RESEARCH PAPER

Transcriptomics based identification of multi-stress responsive genes in *Candida albicans* SC5314

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Abstract:
Candida albicans is a polymorphic fungus found as a commensal organism in the human microbiome. It causes opportunistic oral and genital infections in immuno-compromised individuals. The biotic and abiotic stress condition given to non pathogenic yeast alters morphogenesis in to pathogenic filamentous form. The knowledge on transcriptomic changes in *C. albicans* against immune stress is not fully understood yet. In this report, we used the available transcriptomic RNA-Seq data to investigate global transcriptomic changes under stress conditions equivalent to the host innate immune systems. Interestingly, we noted the critically regulated ~410 genes during immuno-inflammatory stress conditions. Impact of these genes on cellular and molecular function was annotated using GO slim mapper utility available in Candida Genome Database. The oxidative, nitrosative and cell wall damage stresses up regulates the expression of REDOX genes and down regulates the genes involved in filamentous growth and pathogenesis. The presence of serum mediates the transition of filamentous form into yeast form. Further a set of critical twenty five genes including GRX1, CHS1, ECM42, RPA135, THG1, FLU1, HGT13, IQG1, FAR1 and ARG4 were found to show differential expression under most of the stress conditions. The most fragile 25 genes were reported from this study should be marked as diagnostic or therapeutic markers to evaluate the *C. albicans* pathogenicity.
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1. Introduction:

Candida albicans is the most common opportunistic fungal pathogen in humans which causes candidiasis. Under normal circumstances, it can found in ~70% of healthy individuals (Hibino et al., 2009) and survives as a commensalic microbe and colonizes in human digestive tract, oral, skin and vaginal cavities (Kim et al., 2011; Tsai et al., 2013). Once commensalism is disturbed by impaired host defenses or alterations in the normal microbial flora, *C. albicans* is capable of causing a wide range of diseases by invading and damaging underlying tissues (Grubb et al., 2008; Merenstein et al., 2013). *C. albicans* infections are commonly present in immuno-compromised individuals, including HIV-infected patients, transplant recipients, cancer patients undergoing chemotherapy and low-birth (Cheng et al., 2012). *C. albicans* causes oral and vaginal thrush and deep-seated life-threatening infections such as disseminated candidiasis (Sharon et al., 2010; Sobel et al., 2015). Factors like adherence to host cells, secretion of hydrolytic enzymes such as proteases (Naglik et al., 2003), phospholipase (Knight et al., 2005), sequestration of iron (Knight et al., 2005), mechanisms for survival within phagocytes (Lewis et al., 2012), yeast-filamentous morphogenesis and phenotypic switching (Shareck et al., 2011) contribute the pathogenesis in *C. albicans*.

The yeast-filamentous transition is important for invasion into epithelial and endothelial cell layers which causes lysis of macrophages and neutrophils (Vonk et al., 2012). These transitions occur in response to a multiple inflammatory condition present in the host, such as high temperature, presence of serum (Feng et al., 1999), basic pH (Davis et al., 2003) and certain carbon sources such as N-acetyl glucosamine (Carlisle et al., 2013). A complex transcriptional circuitry changes the morphogenesis of yeast to elongated filamentous cells and this tightly linked to virulence of *C. albicans* (Mayer et al., 2013). A complex transcriptional circuit ensures the growth of *C. albicans* in multiple tissues with vast different pH values and it also makes resistant to ROS/RNS species in immune system (Jiménez-López et al., 2013).

RNA-Seq is one of the next generation transcriptomic profiling method to study the global expression pattern of genes from cells, grown under different experimental conditions (Linde et al., 2015). The transcriptome of *C. alibicans* str. SC5314 was comprehensively characterized under six different *in vitro* conditions such as hyphae inducing, high oxidative, low oxidative, nitrosative, cell wall damage–inducing and different pH conditions (Bruno et al., 2010). They have identified 602 newly identified transcriptionally active region (TAR) and 41 new introns from the transcriptomes of *Candida* in the above six conditions. Above report was failed to report mRNA expression changes associated with environmental stress. These six environmental stress conditions mimic the condition of *C. albicans* facing under the course of an immune response against the infection. We intend to identify the stress responsive genes of *C. alibicans* and their expression pattern in response to host immune conditions using global RNA-Seq data.

2. Materials and Methods:

2.1 Retrieval of RNA-Seq from NCBI SRA:

The SC5314 transcriptomic sequence data was retrieved from NCBI Sequence Read Archive (http://www.ncbi.nlm.nih.gov/sra) under accession no. SRP002852. Totally 10 sets of sequences were obtained with 2 replicates with different stress conditions such as hyphae inducing conditions [SRX025741, SRX025740,SRX025582, SRX025581] (YPD plus 10% fetal calf serum [FCS] vs. YPD alone), tissue culture medium buffered to different pH's [SRX023465, SRX023464, SRX023462] (M199 media buffered to pH4 vs. pH8), high oxidative stress [SRX023476, SRX023466] (YPD +5mM H2O2 vs. YPD alone), low oxidative stress [SRX023470,SRX023471, SRX023467] (YPD + 0.5 mM H_2O_2 vs. YPD alone), nitrosative stress [SRX023516, SRX023515, SRX023483, SRX023482] (YPD+ 1mMDPTA-NONOate vs. YPD alone) and cell wall damage–inducing conditions [SRX023481, SRX023480, SRX023479] (YPD + 100 mg/mL Congo Red vs. YPD alone).

2.2 Differential gene expression analysis:

The transcriptomic data was analyzed using DNASTAR Lasergene software package v11 (Burland, 2000). Advanced options were used to map the transcript sequences with complete SC5314 chromosomes downloaded through automated scripts available in the package and differential expression of genes were analyzed with their respective control RNA Seq data. The differential expression profile (Heat-Map) was generated using dChip (http://www.dchip.org/) with default parameters (Li, 2008).

2.3 Annotation and classification of genes:

We used *Candida* genome database to assign GO (http://www.candidagenome.org/) terms for annotating the sequences. The Gene Ontology slim mapper utility available in CGD was used to annotate the function of genes based on the biological process, molecular function and cellular component with default parameters based on GO category (Inglis et al., 2012).

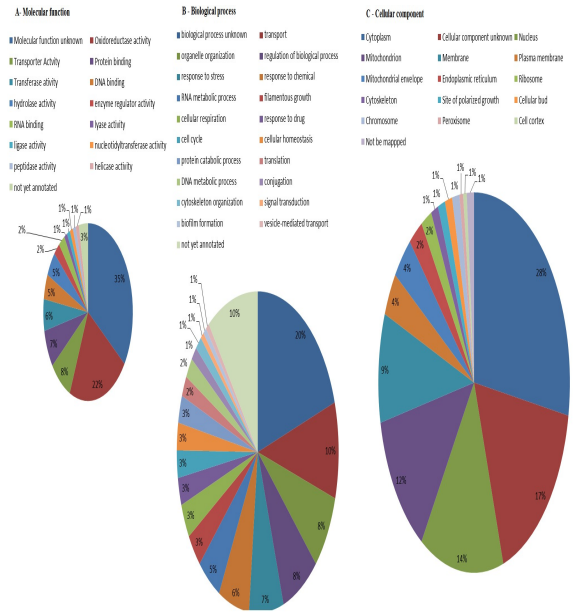

Figure 1: The Up regulated genes (more than 3 fold) were grouped by Molecular function based on *Candida albicans* Gene ontology annotation. Percentages of functions are listed for each category. Because a single gene may have more than one functional annotation, the gene counts do not add up to the total number of analyzed genes.

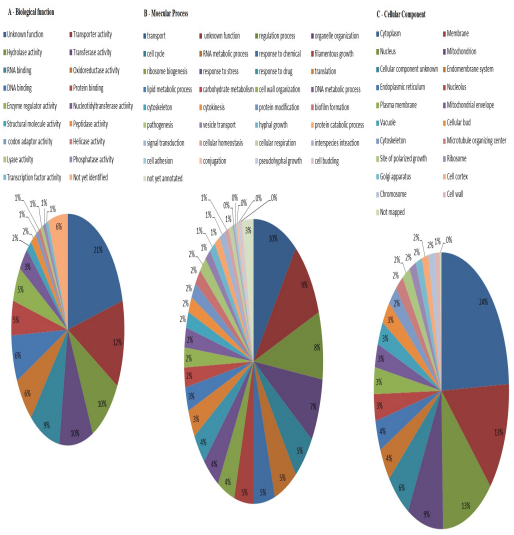

Figure 2: Gene ontology mapping and functional annotation of critically down regulated genes (more the 3 fold). Percentages of functions are listed for each category. Because a single gene may have more than one functional annotation and the gene counts do not add up to the total number of analyzed genes.

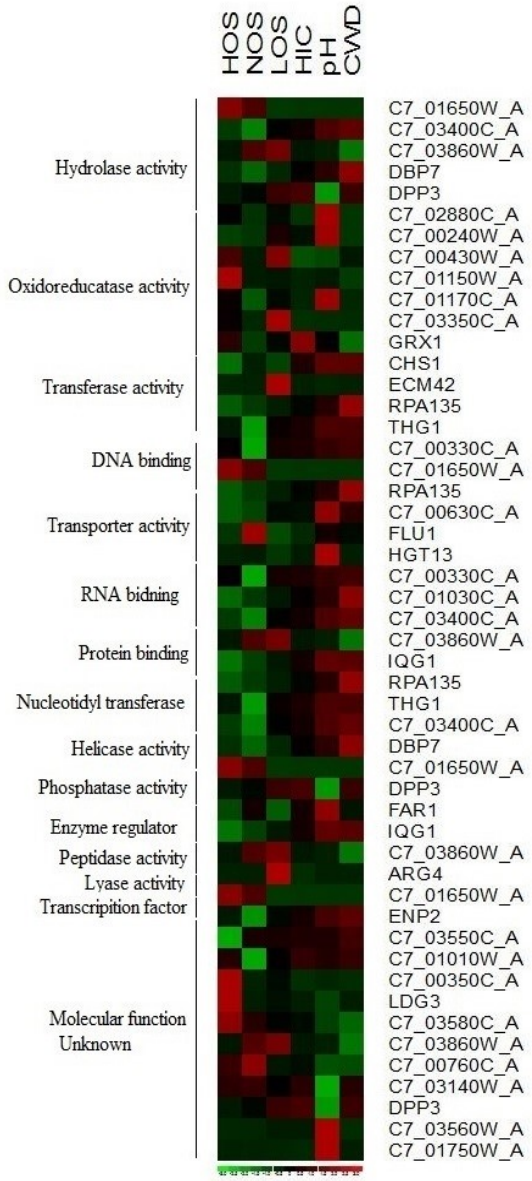

Figure 3: Heat map showing transcriptomic profile of the twenty five fragile genes obtained from oxidative, nitrosative, cell wall damage, alkaline pH, presence of serum conditions. Up regulation: red colour; down regulation: green colour.

Experimental type	Total No. of Differentially Expressed genes	Up regulated (>=3 fold)	Down regulated (>=3 fold)
High-oxidative	412	33	61
Low-oxidative	411	22	21

Nitrosative	410	34	52
Congo-red-normal	412	14	12
pH8-pH4	407	9	21
YPD-serum	419	6	5

Table 1: List of differential expressed genes during multiple stress condition. Approximately ~410 genes are differentially regulated in various stress condition. Numbers of genes which are more than 3 fold up and down regulated in high-oxidative stress and nitrosative stress condition are more than other stress condition, which suggest that gene pool alteration, is high in those two conditions. Whereas in serum containing medium differential regulation above and below 3 fold lesser than other condition.

S_No	**Accession_id%**	**GO-Molecular function***	**GO-Biological process$**
1	C7_01650W_A	Contribute RNA polymerase III type 1 promoter sequence-specific DNA binding	5S class rRNA transcription from RNA polymerase III type 1 promoter
2	C7_03400C_A	ATP-dependent 3'-5' RNA helicase of the DEAD-box family	nuclear polyadenylation-dependent mRNA catabolic process
3	C7_03860W_A	serine-type endopeptidase activity	RNA catabolic process
4	DBP7	Putative ATP-dependent DEAD-box RNA helicase	maturation of LSU-rRNA from tricistronic rRNA transcript (SSU-rRNA, 5.8S rRNA, LSU-rRNA)
5	DPP3	diacylglycerol diphosphate phosphatase activity	farnesol biosynthetic process
6	LIP9	triglyceride lipase activity	lipid catabolic process
7	PHM5	endopolyphosphatase activity	polyphosphate catabolic process
8	C7_00240W_A	oxidoreductase activity	oxidation-reduction process
9	C7_00430W_A	ferric-chelate reductase activity	copper ion import, iron ion import
10	C7_01150W_A	oxidoreductase activity – ferrous iron binding	cellular aromatic compound metabolic process
11	C7_01170C_A	oxidoreductase activity	oxidation-reduction process, cellular response to drug
12	C7_03350C_A	alpha-keto amide reductase activity	cellular amide metabolic process, cellular aromatic compound metabolic process
13	GRX1	protein disulfide oxidoreductase activity	cell redox homeostasis
14	CHS1	chitin synthase activity	cell septum assembly, fungal hyphal growth
15	ECM42	Ornithine acetyltransferase	arginine biosynthetic process
16	RPA135	Contributes to RNA polymerase I activity	transcription of nuclear large rRNA transcript from RNA polymerase I promoter
17	THG1	tRNA guanylyltransferase activity	magnesium ion binding, tRNA guanylyltransferase activity
18	C7_00330C_A	single-stranded telomeric DNA binding activity	regulation of translational fidelity
19	C7_00630C_A	amino acid transmembrane transporter	amino acid transmembrane transporter

		activity	activity
20	FLU1	Multidrug efflux pump of the plasma membrane	fluconazole transport, cellular response to biotic stress
21	HGT13	glucose transmembrane transporter activity	carbohydrate transporter
22	C7_01030C_A	mRNA binding	Biological process un known
23	IQG1	Ras GTPase activator activity	actomyosin contractile ring assembly – mitotic cytokinesis
24	FAR1	cyclin-dependent protein serine/threonine kinase inhibitor activity	pheromone-dependent signal transduction involved in conjugation with cellular fusion
25	ARG4	Argininosuccinate lyase	arginine biosynthetic process

[%] Accession ID for genes in Candida Genome database. [*]GO ontology for molecular function and [$]GO ontology for biological process based on the GO Slim mapper.

Table 2: List of critical genes found to be differentially expressed under multiple stress conditions: The genes were identified by the RNA-Seq analysis through DNASTAR software and CGD GO Slim mapper with possessing significant differential expression (P-value>0).

3. Results:

3.1 Differential gene expression:

The transcriptomic changes were analyzed from the RNASeq data using DNASTAR Lasergene package. Total reads of RNA-Seq data were mapped against *Candida* SC5314 genome. The differential expressions of stress associated genes were identified and number of differentially expressed genes for each condition was listed on Table 1. ~410 genes were found to be differentially regulated under each condition, in which each experimental condition exhibit varying magnitude of gene expression. The functions of the differentially expressed genes were annotated based on Gene ontology using GO slim mapper tool. Responses to stress, upregulated genes increases oxidoreductase, transporter, transferase and protein binding activities and also down regulated gene GO annotation are shown in Figure 2. We have identified 25 critical genes, which are expressed under multiple stress conditions (Table 2). The expression profile of 25 fragile genes were shown using Heat Map (Figure 3).

4. Discussion:

Conditions such as hyphae inducing, high oxidative, low oxidative, nitrosative, cell wall damage–inducing and different pH's mimic the innate immune system of host. These stresses were faced by the pathogen and their transcriptomic changes were discussed below.

4.1 Response to Oxidative Stress:

The innate immune system plays vital role in the primary line of defense against systemic *C. albicans* infections. Upon infection macrophages rapidly produce ROS to kill pathogen. *C. albicans* responds to high oxidative stress and transiently induces their transcriptional machinery. The genes differentially regulated under high oxidative stress were tabulated on Supplementary Table 1. Totally 412 genes were differentially expressed, among them 33 genes were up regulated & 61 were down regulated (cut-off >3 fold). The transport associated genes (C7_00430W_A, C7_01690W_A, C7_02460C_A, GYP7 and PFK2), cellular homeostasis (GRX1and ISU1), Cell cycle associated genes (C7_02460C_A, CDC34), RNA metabolism associated genes (ISU1, ZCF29) and vesicle mediated transport genes (GYP7) were up regulated. The cell cycle associated (C7_03850W_A, CLB4, SFI1) and stress associated (ERG5, PMT1) genes were down regulated. GRX1 (Glutaredoxins) and SOD3 (Superoxide dismutases 3) were highly up regulated to give defense function through catalyzing ROS and RNS. The notably down regulated genes are CHS1 (*Chitin synthase*) which is responsible for cell wall septum assembly and yeast-filamentous stage switch involving in pathogenesis (Munro et al., 2001). Then YOX1 gene was deeply down regulated (15 fold) and it act as transcriptional repressor to negatively regulate G1/S transition of mitotic cell cycle (Ofir et al., 2012). Cup9 was down regulated (>9 fold), which was responsible for repression of SOK1expression and indirectly mediates repression of yeast-hyphae switch (Lu et al.,

2014). Filamentous growth associated genes (LM01, ENA21, CLB4, ERG5, PMR1 and TOM40) were also down regulated during high oxidative stress condition.

C. albicans responds to low oxidative stress and differentially expresses 411 genes, in which 21 genes were down regulated and 22 genes were up regulated more than 3 fold (Supplementary Table 2). These genes were significantly induced under low oxidative condition to protect cells from lethal effects. Notably cell wall biogenesis (CHS1), transport (C7_02000C_A, C7_04140C_A, FLU1), cell cycle (CHS1, FAR1, IQG1), filamentous growth (CHS1, ERG5), signal transduction (FAR1, IQG1) and cytoskeleton organization (IQG1) genes were down regulated and stress responsive (C7_03350C_A, C7_03860W_A, DCC1, PSF1, RAD14, and ZCF29), RNA metabolism (C7_03860W_A, ISU1, ZCF29), DNA metabolism (DCC1, PSF1, RAD14), cytoskeleton organization (DCC1), filamentous growth (ZEF29), cell cycle (DCC1), interspecies interaction between organisms (ZCF29), conjugation (C7_03860W_A) and cellular homeostasis (ISU1) genes were highly induced.

4.2 Response to nitrosative condition:

Innate immune cells such as phagocytes and macrophages also produce RNS to defend against microbial pathogens (Missall et al., 2004). Upon the exposure of NO causes rapid induction of 410 genes and among them 35 genes were up regulated and 55 genes were down regulated (more than 3 fold). The RNA metabolic process (C7_00330C_A, C7_01210C_A, C7_02340C_A, C7_03400C_A, C7_03850W_A, DBP7, RPA 135, ENP1, ENP2, THG1and UTP18), transport (C7_00230W_A, C7_01360C_A, C7_01510W_A, C7_01660C_A,C7_02090C_A, C7_03590C_A, C7_03890C_A, C7_04200C_A, FLU1and TIM9), cell cycle (C7_00410C_A, C7_03850W_A, CHS1, DBF4, IQG1, NOP15, PSF3 and YOX1), organelle organization (BEM2, C7_00330C_A, C7_01360C_A, DBF4,IQG1, NOP15, OGG1and TIM9), response to chemical (C7_01360C_A, C7_03590C_A, C7_03850W_A, ENP2, FLU1, NRG1 and PRT1), response to drug (C7_01360C_A, DBF4, ENP1, NRG1, OGG1 and PSF3), filamentous growth (CHS1, CUP9, ENP1, LMO1and NRG1), cytokinesis (C7_00410C_A, CHS1, IQG1and NOP15), cytoskeleton organization (BEM2, IQG1 and NOP15), vesicle mediated transport (C7_01660C_A, C7_02090C_A and C7_03890C_A), protein catabolic process (C7_02860C_A, C7_03890C_A), cell wall organization (CHS1and LMO1), signal transduction (BEM2 and IQG1), biofilm formation (C7_00490C_A and NRG1), pathogenesis (CHS1and NRG1), pseudo hyphal growth (NRG1), cell budding (C7_00410C_A) and interspecies interaction between organisms (NRG1) genes were down regulated.

Genes encoding transport (C7_00430W_A, C7_04160W_A, FGR2, HGT12, PFK2), protein catabolic process (C7_03240W_A, C7_03860W_A, CDC34), response to stress (C7_03860W_A, FGR2, HGT12), filamentous growth (FGR2, HGT12), cell cycle (CDC34, FAR1), conjugation (C7_03860W_A, FAR1), carbohydrate metabolic process (PFK2), RNA metabolic process (C7_03860W_A), signal transduction (FAR1) and cellular protein modification (CDC34) genes were up regulated.

4.3 Response to Alkaline condition:

The environmental pH determines the morphology of *C. albicans.* At acidic pH, *C. albicans* grows in the yeast form; at alkaline pH, it grows primarily in the filament form. Alkaline-induced filamentation correlates with a number of physiological changes, such as alterations in cell wall architecture and adhesion properties (Davis, 2003). Totally 407 genes were differentially regulated among them nine genes were up regulated and 21 genes were down regulated (more than 3 fold) (Supplementary Table 4). Transport (ATP9/CM_00140C, PFK2), cellular homeostasis (CSA1), biofilm formation (CSA1) were down regulated. Filamentous growth (C7_03480W_A), response to stress (PRX1), cell cycle (FAR1), cellular respiration (MAM33), cellular homeostasis (PRX1), regulation of biological process (C7_03480W_A, FAR1, PRX1, TIM9), transport (FLU1, HGT13, TIM9) and conjugation (FAR1) were up regulated.

4.4 Response to serum:

Human serum promotes yeast-filamentous transition in *C. albicans;* presence of serum leads to progressive changes in the expression of virulence related genes as shown in Supplementary Table 5. Totally 419 genes were critically regulated among them six genes were up regulated and 5 genes were down regulated less than 3 fold. Cytosolic Manganese containing Superoxide Dismutase (*SOD3*) gene was responsible for the metabolism of superoxide radicals and protects against oxidative stress. The gene responsible for filamentous growth, C7_03480W_A (Shareck et al., 2011) was over expressed 4 fold during administration of serum. The cellular iron homeostatis regulating gene, GRX1 was up regulated 7 fold (Lan et al., 2004). FAR1 gene was up regulated more than 3.5 fold which is involved in the regulation of pheromone-mediated mating and cell cycle arrest (Cote et al., 2008).

4.5 Response to cell wall damage:

C. albicans was exposed with 100 mg/mL Congo Red and it inhibit Chitin polymerization leads to cell wall damage (Roncero et al., 1985). In which 412 genes were differentially regulated, among which 14 genes were up regulated and 12 genes were down regulated (cut-off >3 fold change) (Supplementary Table 6). Genes encoding Cell cycle (FMP45), regulation of biological process (GRX1), cell development (FMP45), pathogenesis (LIP8) and cell wall organization (FMP45) transcripts were down regulated. But, Ribosome biogenesis (C7_00160C_A, C7_04140C_A, DBP7, ENP2 and UTP18), transport (C7_00430W_A, C7_00630C_A, C7_04140C_A and MAC1), response to chemical (C7_04140C_Aand ENP2) , cellular homeostasis (MAC1) and biofilm formation (C7_00490C_A) genes were up regulated.

4.6 Cumulative stress response in *C. albicans:*

All the stress responses were shown roughly with similar number of differentially expressed genes, but each stress response have unique pattern of gene expression. We have identified ~25 differentially expressed genes in six diverse pathogenic conditions (Table 2); which could be the transcriptomic response of *C. albicans* against biotic and abiotic stresses. These twenty five genes are C7_01650W_A, C7_03400C_A, C7_03860W_A, DBP7, DPP3, LIP9, PHM5, C7_00240W_A, C7_00430W_A, C7_01150W_A, C7_01170C_A, C7_03350C_A, GRX1, CHS1, ECM42, RPA135, THG1, C7_00330C_A, C7_00630C_A, FLU1, HGT13, C7_00330C_A, C7_01030C_A, IQG1, C7_01650W_A, FAR1 and ARG4. Most of the multiple stress responsive genes were involved in the Oxidoreductase activity such as C7_00240W_A, C7_00430W_A, C7_01150W_A, C7_01170C_A, C7_03350C_A and GRX1. Interestingly, four biofilm forming genes [C7_00490C_A, CSA1, NRG1, and PMT1] were down regulated which indicate the significance of biofilm formation in stress management.

Conclusion:

C. albicans exhibits the transient induction of genes during various environmental conditions. Stresses like oxidative, nitrosative, cell wall damage, alkaline pH and presence of serum conditions mimic the *in vivo* innate immune system. These stress conditions differentially express more the 410 genes and many of the induced genes were linked to cell survival. However, *C. albicans* exhibits unique stress responses against each stress, but some of the genes were induced commonly, which exhibits the coordinate induction among set of genes in response to multiple stresses. Comparison of transcriptomic responses against the multiple stresses has identified twenty five critical genes such as GRX1, CHS1, ECM42, RPA135, THG1, FLU1, HGT13, IQG1, FAR1 and ARG4 were playing vital role in the pathophysiology of *C. albicans*. These genes may be involved in the coordinated cell stress responsive pathways. The ability of *C. albicans* to have dynamic yeast-filamentous transition was repressed during oxidative, nitrosative and cell wall damaging conditions. This study highlights the differential expression behaviors of *C. albicans* genes in response to various stresses and this profiling has identified novel fragile genes. Those novel fragile genes were expressed under most of the unfavorable conditions and such genes were proposed as important stress responsive genes. Those genes might be targeted for diagnostic and therapeutic purposes.

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