

Meta-analysis of transcriptome data on oxidative stress response in *Saccharomyces cerevisiae* cells underlines regulation of carbon, redox and glutathione metabolism

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Abstract

Environmental stress adversely affects living systems within medical as well as industrial context, causing either diseases or resulting in e.g. underperforming production processes. In particular oxidative stress in industrial biotechnology context, manifested as the imbalance in generation of reactive oxygen species and antioxidant capacity causes yield losses both in growth and production in baker's yeast. Oxidative stress response studies for *Saccharomyces cerevisiae* at transcriptome level are using either direct induction methods such as treatment with peroxides or indirect induction methods such as treatment with drugs or toxins. To extract common response mechanisms integrating all conditions is of high value. To this end, this study collects, processes and aggregates published transcriptome data from studies that examined the response using both direct and indirect oxidative stress induction methods. Interestingly, carbon metabolism, oxidation reduction processes and glutathione metabolic process were found to be the common mechanisms involved in oxidative stress response. However, ion homeostasis and hexose transport mechanisms have been shown to be affected from direct induction using peroxides. This result illustrates bioinformatics analysis for large, aggregated transcriptome datasets, as a steppingstone for finding common features and further metabolic engineering targets were developed.

Introduction

Oxidative stress is ubiquitous in living systems from microorganisms to plants and mammalian systems, manifested as the imbalance between the generation of reactive oxygen species (ROS) and the capacity of the biological system to detoxify these intermediates (Inzé & Van Montagu, 1995; Sies, 2000; Storz & Imlay, 1999). The excess free radicals result in damage to fatty tissue, DNA, and proteins causing in turn loss of function, yield or life quality. Coupled with redox imbalance, oxidative stress typically induces system-wide response, involving several transcripts, proteins and biochemical reactions, spanning several omic-layers.

Cells develop complex responses and protection mechanisms to maintain intracellular redox balances against oxidative stress. Responses to oxidative stress are usually on cell survival or cell death mechanisms. Cell

survival mechanisms involves antioxidant enzyme mechanisms (SOD, catalase, peroxidase reactions), metabolic products (glutathione, used in almost all eukaryotes) (Poljak et al., 2003), upregulation of various transcription factors (Yap1p, Skn7p, Msn2/4p (Diezmann, 2014)). Besides, necrosis, apoptosis and autophagy are the cell death mechanisms against oxidative stress. These programmed cell death responses of the cell shed light on neurodegenerative diseases and cancer studies (Figure 1) (Farrugia & Balzan, 2012; Harding et al., 2003; Luo et al., 2017).

Bakers yeast, *Saccharomyces cerevisiae*, has long been used for centuries not only for making bread or various drinks, but also as food supplement, feed additive (Newbold et al., 1996) as well as for production of bioplastics and other biomaterials (Breuer et al., 2002), biofuels (Cardona et al., 2009) and within medical context (Borresen et al., 2012). As such, it is considered

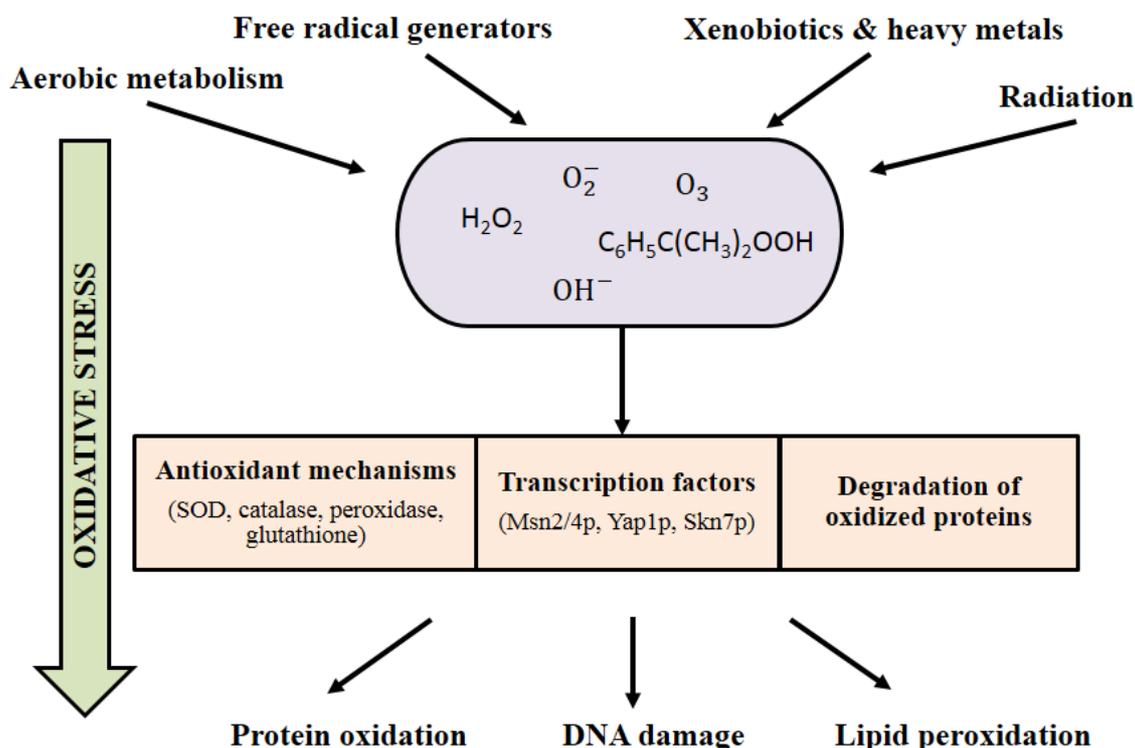


Figure1. A general overview for causes and possible consequences of oxidative stress.

as a model organism for eukaryotic systems as well as an important workhorse for industrial biotechnology (Giaever et al., 2002; Hartwell, 1974; Lee et al., 2002; Li et al., 2004; Mager & Winderickx, 2005; Nevoigt, 2008; Oliver, 1996; Petranovic & Vemuri, 2009). The availability of genome sequence (Wei et al., 2007) as well as various molecular biology tools (Mclsaac et al., 2014) renders yeast central not only to understand how cellular machinery works but also for further metabolic engineering studies.

Yeasts are exposed to various stresses (heat, pH, nutrient limitation, osmotic, oxidative) in the industrial context and/or changing environmental conditions. Oxidative stress is an inevitable part of the aerobic life cycles of yeasts. The oxidative stress response in yeast has been evaluated with different perspectives of finding toxicity level of stress agents (Flattery-O'Brien et al., 1993; Jamieson, 1992), identifying the cellular mechanisms (Davies et al., 1995; Gasch et al., 2000), determining stress related genes with mutant strains (Grant et al., 1996, 1998; Okada et al., 2014) and understanding the main mechanisms (Cyrne et al., 2003; Godon et al., 1998; Gopalacharyulu et al., 2009; Matallana & Aranda, 2017; Peláez-Soto et al., 2020; Piedrafita et al., 2015; Ralser et al., 2007; Yoshimoto et al., 2019). Stress responses have also been studied for living systems for various taxa, ranging from bacteria (Christodoulou et al., 2018; Zhai et al., 2020) to plant cells (Sipari et al., 2020) and other higher eukaryotes (Yu et al., 2020).

In particular, there are several studies focusing on transcriptomic (TX) response. Many studies that investigate transcription factors such as Yap1, Skn7 and

Msn2/4 that regulates oxidative stress response (Carmel-Harel et al., 2001; Livas et al., 2011; Ma & Liu, 2010; Ouyang et al., 2011; Sha et al., 2013), antioxidant defense mechanisms such as catalases, SOD, thioredoxins and other cellular responses such as cell death and apoptosis following oxidative stress can be found in the literature. However these data obtained from different analysis platforms, oxidative stress inducers and many other experimental and analysis techniques (Cheng et al., 2018; Farrugia et al., 2019; Rodriguez-Colman et al., 2010). Although these studies provide useful information, they cannot be compared to other results of experiments, yet aggregation is of great interest to distill common features of stress response in yeast cells.

A significant challenge in analyzing large scale – omic datasets compiled from different sources is to extract key information from experiments performed individually with various agenda, using different techniques or agents, by different labs and/or technicians. In particular for oxidative stress, different labs used various agents (H_2O_2 , CHP) to induce the stress, alternative techniques (cDNA microarray, oligonucleotide microarray, qPCR, RNA-Seq), alternative experimental design (time-course, static, comparison with a selected mutant) and various strains of *Saccharomyces cerevisiae* under different growth conditions. Even the purpose of each experiments ranges from determination of toxic/lethal effect to finding resistance genes to stress. A promising approach to analyze omic-dataset from different backgrounds is to perform so-called, meta-analysis of such data. In its essence, meta-analysis aims to aggregate available data

or information and find key features underlying the system of interest. The approach has been used within various context including oncogenetics (Bhasin et al., 2016), biomarker for plant biotechnology (Zimmermann et al., 2008), stem cell research (Assou et al., 2007) finding stress responsive pathways (Panahi et al., 2019) with even dedicated databases (Hruz et al., 2008).

Rank aggregation is one proposed method for meta-analysis e.g. to combine TX data obtained from different sources (Wald et al., 2012a, 2012b), since the results of high-throughput genomics experiments contain significant amount of noise, and thus reliability of the results should be supported by combining evidences from different experiments or platforms. Therefore, rank aggregation methods provide less noisy results by combining several preference lists. Different approaches proposed in the literature and Robust Rank Aggregation is one of the distribution based approaches which assumes a null probabilistic model to compare each ranked list (Li et al., 2019). The approach consists of focusing on the ranks of genes from individual transcriptome studies, rather than the expression value itself and aggregating list of ranks, assuming beta-distribution for the underlying population of lists and scores each element of the combined list with a corrected p-value. These corrected p-values are sorted to obtain final aggregated ranks. (Kolde et al., 2012; Li et al., 2019)

The advent of high-throughput omic technologies generated ever-growing immense amount of data, which in turn, remains largely under-used and under-interpreted. Making more of the available –omic data is the main approach of our work. The aim of this study is therefore to collect, analyze, aggregate and perform functional analysis of available transcriptome data from response of yeast cells to various oxidative stresses, within the scope of further understanding the effect of this stress on *Saccharomyces cerevisiae* cells and finding common features among different experiments using bioinformatics tools. In doing so, microarray datasets from NCBI database is collected, inspected for differential expression and compiled a large dataset containing differentially expressed genes in each experiment. Upon rank aggregation and downstream functional analysis, the implications within industrial biotechnology is discussed.

Materials and Methods

Data Acquisition and Differential Expression Analysis

All data used in this study has been compiled from public sources. Overall workflow to obtain the transcriptome dataset is presented in Figure 2, including the number of datasets in each step. NCBI Gene Expression Omnibus (GEO) database (<https://www.ncbi.nlm.nih.gov/geo/>) was searched for the term “oxidative stress” and further filtered for “*Saccharomyces cerevisiae*”.

In this paper, we focused on microarray data, due to standardized experimental and analytical protocols and focused experimental context. In particular, the microarray results from the experiments measuring the cellular response against treatments with oxidants such as peroxides (e.g. H₂O₂, CHP), drugs (e.g. Epolauridine) and toxins (e.g. citrinin), directly causing oxidative stress. The list of datasets for the final meta-analysis is given in Table 1. For samples with replicates (23 of 34 samples), from documented commercial microarray platforms, Differentially Expressed Gene (DEG) analysis was performed using R limma package (two dye, dye swap and time course designs are also included) and the results were filtered for p<0.1 and log fold change, logFC>1. For the samples without replicates, the published logFC was used with the same criteria.

Table 1. Datasets used for meta-analysis.

Stress Inducer	Accession IDs
H ₂ O ₂	GSE45370, GSE58992, GSE135546, GSE79037, GSE63030, GSE16346, GSE26829, GSE55081, GSE12220, GSE15936, GSE3406, GSE2977
Linoleic acid hydroperoxide (LoaOOH)	GSE18334, GSE47820, GSE54951,
CHP	GSE7645, GSE26169
Oxygen concentration	GSE22832
Transition from anaerobic to aerobic	GSE7140
TiO ₂ + UV	GSE99660
Mycotoxins: citrinin (CIT) and ochratoxin A (OTA)	GSE84187
Pyocyanin	GSE6185
Eupolauridine-9591 (E9591)	GSE101749
Menadione	GSE3683
Celastrol	GSE5608
Arsenite	GSE6067, GSE6068
Zinc	GSE18411
Potassium	GSE24712

For time-course experiments (11 of 34), the last time point or, 30/60/90-minute time point (if available) was compared to control taken prior to treatment. For each sample, the absolute values of logFC upon filtering were ranked in increasing order and these ranks were normalized with respect to maximum rank in the corresponding sample. Finally, normalized ranks for each gene among all of the samples were merged to generate the rank matrix that contains normalized ranks of 6039 ORF's in 34 samples.

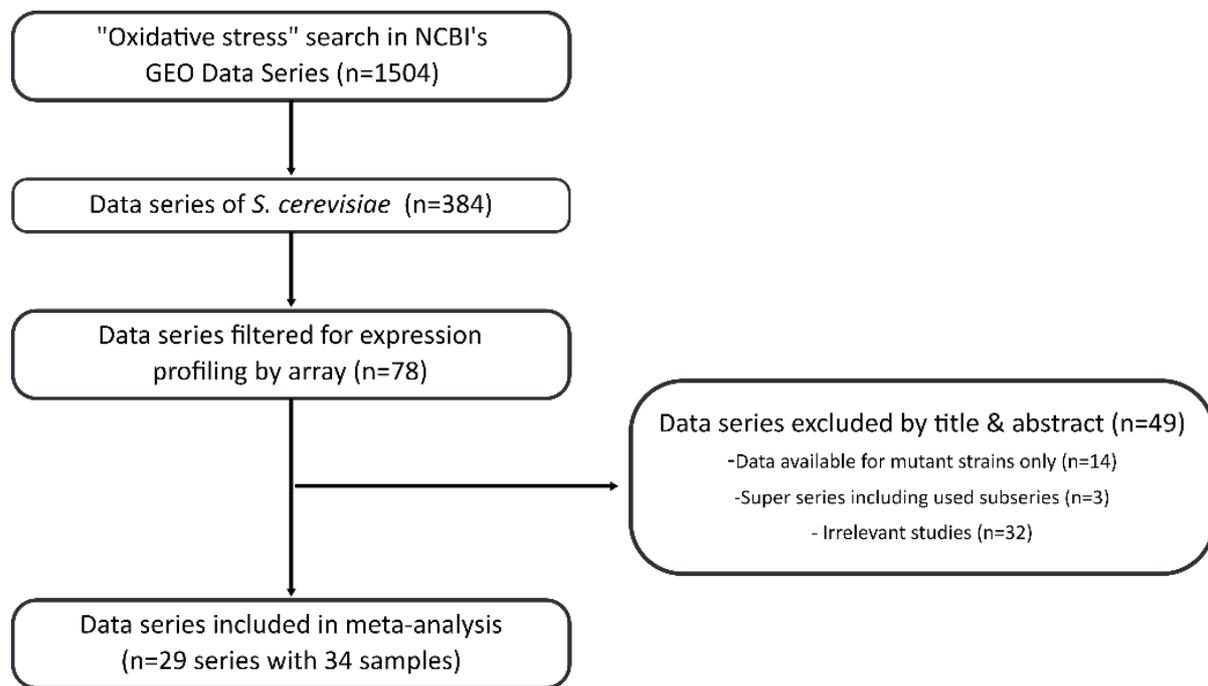


Figure 2. Transcriptome data acquisition workflow to compile the data used in this study.

Aggregation of transcriptome data

The aggregation of transcriptome data is performed using Robust Rank Aggregation algorithm and the R package RobustRankAggreg (Kolde et al., 2012). In case the transcript level for a specific probe, the corresponding entry to the rank matrix was replaced with maximum normalized rank value, namely 1. The rank matrix was aggregated using aggregateRanks function, which calculates p -scores for each transcript and sorts them in increasing order.

Functional analysis of differentially expressed genes in aggregated list

GO and KEGG Enrichment

For the ORF's that are overrepresented in all datasets are determined based on their p -scores, and a cutoff-score of 0.1. For overrepresented genes ($p < 0.1$), gene set enrichment analysis based on Gene Ontology (GO) and KEGG pathways were performed using R packages clusterProfiler and org.Sc.sgd.db Bioconductor genome wide annotation for yeast, and DAVID Gene Functional Annotation and Classification Tools (<https://david.ncifcrf.gov/home.jsp>) and AmiGO database (Carbon et al., 2009). For GO annotation for all GO ontologies, molecular function, bioprocess and cellular component, were performed using enrichGO function using Ensembl ID's as key types, false discovery rate as p value adjustment method and p -value cutoff was set to 0.1 (same in KEGG enrichment). The KEGG annotation was performed similarly using NCBI Gene ID's as keys using enrichKEGG function.

Results and Discussion

This study focuses on finding common and significant gene sets, differentially expressed upon oxidative stress, using meta-analysis of transcriptome data, collected from public databases. The robust rank aggregation method used here allows to overrepresented genes. It should be noted that the final set of genes may or may not be the most differentially expressed all together in a single dataset, rather, the final set of genes are differentially expressed in most (evaluated with statistically significance) of the datasets considered. The overall workflow for selection of microarray transcriptome datasets is given in Figure 2. The selected final datasets with 34 samples include direct or indirect induction of oxidative stress response on wild-type strains, while studies including mutant strains, investigating unconventional conditions such as radioactive materials or freezing were not considered. This way, more focused experimental context was obtained.

DEG analysis was *de novo* performed for series containing replicates or series where raw data is available in .CEL, .txt or .gpr formats. The ranking of transcripts was performed based on absolute logFC, so up- or downregulation was not separately investigated in aggregated list. Normalization of the ranks considering the number of the differentially expressed genes allows lowering the effect of unreliable DEG lists. In case, the raw data or replicates are not available in a specific dataset, statistical significance of the differential expression cannot be known, yet, published information on logFC is used to obtain statistically significant aggregated ranks.

Upon DEG analysis for each sample, the normalized rank lists from each sample were merged to obtain 10715x34 rank matrix (10715 ORF's and 34 samples) containing normalized rank list, one for each sample. Following the work of Kolde 2012, p -values for beta distribution were calculated (and corrected for possible false positives due to multiple hypothesis testing) for each transcript. Finally, 83 ORF's have p -score less than 1 and 42 of these were considered to be overrepresented in all data set ($p < 0.1$, Table 2).

Oxidative stress might be induced directly by perturbing the culture with e.g. a hyperoxide or

indirectly using excess aeration. To assess whether the stress induction method delivers different set of genes or not, a subset of 10 DEG lists that contains only direct induction methods by H₂O₂, LoaOOH and CHP, were aggregated. Comparison of the results were shown in Figure 3. In this case, 23 of the 10715 ORF's had p -score less than 0.1. Interestingly, the 23 ORF's were not a subset of the initial list 43 ORF's obtained from the dataset with 34 samples, though several genes are shared between these two lists (Figure 3).

Table 2. p -scores of significantly differentially expressed genes in analyses containing all samples and only samples with direct induction of oxidative stress.

ORF	Description	p Score (All Samples)	p Score (Direct induction)
YPL171C	NADPH dehydrogenase	2.80E-09	2.26E-06
YKL071W	NADH-dependent aldehyde reductase	1.14E-08	0.001887
YKL086W	sulfiredoxin	6.72E-08	6.57E-06
YDR453C	thioredoxin peroxidase TSA2	2.07E-06	9.28E-05
YOL052C-A	Ddr2p, Multi-stress response protein	1.54E-05	0.017453
YBR072W	chaperone protein HSP26	3.25E-05	0.084638
YCR021C	Hsp30p	4.89E-05	0.043349
YMR090W	Putative protein of unknown function	6.28E-05	-
YLL060C	glutathione transferase GTT2	2.54E-04	0.006030
YOR382W	Fit2p	2.83E-04	0.003935
YHR048W	Yhk8p	3.05E-04	1.12E-04
YER103W	Hsp70 family chaperone SSA4	4.07E-04	-
YHR087W	Rtc3p	0.000776	0.044299
YCL026C-A	type II nitroreductase	0.001375	0.003311
YLR327C	Tma10p	0.001497	-
YGR248W	6-phosphogluconolactonase SOL4	0.002262	0.071480
YML131W	Protein of unknown function	0.002967	-
YKR076W	S-glutathionyl-(chloro)hydroquinone reductase	0.003412	0.035562
YDL243C	putative aryl-alcohol dehydrogenase	0.005133	-
YGR088W	catalase T	0.005402	-
YFL053W	dihydroxyacetone kinase	0.006326	0.024013
YBR244W	glutathione peroxidase GPX2	0.007829	0.015116
YGR224W	azole transporter	0.007841	-
YER067W	Rgi1p	0.008506	-
YFL014W	lipid-binding protein HSP12	0.012983	-
YMR173W	DNA damage-responsive protein 48	0.019120	0.069446
YFL056C	Putative aryl-alcohol dehydrogenase	0.023097	-
YDR171W	heat shock protein HSP42	0.023735	-
YNL194C	Integral membrane protein	0.026158	-
YDR256C	catalase A	0.028125	0.093993
YLR205C	Hmx1p	0.031368	0.011914
YDL204W	Rtn2p	0.035241	-
YGR008C	ATPase-stabilizing factor family protein	0.036289	-

Table 2. (continued)

YML128C	Msc1p	0.038967	-
YLR346C	Cis1p	0.045650	-
YHR139C	Sps100p	0.046043	0.054276
YDR533C	glutathione-independent methylglyoxalase	0.050285	-
YOL151W	methylglyoxal reductase (NADPH-dependent) GRE2	0.056597	0.040635
YGR035C	Putative protein of unknown function,	0.065623	-
YDL246C	L-iditol 2-dehydrogenase SOR2	0.071729	-
YKL070W	uncharacterized protein	0.095622	-
YLR136C	Tis11p	-	0.037149
YFR053C	hexokinase 1	-	0.050526
YBR047W	Fmp23p	-	0.054616
YMR011W	hexose transporter HXT2	-	0.072490
YJR005C-A	Lso1p	-	0.097781
YPR030W	Csr2p	-	0.098063

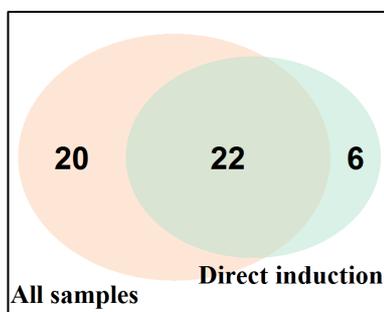


Figure 3. Venn diagram of the number of ORFs that are differentially expressed in aggregated list of all samples and the samples that were obtained from direct induction experiments with replicates.

To gain further insights on the functions of the aggregated list of genes, gene set enrichment analysis based on GO-terms was performed. Enriched GO-terms in the resulting gene set in terms of biological process and molecular function are presented in Figure 4a and 4b. Most overrepresented GO-terms are oxidative stress (30% of the genes), cellular response to chemical stimulus (36% of the genes) and oxidation-reduction process (40% of the genes) for both “all samples” and “direct oxidative stress method samples” lists.

Interestingly, 2 genes in both lists are annotated to be involved in glutathione metabolic process. Differences also exist in enriched GO-terms, in both lists. In direct induction list, 5 (out of 28) genes are annotated in chemical homeostasis and 2 genes are annotated in fructose/glucose transmembrane transport. In molecular function, similar GO-term landscape is observed. In “all samples list”, 14 genes are annotated in oxidoreductase activity, 2 genes in glutathione reductase activity. Lastly for cellular component, 60% of the ORFs were located in cytoplasm, 15% in cell periphery and 18% in plasma membrane. Further manual annotation using Yeast Genome (<https://www.yeastgenome.org>) website resulted in 16

manually curated GO-cellular component annotation, 8 in cytoplasm and 5 in nucleus.

To get more insight into gene sets, we further focused on the set of genes in two GO terms, (i) glutathione metabolic process (GO:0006749) and response to oxidative stress (GO:0006979), containing 19 ORF's and 125 ORF's respectively according to AmiGO. For those ORFs, the p -scores were plotted, showing the count of the samples that the specific ORF was differentially expressed (Figure 5). For glutathione metabolic process, 18 of the genes were found to be differentially expressed in more than two samples, but only two of them YKR076W (*ECM4*, differentially expressed in 18 samples) and YLL060C (*GTT2*, differentially expressed in 20 samples) were found to be significantly different in all samples. For response to oxidative stress, twelve of 125 genes were found to be significantly differentially expressed in all samples (average number of samples that these genes were found to be differentially expressed 16).

Upon aggregation, 28 genes were found to be significantly overrepresented in the lists of differential expressed genes from individual experiments. These genes are categorized as responsible for antioxidant capacity, oxidoreductase activity (acting on peroxide as acceptor, acting on a sulfur group of donors, and acting on NAD(P)H), peroxidase mechanisms, glutathione transferase activity, peroxidoredoxin mechanisms, heme binding and tetrapyrrole binding activities. The majority of the above stated functions are related to the electron transfers or mechanisms for reducing the oxidative stress.

These genes are further inspected in KEGG database to further probe their biological context. Significant hits are observed at longevity regulating pathway, carbon metabolism, tryptophan metabolism, fructose and mannose metabolism, protein processing in endoplasmic reticulum, glyoxylate and dicarboxylate metabolism, MAPK signaling pathway – yeast,

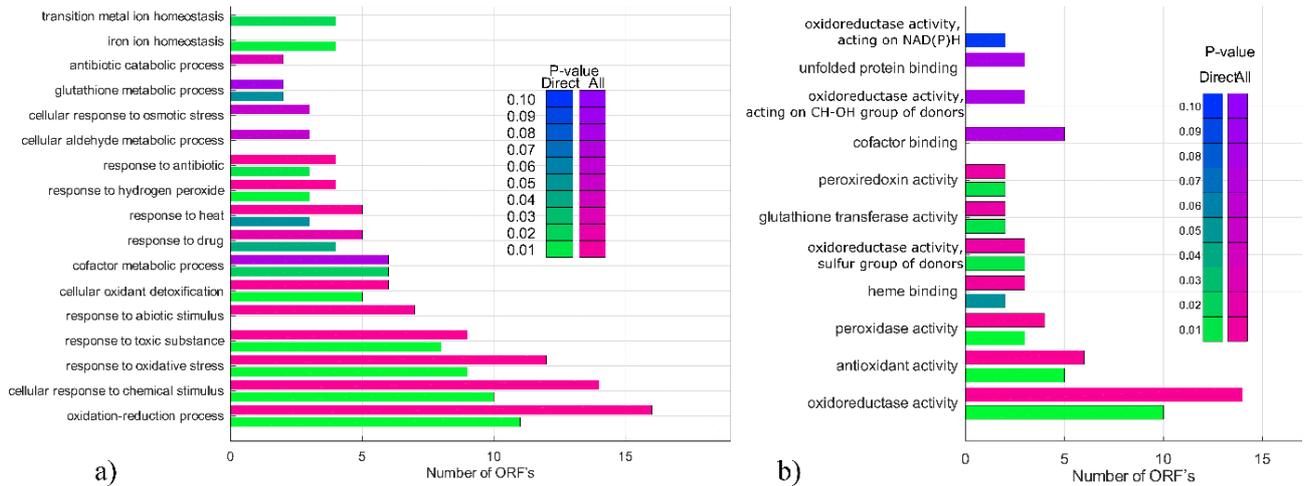


Figure 4. GO enrichment results for all list of samples which direct induction applied **(a)** GO-Bioprocess **(b)** GO-Molecular function.

peroxisome, pyruvate metabolism, pentose and glucuronate interconversions and propanoate metabolism. Interestingly, when the focused dataset (direct oxidative stress), carbon metabolism and fructose and mannose metabolism are the main hits metabolic pathways, especially with hydrogen peroxide-induced oxidative stress, aiming at increasing NADPH, an important cofactor in the oxidation reduction mechanisms (glutaredoxins, thioredoxins). Also, trehalose synthesis and synthesis of three enzymes

(glucose-6-phosphate dehydrogenase, transketolases and transaldolase) of pentose phosphate pathways induced (Godon et al., 1998) overall increasing NADPH levels.

Next to cofactor balances, oxidative stress also induces antioxidant defense mechanisms, a protein degradation pathway. Glutathione plays a role against oxidative stress in yeast both as a metabolite in non-enzymatic mechanisms and as a cofactor in enzymatic mechanisms (glutathione peroxidase, glutathione

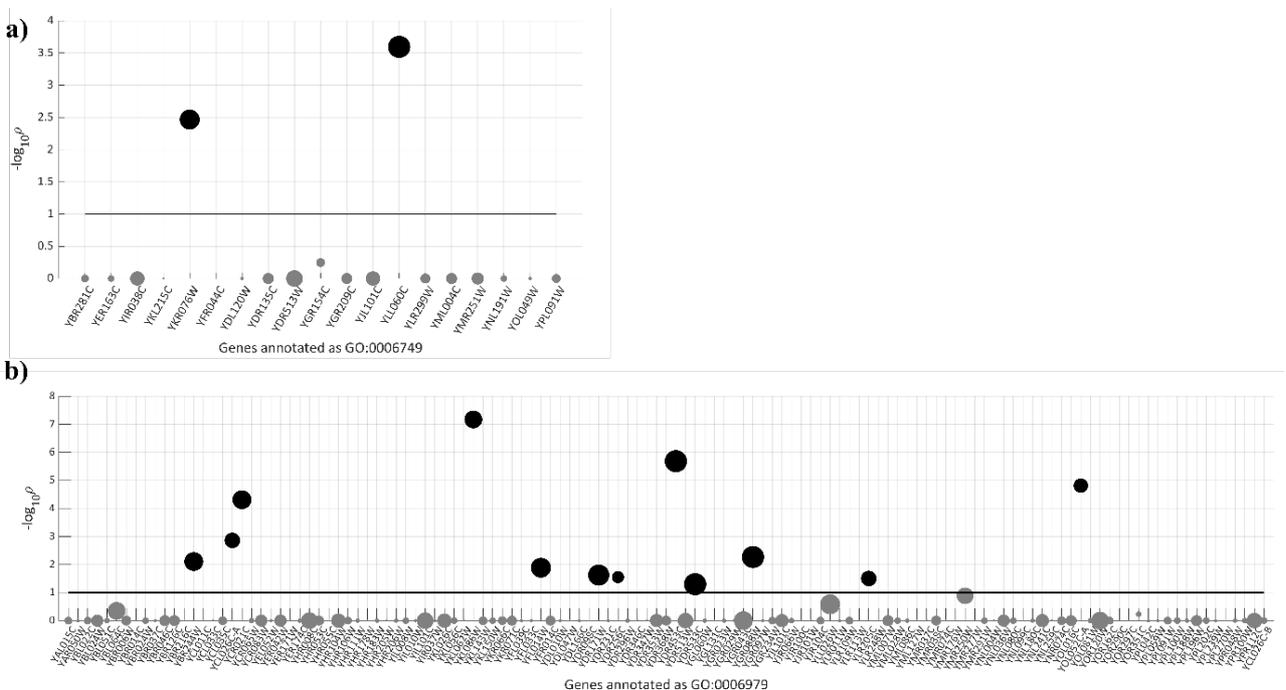


Figure 1. **(a)** Rank scores of ORFs involved in glutathione metabolic process. ORFs that differentially expressed were shown with black dots, line represents significance level ($\rho=0.1$) and marker sizes refer to number of samples that these ORFs were found to be differentially expressed. **(b)** Rank scores of ORFs involved in response to oxidative stress. ORFs that differentially expressed were shown with black dots, line represents significance level ($\rho=0.1$) and marker sizes refer to number of samples that these ORFs were found to be differentially expressed.

reductase (Douglas, 1987, Meister, 1988). The protein degradation via H₂O₂-induced oxidative stress causing oxidation of major proteins (pyruvate decarboxylase, fatty acid synthase, and glyceraldehyde-3-phosphate dehydrogenase (Tdh) are also separately reported in literature (Cabisco et al., 2000).

This work combines several datasets related to oxidative stress in yeast. It should be noted that a typical extension is a detailed analysis that would require careful grouping taking into account each stressor as well as corresponding (known) defense or response mechanisms and intracellular indicators (protein carbonylation, Thiobarbituric Acid Reactive Substances (TBARS) etc.). In selecting the datasets (Figure 2), we adopt a top-down approach and care is taken not to “over-slice” the data by too-detailed-subgrouping, allowing not to lose general features.

In performing meta-analysis studies, one expected pitfall is on dosage experiments, where the level of stressor triggers different or additional response/defense mechanisms. In that case, the ranking of a selected transcript will like change. However, considering nearly 6000 all genes in yeast, it would be highly unlikely to find such a finely tuned transcript that would be common key to all experiments due to robustness of metabolism. One specific transcript will be of key importance of that specific, isolated experiment, and is expected to be diluted over other experiments. In contrast, the transcripts in first couple of rows in Table 2 are found nearly always among top 20 differentially expressed genes.

Conclusion

Identification of key processes as a response to environmental stress is one of the key problems in biology, not only for our fundamental understanding but also to rational design of improved industrial strains and processes. Focusing on oxidative stress response, robust rank aggregation was performed to extract useful information from various experiments as individual experiments uses different techniques, have different agenda and are performed by different labs. This work strived for finding metabolic engineering targets for improved yields and productivities of industrially important microorganisms. Analysis underlined that key processes center around carbon, redox and glutathione metabolism and pointed interplay among those. In conclusion, this study illustrates bioinformatics analysis on capturing common features in a large, aggregated datasets and points to key common features and further metabolic engineering targets. Further investigation on distribution and possible redirection of metabolic fluxes allow further pinpointing key reactions.

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