PHILIPPINE INFORMATION TECHNOLOGY JOURNAL. VOLUME 1, NUMBER 1, FEBRUARY 2008

Energetic constraints in adaptive gene expression responses of yeast under environmental changes

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ABSTRACT

A successful adaptive response of yeast under stress requires the synthesis of protective molecules that help minimizing cellular damage. The amount and type of these molecules depends on the type of stress. We search for functional constraints that can explain fine tuning of gene expression under stress. For instance, under resource depletion, one may expect to find downregulation of the expression of large and abundant proteins, and upregulation of the expression of shorter proteins. Such a trend may be less evident if the stress does not compromise resource availability. In this work we analyze the existing data and find evidence that is consistent with economy in metabolism as an important pressure for shaping regulation of proteins synthesis in yeast stress response.

Keywords

Yeast; stress response; transcriptional changes; energetic constraints

1. HYPOTHESIS

We hypothesize that, for different types of stress, the pattern of regulation of gene expression is consistent with protein cost being an important selective pressure in the evolution of stress response. If the gene expression profiles (GEP) for stress responses are constrained by availability of energy and resources, one should expect:

a) Down-regulation of genes that are highly expressed under normal conditions and thus code for highly abundant proteins. By repressing these genes, the cell can significantly save resources that can then be used in the stress response [1]. For example, ribosomal proteins make for a large fraction of a cell's protein complement, and the resources invested in keeping pools of ribosomal proteins are high [2]. It is well known that the expression of ribosomal genes is significantly repressed under many different stress conditions.

b) Up-regulation will preferably occur in genes that have low expression levels under normal conditions. Although there is episodic evidence to sustain this pattern of correlation between protein abundance and changes in gene expression, a systematic study of this correlation for all yeast protein in different stress responses is still lacking.

These two trends are easy to rationalize if we think that, to cope a stressful situation, the cell would preferably up-regulate specific proteins that were not needed under basal conditions. Under such conditions, the cell can mostly down-regulate proteins that were already present at basal conditions and whose abundance was detectable.

Two additional trends can be expected:

c) Down-regulation of genes that code for large proteins. This is so because such a pattern would save resources to the cell.

d) Up-regulation will be found preferably in the expression of genes that code for small proteins. This would save resources and allow for faster protein synthesis.

2. MATERIALS AND METHODS

MIROARRAY DATA: Data from 223 published microarray experiments that measure changes in yeast gene expression under a battery of different environmental stresses have been used [3, 4]. The considered stress responses are: heat shock, menadione, peroxide of oxygen, DTT, diamide, acid, alkali, changes of C sources, NaCl, N and AA depletion, hypo- and hyper-osmotic stresses.

PROTEIN PROPERTIES: Protein properties and the list of protein complexes were obtained from the *Saccharomyces Genome Database* (SGD). Data for protein abundance in yeast growing exponentially in a rich medium was obtained from [5]. Categorization of protein function, biological process, and location was done using Gene Ontology (GO) terms provided by the SGD tool *Go Ontology Slim Mapper*.

MAXIMUM GENE EXPRESSION CHANGES: We identified the genes whose expression significantly changes under each stress condition and obtained the ratio of the changes in mRNA levels with respect the reference condition for up-regulated genes (Up-CF) and down-regulated genes (Down-CF). Changes in gene expression during stress response are dynamic and, for the most

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Conference'04, Month 1–2, 2004, City, State, Country.
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part, transient. We take the maximum amount of up-regulation or down-regulation of expression as an approximation of the measure of the change in the transient context of the stress response. To minimize the error in estimating changes in gene expression, for any given ORF ORF, we use quantile 98% of its change in expression.

3. RESULTS

3.1 Classification of environmental changes

As an overall measure of changes in gene expression under different types of stress with define an index y_{ij}, where i refers to stress condition *i* and j refers to all proteins changing expression that belong to the GO category *j*. This index is calculated as follows.

$$y_{ij} = \sum_{k=1}^{n} 1 - \left(UpCF_{ijk} \times L_{ijk}\right) - \sum_{k=1}^{n} 1 - \left(DownCF_{ijk} \times L_{ijk}\right) \qquad j = 1,...,25$$

where L_{ijk} is the length of protein k. We then cluster stress responses according to this index. Two major clusters are observed. Responses to hyper- and hypo-osmotic shock, changes in C source, and acid shock cluster together (Cluster 2). The remaining conditions form Cluster 1.

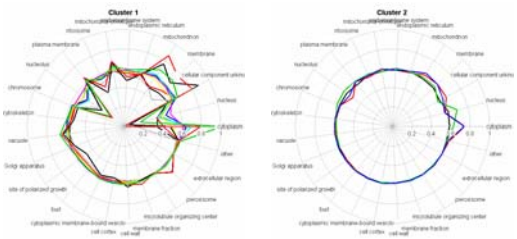


Figure 1. Comparison of y_{ij} for the different stresses and cellular component GO categories. Values are normalized so that the maximum calculated value of the index is 1 and the minimum is 0. The basal condition scales to 0.6 and plots as a circle.

3.2 Transcriptional changes related to protein length

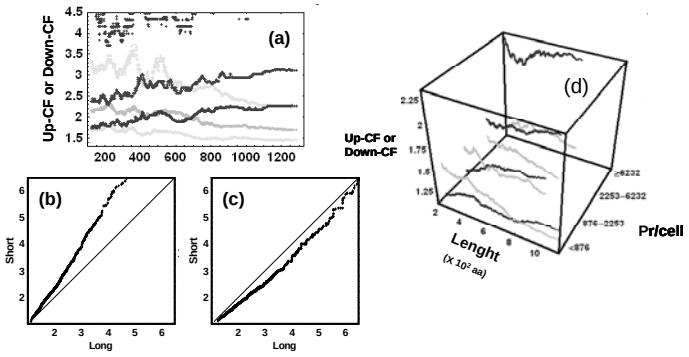
3.2.1 Analysis for individual stresses

Table 1. Gene expression change-fold comparison between short and large proteins for each type of stress. Analysis of lower and Upper length thresholds indicate the cutoff limits for selecting short and long proteins. z>0 indicates that proteins in the Lower group present higher up-expression and lower down-expression than those in the Upper group as compared by the Mann-Whitney test. z<0 indicates the opposite result. The corresponding p-values obtained using this test are shown (***) indicates $p<10^{-4}$. A positive and significant z-value for Up-CF and Down-CF is consistent with our hypothesys.

Environmental condition	Thresholds		Up-CF		Down-CF	
	Lower	Upper	z	p	z	p
C Source	413	662	-15.20	***	-8.79	***
Hypoosm	415	656	-7.72	***	-8.64	***
Acid	431	691	1.03	0.1504	-1.57	0.0585
Hyperosm	416	666	1.58	0.0568	-1.19	0.1167
NaCl	415	671	3.05	0.0011	4.20	***
DTT	411	658	13.69	***	5.64	***
Ndepl	415	662	9.91	***	3.69	0.0001
Alkali	434	703	2.89	0.0020	2.73	0.0032
AAdepl	416	667	1.61	0.0537	2.65	0.0040
Diamide	408	660	11.07	***	7.15	***
Diauxic	405	639	9.47	***	3.62	0.0001
Menadione	435	702	7.51	***	-4.91	***
Peroxide	421	677	4.72	***	8.11	***
Heat	435	700	1.70	0.0443	2.91	0.0018

3.2.2 Analysis of Cluster 1

Figure 2. a)Trends in the expression of proteins with respect to their size. The moving quantile plots show *quantiles* 0.75, 0.5 and 0.25 with a moving window of 400 elements. Light grey is used for Up-CF genes and dark for Down-CF genes. b) and c) Comparison of the change fold between short and large proteins. *Quantile-quantile plots* show the divergence between the two extreme lists by the deviation of the points from the line with a slope of 1. We compare of the change-fold of genes coding for the tercile of longest proteins (>533 aa) with the change-fold of genes coding for the tercile of shortest proteins (<307 aa). b) Up-CF genes. c) Down-CF genes. d) Change-folds of genes with respect to their length and binned by basal protein abundance; moving-median plot (window of 300 elements).



4. CONCLUSIONS

We observe significant correlation between transcriptional changes and the cost of group protein biosynthesis, one of the most expensive cell activities. We find that preferential overexpression of small proteins and downregulation of proteins that are both large and abundant under basal conditions are strong trends in stress response; Similar trends are found for complexes of proteins (data not shown).

5. ACKNOWLEDGMENTS

Work financed through Portuguese-Spanish int.action E-6/07 and BFU2005-0234 from Spanish MEC.

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