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Insights into Responses to Extreme Environmental Conditions in Humans from Studies on *Saccharomyces cerevisiae*

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ABSTRACT

The versatility of the yeast experimental model has aided in innumerable ways in the understanding of fundamental cellular functions and has also contributed towards the elucidation of molecular mechanisms underlying several pathological conditions in humans. Genome-wide expression, functional, localization and interaction studies on the yeast *Saccharomyces cerevisiae* exposed to various stressors have made profound contributions towards the understanding of stress response pathways. Analysis of gene expression data from *S. cerevisiae* cells indicate that the expression of a common set of genes is altered upon exposure to all the stress conditions examined. This common response to multiple stressors is known as the Environmental stress response. Knowledge gained from studies on the yeast model has now become helpful in understanding stress response pathways and associated disease conditions in humans. Cross-species microarray experiments and analysis of data with ever improving computational methods has led to a better comparison of gene expression data between diverse organisms that include yeast and humans.

Keywords: *Saccharomyces cerevisiae*, gene expression, environmental stress response, cross-species microarray

1. INTRODUCTION

All organisms respond to stress by the induction of both systemic and cellular stress response functions to maintain cellular homeostasis leading to adaptation to the stressor(s). Stress response functions can however act effectively within a limited range of stress exposure. Chronic exposure to extreme stress conditions often leads to organ overload followed by organ malfunction and systemic failure. A possible explanation for the above phenomenon in some stress exposure scenarios may lie in the "overshooting" of stress response functions[1]. The inherent flexibility of gene expression patterns lends itself to alterations, sometimes long term during exposure to stressful environments. Long-term changes in gene expression induced by acute or chronic exposure to environmental or psychological stress often lead to pathological conditions.

The model eukaryote *S. cerevisiae* offers a versatile experimental system to study stress response due primarily to its small genome, well characterised genetics of the system, availability of gene deletion mutants, genome wide tagged clones, amenability to experimentation and simple growth conditions. Consequently, *S. cerevisiae* cells have been used to study stress induced gene expression patterns. The availability of *S. cerevisiae* gene deletion library wherein all non-essential genes are deleted has allowed genome-wide functional and fitness studies in *S. cerevisiae*. Studies on protein localisation have made use of the yeast library of tagged clones. In addition, global studies on protein-protein interaction have led to the construction of the yeast interactome. Genetic screens have been devised in yeast to clone genes associated with human disease conditions so that detailed mechanistic studies may be carried out on the cause, effect and efficacy of drugs for the treatment of such conditions.

Given the above wealth of information garnered from studies on yeast and unavoidable human exposure to stress, it was both logical and imperative to examine if it was applicable to humans both for a better understanding of stress response and associated disease conditions and for devising methods for improvement of human performance under stressful conditions. While evolutionary divergence precludes a one on one correlation of yeast and human data, modern day cross-species microarray experiments and analysis using sophisticated computational methods have yielded promising results.

In this review, we have summarised the advances in genome-wide expression studies in response to various environmental stress conditions in *S. cerevisiae*. We have also touched upon genome-wide functional studies in yeast and discussed its relevance to humans. The essence of cross-species microarray experimentation and analysis which is essential in applying the knowledge obtained from studies on a simple eukaryote to higher organisms has also been discussed.

2. THE COMMON STRESS RESPONSE PATHWAY IN *S. CEREVISIAE*

2.1 The Environment of Yeast Cells

Unicellular organisms like yeast are exposed to extreme environmental conditions because such organisms do not have

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the essential homeostatic mechanisms present in multicellular organisms to control environmental fluctuations of various factors that include temperature, extra-cellular redox state, nutrient levels, acidity, osmolarity, toxic agents and radiation. Higher eukaryotes have evolved mechanisms that are able to regulate/buffer several such conditions via systemic responses and cell-cell communication.

2.2 Early Responses: Modification and Degradation

Changes that occur immediately following exposure to environmental stress are essentially directed towards the activation of (1) processes that affect late changes and (2) processes that ensure rapid clearance of damaged cellular macromolecules. Covalent modification and consequent activation of signal transducers ensures commencement of late phase changes while activation of the Ubiquitin proteasome system (UPS) ensures degradation of proteins damaged by environmental stress. The UPS is one of the major pathways for the degradation of damaged or misfolded proteins[2,3] and is essential for cell survival under stressful conditions. Covalent modification of UPS components particularly the phosphorylation status of Ubiquitin conjugating enzyme 1 (Ubc1) has been shown to influence tolerance to thermal and reductive stress in *S. cerevisiae*[4]. Homologous recombination is another cellular process that is induced at early time points in *S. cerevisiae* following exposure to cobalt chloride - a hypoxia mimetic agent[5].

2.3 Late Phase: Transcriptional Changes[6]

Long term effects involve transcriptional changes. Studies on the yeast *S. cerevisiae* have contributed towards understanding the molecular basis of response to different stressors. Following its discovery in Drosophila, experiments in yeast cells further established that exposure to heat shock conditions leads to the rapid induction of a large group of genes encoding heat shock proteins (Hsps) that are necessary for the stabilisation of cellular proteins and renaturation of proteins denatured during exposure to thermal stress[7]. Hsps may also functions as regulators of enzymatic activity through their chaperoning function; as exemplified by the regulation of Plasma membrane H^+-ATPase (Pma1) activity by Hsp30 during exposure to thermal stress in *S. cerevisiae*[8]. Continuing investigation has revealed insights into the mechanisms that the yeast *S. cerevisiae* uses to adapt to diverse environmental conditions. Yeast cells gain cross protection against different stresses i.e., cells exposed to a sub-lethal dose of one stressor become resistant to a lethal doses of other stressors[9,10]. This observation suggested that a general stress response mechanism is activated in yeast cells in response to a multitude of environmental stress conditions. The above idea was further substantiated by the fact that 'heat shock' genes were induced by numerous other stress conditions in addition to heat shock[11-12]. More recent microarray studies have demonstrated that yeast cells elaborate a common transcription program termed the ESR in response to a wide variety of stress conditions[13-15]. In *S. cerevisiae* this response involves roughly 900 genes, of which 600 genes are down-regulated and 300 genes are up-regulated. The down-regulated genes code for functions required for cell growth, RNA metabolism, and protein synthesis. Of the up-regulated genes only 40 per cent are functionally characterized; they encode functions in carbohydrate and fatty acid metabolism, metabolite import and export, homeostasis of cellular redox potential, quenchers of Reactive Oxygen Species (ROS), autophagy, molecular chaperones and UPS components, cell wall integrity, DNA-damage repair, vacuolar and mitochondrial functions, signal transduction pathways and other activities.

2.4 Alterations in Energy Metabolism under ESR[16]

In a stressful environment, glucose is metabolised by four different pathways in *S. cerevisiae* namely, trehalose synthesis, glycogen synthesis, catabolism of glucose through glycolysis, and NADPH regeneration by the pentose phosphate pathway. The expression of most of the genes encoding glycolytic and gluconeogenic enzymes remain unaltered during environmental stress. However, genes encoding both the synthesis and degradation of the key regulator of glycolysis namely, fructose 2, 6-bisphosphate were induced. Similarly, most of the genes involved in fatty acid metabolism were unaffected by environmental stress; but genes encoding peroxisomal import and export of fatty acids were induced. The above i.e., the induction of genes encoding both anabolic and catabolic regulators as well as those required for both import and export of cellular metabolites appears to be a general theme is stress induced alterations in gene expression; this probably allows rapid environmental regulation of glucose and fatty acid utilization without affecting all the genes of the pathway. In addition, energy expenditure in cells is reduced during exposure to environmental stress by the down-regulation of processes that use ATP e.g., proton pumps[8] and other active transport processes; this probably compensates for the increased ATP usage by stress proteins namely Hsps that require ATP for their function.

2.5 Response to Cold Stress

Response to cold stress in *S. cerevisiae* is essentially biphasic. The early phase response is directed towards counteracting the effect of low temperature on membrane fluidity and nucleic acid base pairing. The above induces fine-tuning of membrane fluidity and causes destabilization of RNA secondary structures; the later allows efficient mRNA translation. The late phase involves the ESR, it has been hypothesised that it is induced by the altered physiological state of the cell caused by low temperature induced down-regulation of a number of cellular processes that include transport of nutrients into the cell, clearance of misfolded proteins from the intracellular milieu, and enzyme activities. In addition to the ESR, low temperature specific mechanisms are also induced in response to cold stress[17].

2.6 Response to High Hydrostatic Pressure

High hydrostatic pressure **(**HHP) affects macromolecular structures. HHP reduces fluidity of lipid molecules in the membrane; it induces conformational changes in DNA to

convert it from the more common B-form to the denser Z-form and induces protein denaturation and reversible dissociation of protein complexes[18]. As a consequence of alterations in DNA conformation, DNA-protein interaction is perturbed which may influence processes that require DNA-protein association e.g., chromatin structure, replication, transcription, cell cycle progression and other associated processes. Genome wide expression studies in *S. cerevisiae* cells exposed to HHP indicated that most of the up-regulated genes code for functions in carbohydrate metabolism and stress response functions. Given that HHP induces cell cycle arrest it was not surprising that the down-regulated genes code for proteins involved in cell cycle progression and protein synthesis[18]. The indicated studies also revealed that pressure-shock specific genes were also induced[19].

2.7 Response to Low Shear Modelled Micro-Gravity Environment

It is well established that gravity plays an important role in the normal developmental process in higher eukaryotes and plants. Gravity affects embryonic development, it influences the immune system and affect cell-cell attachment. Low shear modelled micro-gravity environment **(**LSMME) created in rotating suspension culture bioreactors allows investigation on the effects of microgravity on eukaryotic cells. Genome wide expression analysis in cells grown in rotating suspension cultures altered the expression of a large number of genes (1372); 26 per cent of the genes that were either induced or repressed during the said exposure fall into the ESR category, the rest 74 per cent probably reflect functions exclusive to micro-gravity[20]. Interestingly, exposure to micro-gravity environments affected cell polarity and bud formation in *S. cerevisiae*. The above studies on the effect of microgravity in microorganisms may provide critical insights into alterations in cellular functions in higher eukaryotes during space flights.

2.8 Response to Hypoxia[21]

Response to hypoxic conditions in yeast is for the most part mediated through a DNA binding transcription factor Rox1. Under normoxic conditions, Rox1 represses the expression of genes that are required for cell survival in a hypoxic environment by binding to the low oxygen response elements (LORE) in the promoters of said genes to repress their expression. Hap1 and Hap 2/3/4, two heme containing proteins are required for the expression of Rox1. During hypoxia Hap1 and Hap2/3/4 are inactivated (since heme biosynthesis is inhibited in the absence of O_2) leading to the down-regulation of Rox1 which results in the de-repression of hypoxic genes. Other than Rox1p, several transcription regulators are reported to be involved in response to hypoxia in yeast e.g., activators Sut1, Mot1 and Upc2 and repressors Mox1, Mox2 and Mot3. Transition metals such as cobalt and nickel appear to mimic hypoxic condition and induce the expression of several hypoxia regulated genes. The expression of certain genes e.g., *YLR162W* renders *S. cerevisiae* cells susceptible to the hypoxic conditions induced by cobalt chloride[22].

3. GENOME-WIDE FUNCTIONAL STUDIES IN YEAST

One of the major advantages of the yeast system is its high experimental manipulability and the availability of gene deletion libraries encompassing all non-essential genes in both haploid and diploid backgrounds; this has lead to genome-wide functional studies in yeast that is almost impossible to perform in other organisms or with cells in culture[23]. The functional studies mainly include studies on drug sensitivity and survival of the mutant strains exposed to environmental conditions. In the drug-induced haploin sufficiency screen, a library of diploid yeast cells deleted in only one copy of all the genes is tested for sensitivity to drugs; in essence it determines which gene when present as a single copy (as opposed to two copies in the wild type diploid) renders cell sensitive to the experimental drug. Such experiments are useful in determining the mechanism of drug action[24]. Global synthetic lethal interaction screens performed in yeast cells are able to identify mutations that render cells non-viable when present together but do not affect cell viability when present individually. Given that mutations are an integral part of cellular transformation, the discovery of a synthetic lethal interaction of the mutation present in cancer cells would indirectly identify a molecular target for the development of anti-cancer drugs[25]; this involves the designing or screening of drugs that would render the wild type interaction partner to be inactive. In addition, global analysis of protein localisation using GFP (Green Fluorescence Protein) tagged proteins in *S. cerevisiae* and has led to a better understanding of protein-protein interaction in yeast resulting in the genesis of the yeast interactome[26].

The volume of research done on yeast biochemistry and cell biology has contributed substantially towards Gene Ontology (GO) annotations covering biochemistry and cell biology[27]. Thus, research on the yeast system has aided in the validation of the modern day microarray data. In addition to the above, understanding fundamental mechanisms involved in the inheritance of complex loci have also begun in yeast. In humans, inheritance of traits associated with disease conditions cannot be attributed to one or a few genes. Although several common polymorphisms have been associated with disease conditions and susceptibility to environmental conditions, they are unable to account for the observed inheritance. The yeast system has contributed substantially in this regard as well. A comparison of two strains of yeast from two different genetic backgrounds by Brem[28], *et al*., showed that 'gene expression' - the trait, exhibits complex inheritance.

4. YEAST *vis-à-vis* HUMANS

The most important factors to consider before embarking on a comparative analysis of stress-induced gene expression data from yeast and humans is that humans are enormously more complex multicellular organisms with cells dedicated to specialized functions; different cell types communicate with one another and systemic functions play an important role in homeostasis. Furthermore all cell types in humans are not exposed directly to environmental stress. Thus, in contrast to unicellular yeast and bacteria, human cells do not have general stress response functions. Stress response gene expression programs in humans have been studied in different cells in

culture exposed to a multitude of stress conditions[29]. It is quite possible that the cultured cells are already in stress and hence do not elaborate a significant general stress response. Several generalities have however evolved from studies on human cells in culture. There appears to be no ESR in human cells exemplified by the induction of very few genes (only three genes) in human cells in culture upon exposure to multiple stressors. Under similar conditions yeast cells showed altered expression of 800-900 genes as part of the ESR. Exposure to heat shock, reductive and oxidative stress and stationary phase altered the expression of only 25 genes in human cells in culture. The number of genes that responded to a single stressor in human cell cultures was much higher (123) which was however considerably low when compared to the number in yeast cells (1042). As observed in yeast cells, stress response in human cell lines is also biphasic. Of a total of 83 early response genes, 36 encoded transcription factors and 57 encoded molecules involved in signal transduction pathways. Genes that are induced late, encode a variety of functions e.g., secretion, lipid metabolism, proteins required for protection against oxidative and reductive stress, transcription factors that activate cellular response to extracellular stress (ATFs 2,3 and 4), inhibitors of cell cycle progression and DNA damage repair proteins. The expression of about 1000 genes was reduced after multiple stresses. These genes code for a wide variety of functions required for cell growth, proliferation and cell-cell communication. They include components of the cytoskeleton, proteins necessary for nutrient uptake, metabolic enzymes, elements of signal transduction pathways, transcription factors, proteins required for RNA synthesis and maturation, translation factors, components of the UPS system, constituents of the secretory pathway and cell cycle regulators[29].

Studies on global transcription response to stresses in human cells in culture have resulted in several important conclusions as follows;

i. Responses to extracellular stress are specific to cell type and nature of the stressor. For e.g., HeLa cells and fibroblasts express different sets of genes during exposure to multiple stress conditions. For e.g., genes that code for proteins required for cell adhesion are usually expressed at higher levels in fibroblasts compared to HeLa cells but are repressed following exposure to multiple stressors in the former but not in the later. The above probably reflects the specialised functions of the indicated cell types[29].
ii. A role of cell-cell communication in stress response - suggested by the observation that gene expression in cultured cell following exposure to stress was different from those in organs isolated from animals following exposure to similar conditions[29,30].
iii. The apparent absence of a strong ESR in cultured humans cells may be attributed to (a) cultured cells are already stressed and hence it has not been possible to detect signals over the background and (b) studies on cultured cell do not necessarily reflect the *in vivo* situation.
iv. Expression of genes encoding proteins required for general cell growth, proliferation and maintenance are down-regulated in humans by multiple stress conditions as observed in yeast cells.

5. CROSS-SPECIES COMPARISON OF MICROARRAY DATA

From the above discussion it is clear that a direct comparison of gene expression data not only between yeast and human but also between other species would lead to a better understanding of stress response and stress related pathology in humans. Such analyses have become feasible since biological systems in general function in very similar ways in diverse organisms and genes participating in these systems are sometimes conserved across species[31] or have appropriate orthologs. Cross species analyses of sequence, expression and interaction data rely heavily on computational methods which however is a challenging task since comparison of microarray data across species poses several problems arising from the following:

i. The differences in microarray data from different laboratories,
ii. The inherent differences between systems to be compared, for e.g., while the general and regulatory events that control the yeast and human cell cycle are similar their durations are different. The doubling time of yeast cells is 90 min compared to 24 h for human cells.
iii. The differences in analytical methods used to analyze microarray data.

Cross-species gene expression analysis is in the process of being developed, although several important studies have been performed that elucidate gene expression patterns and interaction networks aimed at the identification of evolutionarily conserved core regulatory elements in biochemical pathways/ physiological processes, it is yet to contribute substantially towards the understanding of cellular stress response mechanisms.

Cross-species analysis of gene expression data constitutes of co-expression meta analysis and expression meta analysis. In the former analysis is performed with genes co-expressed across species. In one experiment, gene expression across species ranging from bacteria to humans identified principles that govern gene expression - the level of induction was found to be proportional to the basal level of gene expression across all the species studied[32]. In another study using data from more than 3000 gene expression studies from evolutionarily diverse organisms were computed to investigate coexpression of genes involved in similar functions[33]. Results indicated that in most instances genes involved in similar functions were coexpressed. Other cross-species studies have concluded that highly connected genes coding for important cellular functions are usually conserved. In expression meta analysis, the expression of orthologous genes is analyzed[34]. Interpretations as to the similarity of expression of orthogenes across species differ significantly depending upon the method of analysis. A comparative analysis of gene expression data from over 50 mouse and human tissues did not find similarity in the expressions of orthologous genes by considering only genes that are expressed significantly in individual experiments. However, analysis of correlated expression showed considerably higher levels of similarity in the expression of orthogenes. Analysis of heat stress induced gene expression in mice, Drosophila, Arabidopsis, and yeasts, (*S. pombe* and *S. cerevisiae*) led to the

identification of genes that were expressed in all the organisms during exposure to the indicated stressor[34]. Investigation into Early Life Stress (ELS) in a cross-species experiment involving CD3+ cells from human cord blood, CD3+ T cells from blood of neonatal and juvenile *Macaca mulatta* (Rhesus monkey) and the prefrontal cortex of adult rats led to the identification of differential methylation of *MORC1* (MORC family CW-type zinc finger 1) in ELS[35].

The methods elaborated above uses microarrays that are specific for a particular species; it employs different probe sets which have different hybridization properties which add another level of complication in the comparison of data across species. To overcome the above problem, microarray for one species was used to determine gene expression of another species however; such experiments were limited to studies on the expression of orthologous genes only since orthogenes share sequence similarity. This method has been usefully applied to validate animal models of cancer by comparing expression of orthologous gene in the animal model with that in the primary tumour in humans. Following establishment of the model it has also been used in the screening of cancer drugs - gene expression is examined in animal models with transplanted tumours at various time points during the progression of the disease as well as during treatment with experimental drugs. In another strategy multi-species array which contains probes for orthologous genes for all the species that are to be compared are also being used. A comparison of gene expression in bovine, mouse and frog oocytes indicated that 8 per cent of the 3456 genes represented in a multi-species microarray are conserved in all the three species[36].

More recent approaches use a combination of the above methods wherein species specific arrays are used but the analysis is performed concurrently. Initially the method was used to study expression of cell cycle regulated genes. A comparison of such genes between two yeast species, plants and human led to the identification of only 1 per cent of orthologous genes that showed cell cycle dependent expression. More recent computational methods have indicated that the degree of conservation is higher than 1 per cent and stands at around 5-8 per cent.

Clearly advancements in computational methods and experimental design will lead to a better comparison of gene expression data across species and shed light on human gene expressions patterns, stress response and pathology.

6. FUTURE PERSPECTIVES

Based upon the stress induced gene expression results described above, maintenance of cellular homeostasis during exposure to environmental stress appears to be controlled by, transcriptional, translational, post-translational and finally systemic mechanisms. In this regard a comprehensive understanding of yeast cell stress response is and will be useful in interpreting large-scale gene expression data from other organisms. A better appreciation of stress response and stress related pathology in humans from microarray and functional studies on simpler organisms would require further cross-species gene expression experiments as well as improved computational methods.

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