What the bacteriologists have learned about heat shock

In the spring of 1982, word that something very like the heat shock response of *Drosophila* and other eukaryotes had been found in *Escherichia coli* excited great attention among the attendees of the first Cold Spring Harbor heat shock conference. The finding implied that this multigenic response of cells to high temperature must be nearly as ancient as cellular life itself. In addition, there was a general expectation that work with *E. coli*, as usual, would move very quickly, and before long would be generating information of value to the whole heat shock field.

To what extent have these expectations been realized by the work of the ensuing 5 years? Progress on molecular mechanisms has been satisfying, as can be judged from three closely related papers that have appeared within the past few months. These papers do not bring the analysis to an end, but the remaining questions about mechanism in the bacterial system can now be phrased with such precision that the complete solution seems not far off.

As in many other cells, the heat shock response in bacteria consists of the transient induction of a set of some 20 proteins upon a shift from low to high temperature. The induction is brought about by stimulation of gene transcription by an active regulatory system, not by a direct effect of heat on the responding genes (references in Neidhardt et al. 1984).

Work from several laboratories over the past 5 years has established that the heat shock genes of *E. coli* are found in unlinked operons and constitute a single regulon (regulatory unit) under the control of a positive-acting protein. This protein has been shown to function as an RNA polymerase sigma factor, and to have structural similarity to the major sigma factor, σ70. Originally called HtpR, as product of the *htpR* gene, and identified on gels as protein F33.4, it is now referred to as σ32; its gene bears the alternative designation *rpoH*. The half-dozen known sequences for promoters of heat shock genes share a family resemblance, distinguishable from those of other *E. coli* promoters. But, σ32 appears to do more than simply determine the promoter specificity of RNA polymerase. Evidence both in vivo and in vitro suggests that the level of σ32 directly determines the activity of heat shock genes (references in Neidhardt et al. 1984 and Neidhardt and VanBogelen 1987).

The paper by Grossman et al. (1987) in this issue of *Genes & Development* provides support for this simple model. First, these authors confirm and extend earlier findings that the level of σ32 is rate limiting for synthesis of heat shock proteins. Increasing the rate of synthesis of σ32 [by inducing expression from a P*lac* or a P*lac* *htpR* (rpoH) fusion on a plasmid] increases the synthesis of heat shock proteins in the absence of a temperature shift. Second, they confirm the fact that σ32, at least under conditions of massive oversynthesis, is an unstable protein (half-life of approximately 4 min) at 42°C. Finally, they show that when σ32 is expressed from the phage λ *P*₆ promoter, it is synthesized transiently at a high rate after temperature upshift, and then repressed by some post-transcriptional process. The repression of σ32 synthesis is abolished in a strain carrying a mutant form (dnaK756) of one of the heat shock genes previously implicated as a modulator of the heat shock response (references in Neidhardt et al. 1984 and Neidhardt and VanBogelen 1987).

In sum, these findings support a relatively simple model in which the control of heat shock genes might be solely accomplished by changes in the cellular level of σ32 brought about by increasing its rate of synthesis or decreasing its rate of degradation.

Tilly et al. (1986) contribute another element to this picture by showing that cellular levels of transcripts of the *htpR* (rpoH) gene increase quickly [within minutes] and markedly [fivefold] after temperature upshifts. The time course of increase correlates with the synthesis of heat shock proteins. Interestingly, *htpR* (rpoH) mRNA levels were observed to rise after temperature shifts even in *htpR* mutants which are unable to stimulate heat shock genes, so the increase must occur by a mechanism different in some way from that operating on the heat shock genes themselves.

A third paper continues the theme of heat shock regulation by the level of σ32, but deals with the intriguing involvement of the heat shock response with viral infection. Bahl et al. (1987) have pursued the mechanism by which phage λ induces heat shock proteins in *E. coli* shortly after infection. It had previously been demonstrated that this induction depended both on σ32 and on early gene expression from the leftward *Pl* transcription unit of the phage, but the specific inducing factor was not known [references in Neidhardt and VanBogelen 1987]. These investigators report that overproduction from a plasmid system of one of the proteins encoded by this transcription unit, the λ cIII protein, leads to induction of heat shock proteins at low temperature and prolongation of the response following a temperature upshift. Overproduction of another λ protein, Eα10, does not alter the response after temperature upshift, so the cIII effect is presumed to be specific. The known properties of cIII include its ability to protect the λ cII protein from proteolysis by a variety of cellular proteolytic systems, and the current work shows that cIII overpro-
duction also stabilizes (by a fourfold factor) $\sigma^{32}$. This study confirms the ability of elevated levels of $\sigma^{32}$ to activate heat shock genes, and provides a strong case for elevation of these levels by stabilization of $\sigma^{32}$ by cIII.

There is attractiveness in a model that postulates a single transcriptional activator for a large, multigenic system. But, as the title of the Grossman et al. (1987) paper cautions, the evidence solidly demonstrates only that $\sigma^{32}$ synthesis can be made to regulate the synthesis of heat shock proteins; it does not prove that this is the normal mechanism employed by the cell. The weakness in the current picture (fully recognized by all these authors) stems from the use of plasmid systems for over-producing regulatory proteins of interest. Unnatural levels of $\sigma^{32}$ could act in any one of a number of ways to increase transcription from heat shock promoters (including possibly just by being a large quantity of unstable protein, in keeping with the ideas of Goff and Goldberg 1985). The htpR (rpoH) mRNA measurements of Tilly et al. (1986) do not suffer from this problem, because they were made in normal cells responding to temperature upshift. The final word on this model must await measurements of the level of $\sigma^{32}$, and of its rates of synthesis and degradation in cells producing it from a normal, chromosomal gene. Such measurements are underway using antibody to $\sigma^{32}$, and preliminary results confirm the predicted change in $\sigma^{32}$ level during heat shock (D.B. Straus and C.A. Gross, pers. comm.).

Although we still must learn about controls unique to individual heat shock genes, it seems clear what unites them as a regulon.

Less progress has been made in aspects of the heat shock response other than identification of the regulator. We know almost nothing about the link between the environment and the heat shock response. What ”shock” is caused by raising the temperature? How does this shock activate the $\sigma^{32}$ control? When toxic metals, oxidants, and solvents induce heat shock proteins [VanBogelen et al. 1987 and references therein], do they do so by causing the same cellular damage, or can a variety of injuries lead to an elevation of the cellular concentration of $\sigma^{32}$?

More vexing is the question of what the heat shock response accomplishes. Ideas abound [references in Neidhardt and VanBogelen 1987], but until more of the heat shock proteins can be assigned precise activities, and all of them can be related to cellular processes, the question of function will remain up in the air.

This assessment serves as a reminder that cloning, sequencing, and engineering genes have made bacterial physiology easier in the 1980s, but not easy enough. It will take much more work to learn how heat and certain other conditions lead to an increase in the active regulator of heat shock transcription, what induction of the 20-some heat shock proteins accomplishes, and why no cell has succeeded in eliminating this response from its repertoire of gene regulation.

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