

Genomic expression programs of human cell lines in response to physiological stress

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ABSTRACT

We are studying the changes in RNA levels in human cells following exposure to environmental stress using cDNA microarrays containing more than 40,000 individual clones. In a previous study of gene expression, the yeast *Saccharomyces cerevisiae* was shown to change its gene expression dramatically in response to a wide variety of stresses¹. The large transcriptional response, which is activated in response to a wide variety of stresses, consists of over 1000 genes. This response, termed the environmental or general stress response, which has not yet been observed in human cells, is likely to have evolved to allow the yeast to survive the wide variety of environmental conditions it is exposed to in the course of its natural existence. Human cells *in vivo* are not subjected to the wide variety of environmental conditions seen by a unicellular organism such as yeast. In addition, mammalian cells have physiological responses to stress that are entirely absent in yeast, for example apoptosis and changes in cell-cell interactions. We might therefore expect the stress-induced changes in gene expression in mammalian cells to differ from those observed in yeast. Transcriptional systems used by mammalian cells in response to stress are also interesting because of their potential roles in human diseases. For instance, many human diseases, including most cancers, are characterized by a reduced ability of cells to respond to certain stresses.

In order to characterize the mammalian stress response, we have measured gene expression under a diverse set of conditions including oxidative stress, exposure to ultraviolet light, crowding and starvation, cold, heat and denaturing extracellular conditions in HeLa S3 cervical carcinoma cells. While this cell line is known to be deficient in several important regulators of stress response and cell cycle progression, including p53, we

demonstrate that it still modulates gene expression in response to all of the experimental conditions tested. Future work with additional cell lines and additional culture conditions will allow us to find additional facets of the mammalian stress response.

While the transcriptional stress response to stress in HeLa cells may not be characteristic of a “typical” human primary cell type, we can make several important observations based solely on the data that has been generated in this cell line. HeLa cells show much more selective responses to stress than yeast – only a handful of genes consistently show changes in RNA levels across all experiments. However, the specialized responses are at least as strong as those found in yeast. For example, HeLa cells treated with 2.5 mM dithiothreitol, which causes reduction of disulfide bonds in the ER, specifically increase expression of a large set of genes, including many genes known to be involved in protein folding in the ER.

Finally, it has been previously shown in yeast that genes that show similar expression patterns over a wide variety of experiments are very likely to be involved in the same biological process. We have used hierarchical clustering to find groups of genes that are coexpressed in response to stresses in HeLa cells and can make predictions about which processes many unannotated genes are involved in based on their expression patterns.

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REFERENCES

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