

E. coli and *S. cerevisiae* belong to so-called facultative anaerobes which are capable of growing either anaerobically or aerobically. The intracellular concentrations of reactive oxygen species (ROS) are

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Figure 1. Transcriptional regulation of adaptive response to hydrogen peroxide in the bacteria *Escherichia coli*. Designations: SoxR, transcriptional factor of *SoxRS* regulon; OxyR, transcriptional regulator of *OxyR* regulon; GR_{red} and GR_{ox}, reduced and oxidized glutaredoxin; GSH and GSSG, reduced and oxidized glutathione.

tightly maintained at very low levels [5,6]. Therefore, facultative anaerobes posses a highly specialized antioxidant system that provides for their survival after a sudden shift in environmental conditions: from anaerobic to aerobic. Coordinated reorganization of gene expression is one of the most important aspects of cellular adaptation. Expression of the respective genes is associated with their relative importance for cell survival during oxidative stress. A set of genes encoding antioxidant enzymes is regulated by specific proteins, which can sense relatively small changes in cellular oxidant status [7]. Such a global response makes it possible to induce an adaptive metabolism including ROS elimination, the bypass of injured pathways, reparation of oxidative damages and maintenance of reducing power [8,9].

In the bacteria *E. coli*, most genes induced by oxidative stress are grouped into two regulons S*oxRS* and *OxyR* (Figure 1)*. The first one is under two-stage control of the transcriptional factor SoxR. Superoxide-generating compounds activate SoxR regulator by the one-electron

oxidation of the 2Fe-2S clusters [10]. Oxidized SoxR then induces the expression of SoxS protein, which in turn activates the transcription of structural genes of the *SoxRS* regulon: *sodA* (Mn-superoxide dismutase (SOD)), *zwf* (glucose-6-phosphate dehydrogenase (G6PDH)), *acnA* (aconitase A), *nfsA* (nitrate reductase A), *fumC* (fumarase C), *nfo* (endonuclease IV), *etc*. [1,2,7,11,12]. Important antioxidant enzymes such as G6PDH provide the cell with reducing power NADPH and stress-inducible Mn-SOD are among *SoxRS* regulon members. Another form of SOD in *E. coli* is Fe-containing protein which does not respond to oxidative stress [1,2]. It has been estimated that SoxR is >90% reduced under normal aerobic conditions [13]. Being reduced, it cannot activate the *SoxRS* regulon. Several hypotheses were checked, but the question of how the oxidized SoxR is reduced after removing the oxidative challenge is still open [8,14].

For a long time it was widely believed that the *SoxRS* regulon cannot be induced by hydrogen peroxide [2,15,16]. At present, there are several reports on weak

activation of some genes of this regulon by hydrogen peroxide [17-20]. Although the mechanisms responsible for this effect are not clear, several explanations can be given. It is known that hydrogen peroxide indirectly provokes a decrease of the NADPH pool, which is necessary for thiol reduction [12,21-23]. The $NADP^+$/NADPH ratio plays a critical role in the maintenance of redox homeostasis and its change may act as a signal for either SoxR oxidation or reduction. Direct oxidation of SoxR 2Fe-2S clusters by hydrogen peroxide also cannot be excluded. At the same time, hydrogen peroxide may lead to the generation of some other signals activating SoxR. Gaudu and colleagues suggest that the modification of SoxR protein can be affected by any event interfering at some level of that redox pathway [24].
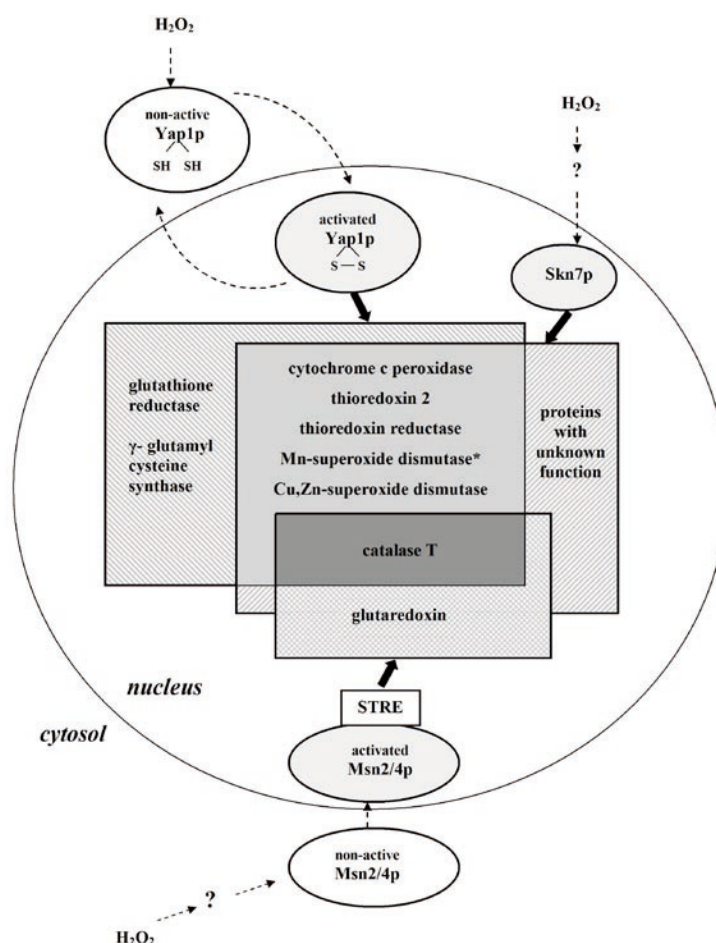
Studies of *E. coli* response to hydrogen peroxide have shown that the mRNA level of 140 genes were elevated in response to hydrogen peroxide exposure, which include about 30 members of the *OxyR* regulon (Figure 1) [18]. Expression of the *OxyR* regulon is regulated by the transcriptional factor OxyR, which can be oxidized by hydrogen peroxide *via* formation of an intramolecular disulfide bond [22,25,26]. OxyR oxidation is a very rapid and sensitive process – it occurs within 30 seconds with an intracellular H_2O_2 concentration as low as 0.1 μM [7]. Oxidized OxyR protein binds to the promoters of several H_2O_2-activated genes, including *katG* (hydroperoxidase-catalase HPI), *gorA* (glutathione reductase), *grxA* (glutaredoxin 1), *trxC* (thioredoxin 2), *ahpCF* (alkyl hydroperoxide reductase), *dps* (nonspecific DNA binding protein) and *oxyS* (a small regulatory RNA) [1,2]. Reduced OxyR binds only to the *oxyR* promoter, and in this way provides autorepression [24]. It is interesting to note that HPI protein, a part of the *OxyR* regulon, is a stress-inducible form of catalase with bifunctional activity (it acts as catalase and peroxidase). *E. coli* produces another form of catalase named HPII which is a monofunctional enzyme and cannot be affected by environmental stress [27,28]. The latter one does not belong to the *OxyR* regulon.

Some mechanisms involved in the regulation of *E. coli* response to hydrogen peroxide were found in other organisms, including *S. cerevisiae*. The prokaryotic and eukaryotic cells sense H_2O_2 in a similar manner. Hydrogen peroxide activates the OxyR protein in *E. coli* and the Yap1 transcriptional regulator in *S. cerevisiae via* oxidation of their cysteine residues [7,29-31]. However, if *E. coli* adaptation to hydrogen peroxide was shown to be related mainly to OxyR protein, *S. cerevisiae* response involves a set of general stress-responsive proteins [7,32,33]. In contrast to bacteria, the subcellular localization and compartmentalization of

regulatory factors is an important aspect of regulation of eukaryotic stress response. Therefore, oxidative stress in prokaryotic and eukaryotic cells shares common features, but in eukaryotes the response is more complex and modulated by several different regulators.

S. cerevisiae are also able to adapt to both hydrogen peroxide and superoxide. Similarly to *E. coli*, the yeast possess two distinct but overlapping stimulons activated by hydrogen peroxide and superoxide anion [34-37]. In *S. cerevisiae*, ROS induce the expression of various defense genes. For instance, adaptation to H_2O_2 correlates with the rapid induction of a stimulon of at least 115 genes and the repression of another 52 genes [36]. Among the identified gene products, 71 proteins are stimulated and 44 are repressed by H_2O_2. The yeast cellular functions affected by hydrogen peroxide are quite different: from carbohydrate metabolism to heat shock proteins and proteases [36,38]. The primary and secondary antioxidant enzymes induced by hydrogen peroxide in *S. cerevisiae* are cytosolic Cu,Zn-SOD (*SOD1*), mitochondrial Mn-SOD (*SOD2*), cytosolic catalase T (*CTT1*), cytochrome *c* peroxidase (*CCP1*), γ-glutamylcysteine synthase (*GSH1*), glutathione reductase (*GLR1*), glucose-6-phosphate dehydrogenase (*ZWF1*) and thioperoxidase (*TSA1*) [36,38]. The yeast *S. cerevisiae* like the other eukaryotes, possess two forms of SOD, encoded by the *SOD1* and *SOD2* genes. SOD2 is a mitochondrial, manganese-containing enzyme (Mn-SOD), which provides protection from the ROS produced by mitochondrial respiratory chain [39,40]. *SOD1* encodes a copper- and zinc-bound SOD (Cu,Zn-SOD), which is located primarily in cytosol, and in part in mitochondria, nucleus, and lysosomes [41-43]. In aerobically growing yeast, Cu,Zn-SOD represents up to 90% of the total SOD activity [42,44] and about 1% of soluble protein [42,45]. Cu,Zn-SOD appears to be a key enzyme providing cells protection from the oxidant agents caused by different environmental conditions. Although much is known on antioxidant function of SOD, the physiological role of the enzyme is extensively discussed [46-49]. Some authors suggested the prooxidant role of SOD *in vitro* [50-52]. In our recent articles, the results were discussed from the point of view that *in vivo* SOD of *S. cerevisiae* can demonstrate both anti- and pro-oxidant properties [46,47].

Baker's yeast possesses two catalase forms - A and T, encoded by different genes. Catalase T, the product of gene *CTT1*, is found mainly in cytosol, and catalase A, the product of gene *CTA1*, is localized mainly in peroxisomes [53]. If the cytosolic form is a member of the H_2O_2-stimulon in *S. cerevisiae*, the peroxisomal one is mainly regulated by fatty acids metabolism [54].

Figure 2. Transcriptional regulation of adaptive response to hydrogen peroxide in the yeast *Saccharomyces cerevisiae*. Designations: Yap1p, transcriptional factor of *Yap1* regulon; Skn7p, transcriptional regulator of *Skn7* regulon; Msn2/4p, transcriptional regulator of *Msn2/4* regulon; STRE, stress-response element. * MnSOD mitochondrial enzyme, which is encoded by *SOD2* gene located in nuclear genome.

Hydrogen peroxide also up-regulates antioxidant enzymes which assist the main enzymes in detoxifying secondary products of free radical modification and maintaining necessary intracellular concentrations of reducing equivalents and low molecular mass antioxidants. For example, GR and G6PDH, maintain intracellular pool of reduced glutathione and NADPH, respectively. It is important to note that the secondary antioxidant enzymes are under the control of sensors of oxidative stress in *E. coli* and many other organisms as well.

The control of H_2O_2-adaptive response in *S. cerevisiae* involves Yap1p, Skn7p and Msn2p/Msn4p (Msn2/4p) transcriptional factors (Figure 2) [7,23,26,32,33]. Mutants deleted for *YAP1* or *SKN7* as well as *MSN2* and *MSN4* genes were found to be unable to induce most antioxidant proteins of the H_2O_2 stimulon, indicating that they were hypersensitive to hydrogen peroxide

[55-58]. Under stress induced by hydrogen peroxide, a strain deficient in *SKN7* behaved identically to a strain lacking *YAP1*, at the same time a *Δskn7Δyap1* double mutant demonstrated the properties similar to single mutants deleted for either *YAP1* or *SKN7* [55]. Figure 2 shows that Skn7p controls the expression of a set of antioxidant enzymes also regulated by Yap1p, for instance, catalase T, Cu,Zn-SOD, Mn-SOD and cytochrome *c* peroxidase [56,59]. The cytosolic catalase T, which may be regulated by either Yap1p or Skn7p, was also found to be a member of the *Msn2/4* regulon in *S. cerevisiae* [58]. This fact justifies a crucial role of catalase T in the yeast defense against hydrogen peroxide. If the expression of abovementioned proteins can be upregulated by a single regulatory protein or both of Yap1p and Skn7p, the induction of thioredoxin 2 (*TRX2*) and thioredoxin reductase (*TRR1*) requires co-operation between Yap1p and Skn7p [55]. On the

other hand, Yap1p and Skn7p regulators do not always act together and have some independent specialized functions [32,56,59]. Yap1p is also involved in heavy metal, diamide and diethylmaleate tolerance, whereas Skn7p is important for cell wall biosynthesis, cell cycle regulation and adaptation to osmotic stress [56,60-62]. However, the functions of most genes regulated by Skn7p are still unknown [32,56].

In *S. cerevisiae*, the activation of Msn2/4p transcriptional regulators is an important way to induce antioxidant defense against hydrogen peroxide (Figure 2). Hasan and colleagues reported a distinct role of Yap1p and Msn2/4p regulators in adaptation to H_2O_2-stress [58]. Their study demonstrated that *Yap1* regulon contained most of the antioxidant enzymes and several proteins of the glutathione and thioredoxin pathways [56]. In contrast, *Msn2/4* regulon mainly consisted of the proteins responsible for reparation and degradation of oxidatively damaged molecules [58]. The authors suggested an important role of Yap1p in the prevention of oxidative stress-induced damage *via* ROS elimination and a predominant function of Msn2/4p during the recovery from the stress. Similarly to Yap1p and Skn7p, Msn2/4p factors are involved in *S. cerevisiae* adaptation to different environmental challenges, including starvation, osmotic, weak acid, heat, freezing and alcohol stresses [63-65].

The subcellular localization or compartmentalization of regulatory factors is an important aspect in regulation of eukaryotic stress response. The cellular compartmentalization of transcriptional factors in *S. cerevisiae* under oxidative stress is regulated by intracellular redox potential, which in turn depends on many circumstances [29,33,66,67]. Under hydrogen peroxide challenge, the Yap1p activation is a result of the rapid formation of intramolecular disulfide bonds between cysteine residues [29-31]. This leads to the change of Yap1p conformation masking recognition of nuclear export signal and nuclear accumulation of the protein. It should be noted that Yap1p is not directly oxidized by hydrogen peroxide. Toledano *et al.* have identified one more component of the Yap1p oxidizing pathway [7,68]. It is the glutathione peroxidase-like enzyme Gpx3 acting as a sensor and tranducer of H_2O_2 signal to Yap1p. The authors have shown that hydrogen peroxide cause disulfide intermolecular bonds between Cys residues in Gpx3 and Yap1p molecules. These disulfide bonds then transform into a Yap1p intramolecular bond activating the regulator. In the nucleus, Yap1p promoted the transcriptional activation of target genes involved in hydrogen peroxide resistance [7,26,56,69]. Over about 30 min, Yap1p was deactivated by Yap1p-controlled thioredoxins provided autoregulation [70].

Msn2/4 proteins are other examples of the transcription factors, whose functional role depends on their translocation from the cytoplasm to the nucleus in *S. cerevisiae* under H_2O_2-induced stress [71,72]. Activation of Msn2p as well as Msn4p is a result of a series of complex steps that enhance their nuclear concentration. In the nucleus, the Msn2/4p transcription factors recognize and bind the stress-response element (STRE) and induce the activation of STRE-dependent promoters under various stressful conditions [71,73,74]. The subcellular localization and STRE-binding activity of Msn2/4p are regulated by reversible phosphorylation [74-77].

Unlike Yap1 and Msn2/4p response regulators, Skn7p factor is localized in the nucleus under normal conditions as well as during oxidative stress [57,78]. Skn7p activity is modulated in response to various environmental changes *via* phosphorylation-dephosphorylation of a conserved aspartyl residue [78,79]. However, under oxidative stress, Skn7p phosphorylation is not required [57,60]. Li and colleagues proposed that in response to oxidative stress, Skn7p may undergo uncharacterized modifications or conformational changes resulting in Skn7p oxidation [79].

Besides the abovementioned proteins, regulatory factors of other regulons are implicated in the global control of adaptation to hydrogen peroxide challenge in *S. cerevisiae* and *E. coli* [2,57]. It seems to be that interplay between different regulators is a key aspect of the general response to stress challenges in either eukaryotes or prokaryotes, but yet it remains largely uncharacterized.

3. Gene expression and protein synthesis of protecting-enzymes in *E. coli* and *S. cerevisiae* under H_2O_2-induced stress

Oxidative stress response in *E. coli* and *S. cerevisiae* is extensively studied, using analysis of the changes in the microorganisms' transcriptome and proteome in response to challenges with hydrogen peroxide [17,18,36,56,80]. Certain studies employing comparative genomic, proteomic and other approaches demonstrate a lack of correlation between either the mRNA and protein amounts of many genes or the levels and functional activities of some proteins [81-85]. We have analyzed the literature reported on *E. coli* and *S. cerevisiae* adaptive response to hydrogen peroxide at different stages of the flow of the genetic information: from transcription and translation to enzyme activity (Tables 1 and 2). As seen

in the tables, the effects obtained at various levels of cellular organization may be dramatically different. For example, in *E. coli* cells treated by H_2O_2, the increase in peroxidase activity of OxyR-regulated bifunctional catalase-peroxidase HPI was lower than the induction ratio of *katG* gene coding HPI (Table 1). It should be noted that the same parameters obtained with various methods can be different. For instance, Table 1 shows that the induction ratio of *katG* transcription found with multiplex reverse transcription-PCR technique [17] was 3-fold lower than that obtained in the DNA microarray experiments [18]. From our point of view, it is important to analyse results obtained by different techniques, because such comparison may help to map out the global adaptive response to stress.

As one more highly possible explanation of the various H_2O_2 effects on the microorganisms shown in Tables 1 and 2, various strains and experimental conditions were used in the studies. That is why in our experiments we investigated widely used strains obtained from other laboratoties. However, rather different results have been found by Zheng *et al.* [18] and in our laboratory [20] with *E. coli* MC4100 cells using the same stress conditions as well as with *S. cerevisiae* YPH98 strain investigated by Godon *et al.* [36] and us [85].

As mentioned above, it was widely believed that hydrogen peroxide did not affect *SoxRS* regulon expression. This view is still common, although several reports on weak activation of some genes of this regulon by exogenic hydrogen peroxide have appeared [17-20]. It was found that the expression of *sodA* (Mn-SOD), *soxS* (regulator of *SoxRS* regulon expression), *micF* (regulatory RNA) and some other genes were switched on in response to *E. coli* exposure to H_2O_2. It is interesting to note that in the

two abovementioned studies [17,18] no change in the transcription level of the *zwf* gene (G6PDH) was found. However, in our study the expression at the level of G6PDH activity rose with simultaneous increase in SOD activity in response to hydrogen peroxide treatment [20]. Zheng and colleagues registered elevation of transcription of the *sodA* gene (Mn-SOD) at hydrogen peroxide concentrations higher than 100 μM, and at H_2O_2 concentrations lower than 100 μM the effect was observed only for *OxyR* regulon genes (Table 1) [18]. We found that the bacteria treatment with as little as 10-100 μM H_2O_2 resulted in weak, but significant increase in SOD and G6PDH activities [19,20]. The effect was cancelled by chloramphenicol, an inhibitor of protein synthesis in prokaryotes, which shows the necessity of *de novo* protein synthesis to increase the activities of SOD and G6PDH. In our studies, the elevation of both SOD and G6PDH activities was not found in a Δ*soxR* mutant. Thus we have provided the evidence that an increase in SOD and G6PDH activities is a SoxR-dependent phenomenon [20]. It should be noted that earlier SoxR-dependent *SoxRS* regulon activation by H_2O_2 was described by Manchado *et al.* [17].

One more interesting fact can be observed in the response of different strains of *E. coli* to the same stress conditions. For instance, sublethal doses of hydrogen peroxide caused either an elevation or no increase in SOD activity dependent on the strain used (Table 1). In the previous studies, we have found that different strains and even the same strain obtained from different sources displayed various patterns of response to oxidants at the enzyme activity level [20,86].

Similarly to *E. coli*, the budding yeast also demonstrated a strain-specific response to oxidative stress [87]. However, in some cases where the same

Protein function	Gene name	Induction ratio of gene transcription		Ratio of enzyme activity		
				The bacteria strain		
		ND[1] [17]	MG1655[2] [18]	MC4100[3] [20]	AB1157[4] [19,20]	KS400[5] [19,20]
OxyR-dependent						
Bifunctional catalase hydrogen peroxidase HPI	*katG*	15	44	4.8[a] 3.1[b]	1.8[a] 2.6[b]	2.8[a] 1.9[b]
Glutathione reductase	*gorA*	2.3	2.1	1.1	1.5	1.5
SoxR-dependent						
Regulatory protein of *SoxRS* regulon	*soxS*	7.3	19	-	-	-
Inducible Mn-SOD	*sodA*	4.6	8.0	1.3[c]	1.5[c]	0.9[c]
Glucose-6-phosphate dehydrogenase	*zwf*	not found	not found	1.3	1.6	1.4

Table 1. Effect of hydrogen peroxide on *Escherichia coli* stress-protecting proteins.

H_2O_2 concentrations used in the respective studies: [1]0.05, 0.1, 0.5 and 1 mM; [2]0.01, 0.03, 0.1, 0.3 and 1 mM (MC4100 was investigated as well); [3]0.01, 0.02, 0.05 and 0.1 mM; [4]0.02 mM; [5]0.02 mM
ND – not determined; "-"– not studied; [a]–peroxidase activity of catalase peroxidase HPI; [b]– total catalase activity; [c]– total SOD activity

S. cerevisiae strain was used, the changes in protein synthesis did not reflect the alteration in the activities of respective enzymes in cells exposed to oxidants [83,85]. Cyrne with colleagues found, that in stationary phase *S. cerevisiae* EG103 cells treated by menadione, the increases in Mn-SOD, Cu,Zn-SOD and glutathione reductase mRNA steady state levels were not paralleled by increased protein levels and enzymatic activities [83]. In order to complexly elucidate the regulation of induction of these enzymes by menadione, the yeast response at different levels of cellular organization was studied. The authors showed that oxidative stress modified gene expression in a complex way, not only at the transcriptional, but at the post-transcriptional, translational and post-translational levels as well. There are also other different mechanisms responsible for such regulation. Herrero and colleagues recently reported that oxidative stress response in the yeast cells is not only conditioned by gene transcription but also by the mRNA decay dynamics [88]. The authors suggested that such a complex response might be particularly relevant to explain the temporary down-regulation of the respective protein synthesis under stress. Other researchers have found that alterations of balance in the translational apparatus were involved in the yeast response to stress [89,90]. For example, regulation of translation elongation in *S. cerevisiae* predicted to alter the ratio between mRNAs with and without strong entry sites at ribosomes. It has been found that low concentrations of H_2O_2 resulted in increased mRNA levels paralleled with protein synthesis. However, high doses of H_2O_2 promoted polyribosome association but

did not necessarily lead to increased protein production [90].

Godon and coauthors reported that in exponentially grown *S. cerevisiae* YPH98 cells exposed to H_2O_2 sublethal doses, increased mRNA levels of certain genes were followed by increases in their protein levels [36]. In the abovementioned experiment [36], H_2O_2 resulted in the high elevation of protein synthesis of catalase T and two SODs (Table 2). At the same time, no change in catalase A level was found. However, earlier it was shown that sublethal concentrations of H_2O_2 increased the activity of both catalases in *S. cerevisiae* by about 2-fold [88]. In our recent study, besides weak increase in the activities of both catalase A and T, we did not find any changes in SOD1 or SOD2 activity [87]. It should be noted that in the two mentioned above experiments [87,91], the strains other than *S. cerevisiae* YPH98 were used: single mutants of YPH250 defective in catalase T or A [87,91] and single mutants of EG103 lacking SOD1 or SOD2 [87]. However, as seen in Table 2, using the same stress conditions and the same yeast strain YPH98 which were employed by Godon with colleagues [36], we found that hydrogen peroxide only slightly increased catalase activity and did not change SOD activity [85]. Overall, our data on weak elevation of catalase and SOD do not correspond to a high level of synthesis of the respective enzyme molecules observed earlier by Godon *et al*. [36]. Thus, an obvious question arises: what are the possible reasons for a lack of a strong relationship between the expression of certain genes at different levels of the flow of the genetic information, and why does such correlation for other genes under the same stress conditions exist?

Protein function	Gene name	Induction ratio of gene transcription	Induction ratio of protein synthesis	Ratio of enzyme activity		
		The yeast strain				
		S150-2B[1] [37]	YPH98[2] [36,55]	YPH250[3] [84,86]	YPH98[4] [84]	EG103[5] [84]
Yap1- and Skn7-depedent						
Cytosolic catalase T	*CTT1*	2.2	14.7	1.2[a] 3.4[c]	2.1[c]	0.95[c]
Peroxisomal catalase A	*CTA1*	1.2	not found	2.8[b]		
Cytosolic Cu,Zn-SOD	*SOD1*	0.82	4.3	2.1[d]	0.97[d]	0.96[d]
Mitochondrial Mn-SOD	*SOD2*	1.6	5.9			
Cytosolic thioredoxin 2	*TRX2*	23	11.5	-	-	-
Yap-dependent						
Glutathion reductase	*GLR1*	not found	2.1	1.02	-	-
Glucose-6-phosphate dehydrogenase	*ZWF1*	not found	2.0	0.89	-	-

Table 2. Effect of hydrogen peroxide on *Saccharomyces cerevisiae* stress-protecting proteins.

H_2O_2 concentrations used in the respective studies: [1]0.4 mM; [2]0.02, 0.2, 0.4 and 0.8 mM; [3]0.5, 1.0, 2.0, 3.5, 5.0 and 10.0 mM; [4]0.25, 0.5, 1.0, 2.0, 3.5, 5.0 and 10.0 mM; [5]0.25, 0.5, 1.0, 2.0, 3.5, 5.0 and 10.0 mM

"-"– not studied; [a]- activity of catalase CTT1 in isogenic derivative of YPH250 strain defective in CTA1gene; [b]- activity of catalase CTA1 in isogenic derivative of YPH250 strain defective in CTT1 gene; [c]- total catalase activity; [d]- total SOD activity

The expression of genes encoding various enzymes is regulated by different mechanisms. It may be associated with different importance of enzymes for the maintenance of cell viability under certain conditions. Among numerous genes induced by hydrogen peroxide in *E. coli* and *S. cerevisiae* a rather limited amount of them participate directly in the cell protection against H_2O_2. In addition to regulation of the expression of antioxidant defense genes, hydrogen peroxide is known to affect expression of a variety of other genes involved in signal transduction, transcriptional regulation, and protein, carbohydrates or lipid metabolism [18,36,38]. That is why at negligible concentrations H_2O_2 may act as an important signal molecule [31,67,91], however, high doses of H_2O_2 induce oxidative stress, therefore antioxidant defence becomes critical [1,2,32].

It is likely that oxidant/antioxidant balance in the cell is responsible for the correct mechanism switch. According to the data presented in Tables 1 and 2, the induction ratio of gene expression and protein synthesis for some antioxidant proteins is much higher than the ratio of their functional activity. It seems to be that after cell treatment with high concentrations of hydrogen peroxide some preexisted and/or synthesized *de novo* enzymes can be partially inactivated [1,85,87]. At the same time, under mild stress induced by sublethal doses of hydrogen peroxide when the levels of protein synthesis *de novo* is high, it could be expected that a sudden increase in the activities of such strong antioxidant enzymes as catalases and SODs dramatically disturbs the intracellular redox homeostasis. Therefore, it can be supposed that most of the respective protein molecules synthesized *de novo* remain in non-active form under stress induced by H_2O_2 sublethal concentrations. One more question arises: what is the reason to expend valuable energy and other intracellular resources accumulating non-active proteins?

It is well known that the exposure of microorganisms to low sublethal concentrations of oxidants leads to the acquisition of cellular resistance to a subsequent lethal oxidative stress [1-3,34,92]. It may be supposed that the microorganisms' cells exposed to low doses of hydrogen peroxide rapidly respond by the induction of gene expression and translation accumulating non-active stress-protectant molecules of antioxidant enzymes. The latter can become rapidly activated following relief of the stress condition and provide cells with an ability to adapt quickly and survive consequent lethal challenge.

4. Concluding Remarks

All aerobic organisms from prokaryotes to higher eukaryotes tightly regulate intracellular ROS concentrations at relatively similar levels. Hydrogen peroxide at low concentrations plays important roles in host defense, oxidative biosynthetic reactions and also acts as a messenger in cellular signal transduction. When generation of hydrogen peroxide exceeds its elimination, cells suffer from damage to virtually all biomolecules. Analysis of gene expression under oxidative stress conditions reveal a large number of proteins induced in both pro- and eukaryotes by hydrogen peroxide. At the same time, the number of transcriptional regulators of H_2O_2-responsive genes is rather low. Overall, exogenic hydrogen peroxide changes the level of mRNA of about 140 genes in *E. coli*, and at least 167 genes in *S. cerevisiae*. They include many genes coding for metabolic enzymes, demonstrating the importance of reorganization of metabolism under stress conditions. However, under H_2O_2-induced stress several antioxidant enzymes play a critical role, which allow organisms to survive stress conditions. It should be noted that cell response is under complex regulation, and increases in the mRNA levels of antioxidant enzymes do not always correlate with the elevated protein amounts and activities of these enzymes.

Thus, genomic and proteomic tools allowing the identification of H_2O_2-responsive genes and proteins expand our understanding of the oxidative stress global response. However, mechanisms other than transcription and translation can be involved in cell adaptation to oxidative stress and an active enzyme is one of the final and critical stages in cellular adaptation. This is why drawing a complete picture of cell adaptive response to stress, a complex experimental approach, is in need - an investigation of cell adaptation at all possible levels of the flow of the genetic information: from genes to functionally active proteins.

Acknowledgments

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