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The role of chromatin structure in regulating stress-induced transcription in *Saccharomyces cerevisiae*[1]

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Abstract: All cells, whether free-living or part of a multicellular organism, must contend with a variety of environmental fluctuations that can be harmful or lethal to the cell. Cells exposed to different kinds of environmental stress rapidly alter gene transcription, resulting in the immediate downregulation of housekeeping genes, while crucial stress-responsive transcription is drastically increased. Common *cis*-acting elements within many stress-induced promoters, such as stress response elements and heat shock elements, allow for coordinated expression in response to many different stresses. However, specific promoter architectures, i.e., specific combinations of high- and low-affinity stress-responsive *cis* elements embedded in a particular chromatin environment, allow for unique expression patterns that are responsive to the individual type and degree of stress. The coordination of transcriptional stress responses and the role that chromatin structure plays in the regulation and kinetics of such responses is discussed. The interplay among global and gene-specific stress responses is illustrated using the constitutive and stress-induced transcriptional regulation of *HSP82* as a model. This review also investigates evidence suggesting that stress-induced transcription is globally synchronized with the stress-induced repression of housekeeping gene via 2 distinct mechanisms of facilitating the binding of TATA-binding protein (TBP): TFIID and SAGA-mediated TBP binding.

Key words: chromatin, transcription, stress response, heat shock.

Résumé : Toutes les cellules, qu'elles soient à l'état libre ou qu'elles fassent partie d'un organisme pluricellulaire, doivent lutter contre une variété de fluctuations environnementales qui peuvent être dommageables ou létales pour elles. Les cellules exposées à différents types de stress environnementaux doivent rapidement modifier la transcription génique, résultant en une diminution immédiate de l'expression de gènes domestiques, alors que l'expression des gènes de réponse au stress est augmentée de façon draconienne. Les éléments cis-actifs communs comme les éléments de réponse au stress et les éléments de réponse au choc thermique, au sein de plusieurs promoteurs inductibles par le stress, permettent de coordonner l'expression génique en réponse à différents types de stress. Cependant, l'architecture de certains promoteurs spécifiques, i.e. les combinaisons spécifiques d'éléments cis de réponse au stress à haute ou faible affinité au sein d'un environnement chromatinien particulier, permet l'expression de patrons uniques en réponse à des types et des degrés individuels de stress. La coordination des réponses transcriptionnelles au stress et le rôle que joue la structure de la chromatine dans la régulation et la cinétique de telles réponses est discutée. La relation qui existe entre les éléments de stress globaux et les éléments spécifiques à certains gènes est illustrée à partir du modèle de la régulation constitutive et induite par le stress de *HSP82*. Cette revue investigue aussi les éléments de preuve qui suggèrent que la transcription induite par le stress est globalement synchrone avec la répression induite par le stress de gènes domestiques via 2 mécanismes distincts de liaison facilitée de TBP : la liaison de TBP via TFIID *vs* SAGA.

Mots clés : chromatine, transcription, réponse au stress, choc thermique.

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Introduction

Adverse environmental conditions initiate highly conserved stress response pathways that result in global transcriptional changes. As a result of its well characterized genome and ease of manipulation, *Saccharomyces cerevisiae* has long been a powerful model system in which to study stress response pathways. While there are subtle regulatory differences among species, the basic responses to stress are well conserved, and the study of stress response pathways in yeast provides an understanding of the mechanisms of stress response that is applicable to all eukaryotes.

The survival of a stress encounter depends on a cell's ability to mount a rapid and specific defense against that particular stress. Most stress responses follow a similar two-pronged approach: a specific and immediate response, followed quickly by a global protection response. This allows the cell to survive immediate damage while preparing itself for more severe or long-term stress. For example, a cell initially faced with severe hyperosmotic stress undergoes a high influx of sodium into the cell, causing transcription factors, TATA binding protein (TBP), and initiating RNA polymerase II (Pol II) to dissociate from DNA, making transcription of necessary stress response genes impossible. The cell's immediate response is to remove excess sodium by phosphorylating a Na^+/H^+ antiporter using a MAP kinase (Proft and Struhl 2004). This unconventional use of a MAP kinase results in the reduction of sodium ions in the cell, allowing the secondary response, transcription of stress response genes, to occur within 5–10 min of the initial stress (Posas et al. 2000; Rep et al. 2000; Proft and Struhl 2004). As is the case in this example, immediate stress responses must be specific to the stress, and often rely on enzymes that are readily available to the cell in the absence of new synthesis.

Secondary stress responses result in transcriptional changes that enable the cell to adapt to environmental stress, and possibly enable the normal cell cycle to continue. Secondary responses are, of course, dependent on the type and severity of the stress encountered. Some transcriptional pathways initiated by stress are highly specific, yet general response pathways are also normally induced, and this combined approach permits a diverse network of transcriptional outcomes. General response pathways not only protect the cells from the incurred stress, but they also provide protection from other types of stress. Cross-protection is the term used when exposure to one type of stress renders the cell more capable of surviving a different type of stress. The cell's response to osmotic stress is a good example of how this phenomenon works. Cells exposed to a hyperosmotic environment convert the Sko1–Cyc8–Tup1 repressor complex into an activator, which then induces a number of genes that specifically protect the cell from osmotic damage (Proft and Struhl 2002). The activation of this complex also results in the enhanced expression of Msn2, which is a transcription factor that mediates the induction of a number of general response genes (Proft et al. 2005). This would confer a greater protection to many other types of stresses, such as heat shock, oxidative stress, and carbon source starvation.

Obviously, stress-induced transcription is quite complex, yet the cell is able to dramatically alter global transcriptional patterns within a matter of minutes. One mechanism for allowing such quick transcriptional change is to keep many key stress-response genes in a repressed state, where they are poised for transcription. The Sko1–Cyc8–Tup1 complex is also a good example of this type of regulatory system. Under normal growth conditions, this complex binds to a variety of hyperosmotic-induced genes and acts as a repressor. Upon exposure to hyperosmotic stress, the Hog1 kinase phosphorylates Sko1, resulting in the conversion of the repressor complex into an activating complex that recruits both of the chromatin-modifying complexes SAGA and SWI/SNF (Proft and Struhl 2002). This is a powerful mechanism which enables the rapid induction (and presumably equally rapid shutoff) of a whole subset of genes. The conversion of a site-specific repressor to an activator also provides a potent mechanism for achieving extremely rapid induction kinetics. The presence of a previously bound repressor/activator complex obviates the need for initial chromatin binding by an activator, essentially conferring a poised, prebound chromatin structure at these promoters. Overcoming the naturally repressive state of chromatin is critical to all transcription; however, speed and efficiency are especially critical when dealing with stress-response genes. The transcription factor Hsf1 is also constitutively bound to certain promoters to poise them for rapid induction, allowing transcriptional activation to take place, even without the complete basal transcriptional machinery. This is discussed in detail below, in the context of the *HSP82* promoter.

Effects of chromatin structure on stress-induced gene expression

Chromatin, the native compacted form of DNA, is organized into various levels of condensation, and is the mechanism that allows large amounts of genetic material to fit into the relatively small nucleus. The first level of compaction is the wrapping of DNA around a histone octamer comprising 2 copies each of the core histones H2A, H2B, H3, and H4. These DNA–histone complexes, called nucleosomes, are then linked together by a variable length of linker DNA that can be associated with linker histones. Each core histone has an amino-terminal tail, and histone H2A has a significant carboxy-terminal tail as well. Histone tail regions are not critical for nucleosome integrity (Whitlock and Simpson 1977; Ausio et al. 1989); instead, they allow more flexible interactions between DNA and other nucleosomes. Histone tails play a significant role in the further compaction of chromatin through interactions with other nucleosomes (for review see Zheng and Hayes 2003).

DNA packaged into nucleosomes is generally inaccessible to the basal transcriptional machinery. To overcome the naturally repressive state of the chromatin structure, the cell uses chromatin-modifying complexes to manipulate DNA–histone interactions. Site-specific activators exhibit various abilities to recognize their sites in chromatin. Chromatin-modifying complexes, or factors that recruit such complexes, are often recruited to elements within the promoter sequences that are more readily accessible within condensed chromatin as a result of nucleosome positioning or maintenance of nucleosome-free regions, or opportunistic binding to tran-

siently exposed sites. Furthermore, the level of condensation can be modified by global changes in the activities of chromatin modifiers, thus creating a dynamic means of control in which the regulation of gene expression depends on the accessibility of promoter sequences. Chromatin-modifying complexes use differing mechanisms, providing the cell with a number of ways in which it can regulate access to its condensed DNA.

Chromatin remodeling

Chromatin remodeling is a dynamic means of altering chromatin structure so that transcription machinery can access previously condensed DNA. Much of chromatin remodeling occurs through interactions between chromatin remodeling/modifying complexes and histones. Chromatin-remodeling complexes use ATP to mechanically rearrange nucleosomes, while histone-modifying complexes alter the state of chromatin through direct covalent modification of histones. Activation of many genes entails combinations of both mechanisms of chromatin alteration.

There are 7 major chromatin-remodeling complexes in yeast: SWI/SNF, RSC, INO80, CHD1, Isw1a, Isw1b, and Isw2, each containing a related ATPase catalytic subunit (reviewed in Cairns et al. 1996; Tsukiyama et al. 1999; Peterson and Workman 2000; Shen et al. 2000; Tran et al. 2000; Dirscherl and Krebs 2004). The mechanisms by which these complexes rearrange nucleosomes are various, enabling both general transcriptional regulation and promoter-specific regulation. Research has also demonstrated that chromatin remodelers can regulate transcription at the level of elongation (Morillon et al. 2003), and perform regulatory functions via novel remodeling activities, such as histone exchange and (or) histone variant deposition (Krogan et al. 2003; Kobor et al. 2004; Mizuguchi et al. 2004).

While the importance of chromatin remodeling in transcriptional regulation is evident throughout the literature, the role of chromatin remodeling in the specific context of stress is less well studied. Genetic experiments in yeast have demonstrated that strains lacking certain remodeling complex subunits are more sensitive to stress. Tsukiyama et al. demonstrated that the chromatin-remodeling enzymes Isw1, Isw2, and Chd1 play redundant roles in stress response (Tsukiyama et al. 1999). Exposure to mild heat shock or formamide has little effect on the growth of individual *isw1*Δ, *isw2*Δ, or *chd1*Δ mutants; however, any combination of double mutants results in significant sensitivity to these treatments, and a triple mutant strain (*isw1*Δ *isw2*Δ *chd1*Δ) demonstrates a synergistic growth defect. These data suggest that the ISWI-subfamily of remodelers have overlapping functions in yeast stress responses. It is clear that these and other chromatin-remodeling complexes play a vital role in the stress response; however, there is little information on the role that individual remodelers play with specific stress response genes. While these genetic assays are revealing, they do not show direct involvement of these chromatin remodelers at stress-induced genes.

A study by Wilson et al. demonstrates that the nonlethal deletion of *rsc7*Δ results in the improper assembly of the RSC chromatin-remodeling complex and an increased sensitivity to a variety of stresses (Wilson et al. 2006). Further supporting RSC's role in stress response, Damelin et al. implicate RSC in stress-responsive transcriptional regulation, using a chromatin immunoprecipitation (ChIP)-on-chip approach to detect occupancy of the RSC subunit Rsc9 (Damelin et al. 2002). When stress is induced via treatment with H_20_2 or rapamycin, Rsc9 occupancy decreases at a variety of stress response genes. While the presence of Rsc9 at these stress response genes implies the need for RSC's chromatin-remodeling activity at these promoters, there has not been a study demonstrating either remodeling activity or the presence of the entire RSC complex. Furthermore, Rsc9 occupancy is associated with both transcriptional repression and activation, so the role of RSC at these individual promoters remains unclear (Damelin et al. 2002; Ng et al. 2002).

The SWR1 complex may also play a role in stress-induced transcription. SWR1 has been shown to mediate the exchange of the canonical histone H2A with the Htz1 variant histone (Kobor et al. 2004; Mizuguchi et al. 2004). Htz1 deposition, via SWR1, is enriched at intergenic regions of repressed/basal genes and is associated with a transcriptionally poised state (Krogan et al. 2004; Li et al. 2005; Zhang et al. 2005). More specifically, under normal environmental conditions, Htz1 appears to be localized at promoters that lack TATA, possibly recruited by the critical TFIID subunit Bdf1 (Zhang et al. 2005). The deposition of Htz1 at basally repressed promoters is clearly associated with the potential for activation (Guillemette et al. 2005; Li et al. 2005; Zhang et al. 2005; Millar et al. 2006). Millar et al. demonstrated that, while Htz1 is in fact enriched at inactive promoters, acetylated Htz1 is enriched at actively transcribing genes that are depleted of nucleosomes (Millar et al. 2006). Whether this enrichment reflects a role for Htz1 in activation, or is a result of preferential reassembly with Htz1 after transcription, is not yet clear. In vitro experiments demonstrate that Htz1 is more susceptible to displacement from chromatin than canonical H2A (Zhang et al. 2005). This leads to a possible model in which promoters packaged into Htz1-containing nucleosomes are more prone to rapid nucleosome displacement that would allow more vigorous transcription.

While Htz1 enrichment may be important for vigorously expressed genes in general, it could be vital to stress response pathways. Many stress-response genes are highly induced upon activation and nucleosome displacement has been observed within minutes of stress exposure at several heat shock promoters (Erkine and Gross 2003; Zhao et al. 2005). It should be noted that SWR1 has not been directly correlated with stress-induced histone displacement, and in fact ChIP-on-chip assays using cells heat shocked for 30 min do not show significant Htz1 enrichment at heat shock promoters (Zhang et al. 2005). However, because histone displacement occurs within minutes of heat exposure, it is likely that any Htz1 at these promoters would be expelled long before the 30 min time point. It may be interesting to test directly whether Htz1 plays a role in this displacement or other aspects of heat shock gene regulation.

Histone modification

Histone modification is another mechanism used by cells to control access to DNA in chromatin. Histone-modifying complexes alter the state of chromatin through covalent

modification. This involves the addition or removal of many different moieties, such as acetyl, phosphate, or methyl groups (Fischle et al. 2003; Iizuka and Smith 2003). Depending on the type of modification, localized changes in electronegativity can occur. This can alter the DNA–histone binding affinity, thus increasing or decreasing the stability of the single nucleosome or alter internucleosome interactions, resulting in changes in chromatin condensation levels. Histone modification can also result in the generation of novel binding surfaces for other factors, such as chromatin remodelers, repressors, or transcription factors (for review see Spencer and Davie 1999).

The large number of possible histone modification patterns allows highly specific and complex signaling mechanisms, thus it is not surprising that particular histone modification patterns are associated with general transcriptional effects. For example, the acetylation via histone acetyltransferases (HATs) of histone tails is associated with active transcription (Brownell et al. 1996; Struhl 1998), while deacetylation through histone deacetylase (HDAC) complexes normally results in gene repression (Laherty et al. 1997; Nagy et al. 1997; Kadosh and Struhl 1998*a*).

Lysine acetylation, possibly the best studied histone modification, affects chromatin by imparting a negative charge and neutralizing the interaction between the histone tail and the phosphate backbone of DNA. More importantly, lysine acetylation can create a novel binding site that is bound by factors containing bromodomains (acetyl-lysine recognition domains). In one extensive study addressing specific histone modifications, Kurdistani et al. (2004) analyzed the genome-wide acetylation patterns of 11 lysines throughout the core histones. Clustering genes with similar acetylation patterns revealed that functionally related genes are similarly acetylated (Kurdistani et al. 2004). This suggests that functionally related groups are regulated coordinately through histone modification. Further, correlating acetylation clusters with stress-induced expression levels suggests many stress-induced genes belong to the same acetylation cluster. This provides a strong medium for the coordinated regulation of an assorted group of genes to a particular stress.

The Gcn5 HAT has been extensively characterized in yeast, and its activity is mostly associated with the acetylation of H2B and H3 (Zhang et al. 1998; Suka et al. 2001). The Gcn5-dependent SAGA complex appears to play a key role in the regulation of stress-induced transcription, via mediation of TBP binding at stress-responsive promoters (discussed further, below). However, the mechanism by which Gcn5 complexes facilitate TBP binding is not always obvious or direct. Recent results have shown that genome-wide basal histone acetylation levels controlled by Gcn5 can play an essential role in the activation of some genes, in the absence of direct recruitment of Gcn5 to these promoters (Imoberdorf et al. 2006). It has also been shown that Gcn5 and the essential HAT Esa1 have functionally overlapping roles in the acetylation of Htz1 Lys14, which is critical for its deposition during nucleosome reassembly after active transcription (Millar et al. 2006); possible roles for Htz1 in stress-responsive transcription are discussed below.

The dynamic relationship between HAT and HDAC activity results in an active mode of regulation that is responsive to the ever changing demands of the cell (for review see Kurdistani and Grunstein 2003). Just as the acetylation of particular histone residues correlates with active transcription, hypoacetylation correlates with a repressed state. Stress-response genes tend to be quickly expressed at very high levels and are generally downregulated promptly, as well. Both repression during the uninduced state and postinduction downregulation are mediated via recruitment of HDAC complexes. The activity of such genes is thus dependent on the interplay among the activating HAT, repressing HDAC, and of course, the corresponding transcription factors.

The repressor/activator Sko1–Cyc8–Tup1 complex that is activated during the osmotic stress response is a great example of how HATs and HDACs mediate regulation. As stated earlier, this complex, acting as an activator, recruits the HAT Gcn5 in response to hyperosmotic stress (Proft and Struhl 2002). In normal osmotic conditions, Tup1 acts as a repressor (for review see Smith and Johnson 2000) and has been shown to recruit the HDAC Hda1 to the hyperosmotic-induced gene *ENA1,* resulting in reduced acetylation of H2B and H3 at the promoter region (Wu et al. 2001). It should be noted, however, that Tup1-dependent repression also occurs independently of Hda1, possibly via interactions with transcriptional machinery or through interactions with other HDACs. Wu et al. demonstrated that hypoacetylation at the coding region of *ENA1* occurs through a separate pathway that is dependent on another HDAC, Rpd3 (Wu et al. 2001). Rpd3-mediated repression is complex and it has been suggested that Rpd3 can repress genes on a global level, as well as at specific promoters via specific DNA binding partners (Carrozza et al. 2005). Rpd3 has unexpectedly been shown to be enriched at the promoter regions of genes associated with high transcription activity, including heat shock proteins (Kurdistani et al. 2002). Theoretically, this could poise Rpd3 for repression of highly expressed genes that are potentially more difficult to downregulate. Comparisons between Rpd3 enrichment and mRNA levels during heat shock would be quite informative to test the model that Rpd3 is involved in the rapid downregulation seen at many stress-response genes immediately after the initial stress response.

Interdependence of chromatin remodeling and histone modification

Chromatin remodeling and chromatin modification have proven to be key players in transcriptional regulation, and they are not mutually exclusive. Chromatin modification can result in the recruitment of chromatin-remodeling machinery, or vice versa (for a review, see Fry and Peterson 2001). There is often a strong interplay between chromatin remodelers and modifiers. For instance, when chromatin is highly condensed during mitosis, SWI/SNF remodeling is critical for Gcn5-dependent acetylation at a number of genes, including genes that normally do not require SWI/SNF for Gcn5 recruitment during other phases of the cell cycle (Krebs et al. 2000). However, in other cases, parallel recruitment of different remodelers occurs, in which the independent activities of different remodelers contribute to transcriptional activation in no particular order.

In theory, parallel or simultaneous recruitment of different remodelers could support the rapid induction kinetics ob-

served for stress-responsive genes. Transcription of osmotic stress-inducible genes is coregulated by chromatin-remodeling and histone-modifying machinery. Both the SWI/SNF chromatin remodeler and the SAGA HAT are required for overcoming Tup1 repression of osmotic stress-inducible genes (Proft and Struhl 2002). Recruitment of SWI/SNF and SAGA appears to be parallel and is dependent on the same factors (Tup1 and Hog1). Parallel recruitment of these co-activators is also seen at the glucose-repressed *SUC1* gene (Geng and Laurent 2004), suggesting that perhaps this is a frequently used mechanism for activation of stress-response genes. Because many stress-response genes are in a constitutively repressed state, combining chromatin modification and remodeling may be a common mechanism for overcoming repression.

Role of promoter architecture in stress-induced gene expression

Besides the direct interaction between chromatin-modifying enzymes and nucleosomes, cells can also alter chromatin structure through the use of a variety of transcription factors. Transcription factors regulate chromatin structure indirectly through the recruitment of histone modifiers and (or) chromatin remodelers, or directly by influencing nucleosome positioning. In many stress responses, sets of pertinent genes are coordinately activated through use of common transcription factors that recognize *cis*-acting elements found in the relevant promoters.

Evidence strongly suggests that the promoter architecture (i.e., element location and strength, as well as native chromatin structure) of stress response genes plays a vital role in the binding and activation of transcriptional activators (Lis 1998; Santoro et al. 1998). These common *cis*-acting elements are powerful tools, because they allow the coordination of genes while the promoter architecture confers the specificity needed for appropriate responses. Considering that some stress-response genes are constitutively expressed at lower levels, dynamic regulation through promoter architecture is critical to ensure appropriate expression in different situations.

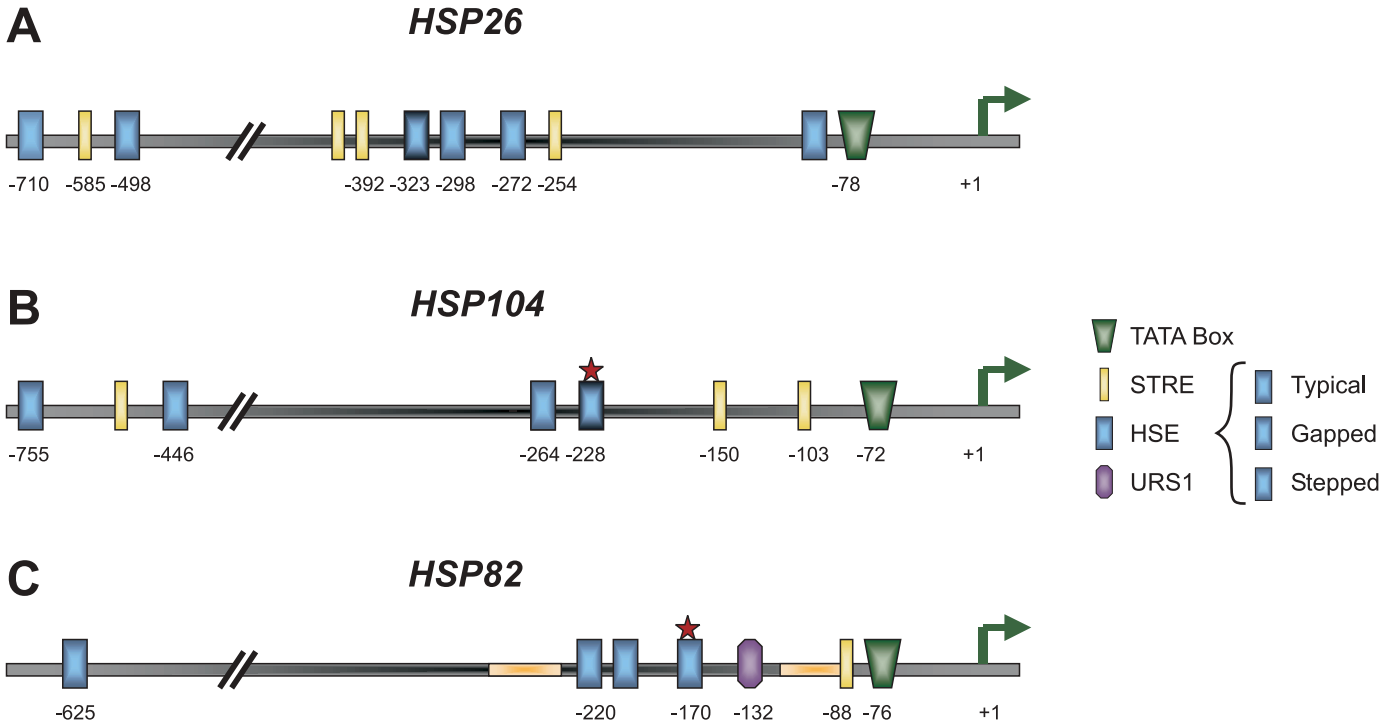
Stress response elements (STREs) and heat shock elements (HSEs) are 2 examples of such regulatory elements. STREs are bound by the functionally redundant Msn2 and Msn4 transcriptional activators (Estruch and Carlson 1993; Martinez-Pastor et al. 1996; Schmitt and McEntee 1996; Gorner et al. 1998) and have a direct role in the induction of approximately 200 genes in yeast (Gasch et al. 2000; Causton et al. 2001). STRE-mediated expression occurs in response to a variety of stressors, including heat shock, oxidative stress, pH change, osmolarity shock, toxicity, and nutritional depletion (Mager and De Kruijff 1995; Ruis and Schuller 1995; Estruch 2000). HSEs are bound by heat shock factor 1 (Hsf1) in yeast. HSE-mediated transcriptional activation of the chaperone family of heat shock proteins (Hsps) is well characterized; however, HSEs influence the transcription of a number of other stress response genes as well (Yamamoto et al. 2005; for review see Pirkkala et al. 2001). Heat shock is the obvious trigger for this stress-response pathway; however, other stresses that result in protein damage can also initiate the heat-shock response.

Many stress-response genes possess both STREs and HSEs in their promoter regions, suggesting that these 2 general stress pathways have overlapping functions. This redundancy could serve as an assurance that the most vital stress response genes are activated under a variety of conditions. Alternatively, the specific combinations of regulatory elements could permit fine-tuning of the stress response, so that the final stress responses are unique to each individual gene and stress type. An illustration of the variety of combinations of HSEs and STREs is shown in Fig. 1, which shows 3 examples of HSE/STRE-containing promoters: *HSP26, HSP104*, and *HSP82*. (The different types of HSEs are discussed below.) Supporting the theory that different combinations of regulatory elements results in more precise responses, STRE- and HSE-mediated regulation has been shown to act both independently and coordinately in a gene- and stress-dependent manner (Simon et al. 1999; Amoros and Estruch 2001; Grably et al. 2002).

A survey of the current understanding of HSEs provides an excellent demonstration of the importance of promoter architecture. A typical HSE, containing 3 contiguous inverted repeats of the sequence *n*GAA*n*, is bound by Hsf1 with high affinity, while variants of the HSE often result in a lower binding affinity (Amin et al. 1988; Xiao and Lis 1988; Perisic et al. 1989; Xiao et al. 1991; Santoro et al. 1998). There are 3 types of HSEs: perfect, gapped, and stepped, each of which have different impacts on Hsf1 binding. A perfect HSE has all 3 inverted repeats in a contiguous array (5′-*n*TTC*nn*GAA*nn*TTC*n*-3′) (Amin et al. 1988; Xiao and Lis 1988; Perisic et al. 1989; Xiao et al. 1991). Gapped HSEs have 2 consecutive inverted sequences, with the third sequence separated by a 5 bp gap (Santoro et al. 1998). Stepped HSEs have 5 bp gaps separating all 3 sequences (Yamamoto et al. 2005). While the type or pattern of HSEs found in the promoter region of specific genes apparently cannot be linked to particular types of stress, it is clear that having multiple types of Hsf1–HSE interactions potentially results in more specific and coordinated responses. The number of HSEs and their relative positions to one another in a given promoter results in further potential variation in regulation.

A series of deletion strains (*hsf1*Δ, *msn2*Δ*msn4*Δ, and *hsf1*Δ*msn2*Δ*msn4*Δ) was used to establish the different contributions of Hsf1 and Msn2/4 to *HSP26* and *HSP104* expression in response to different stresses (Amoros and Estruch 2001). In response to heat, the *HSP26* promoter appears to be regulated relatively equally by both HSEs and STREs. However, in response to other stresses, Hsf1 and Msn2/Msn4 have an additive effect on transcription, suggesting that STREs play a predominant role in non-heat-induced transcription. This could be explained by the fact that the *HSP26* does not have any perfect consensus HSEs (see Fig. 1A). The *HSP104* promoter (Fig. 1B), on the other hand, has a strong HSE, and its regulation appears to be almost entirely dominated by Hsf1. The *msn2*Δ*msn4*Δ strain exhibits normal levels of *HSP104* transcription in response to heat shock, carbon source starvation, or oxidative stress, and shows only a mild reduction in expression in response to osmotic stress. Similarly, the *HSP82* promoter also contains a perfect HSE (Fig. 1C) and is also dominantly regulated by Hsf1 (Erkine et al. 1999; discussed further below).

Fig. 1. Different heat shock promoters have different promoter architectures. Schematics of several representative heat shock promoters discussed in the text. (A) *HSP26* contains 6 putative heat-shock elements (HSEs). The 4 HSEs most proximal to the initiation site correspond to sites identified by Susek and Lindquist (1990). The most distal HSE (–710) may correspond to the perfect HSE characterized by Chen and Pederson (1993), though it carries 1 mismatch in the *Saccharomyces* Genome Database sequence. The 4 stress-response element sequences have been previously identified (Mager and De Kruijff 1995). (B) Putative regulatory elements in the *HSP104* promoter. The promoter contains a single perfect consensus sequence (denoted by a red star) for a typical HSE. This strong HSE may explain the heightened role HSF plays in the regulation of this gene in response to many types of stress. The transcriptional start site for this promoter is approximate within 10 bp. (C) The *HSP82* promoter, as previously characterized, contains a perfect gapped HSE that is required to maintain DNase I hypersensitive sites (denoted by orange bar) (Gross et al. 1993; Erkine et al. 1999).



This demonstrates the unique expression patterns for each gene, even when regulated by the same transcription factors.

The activation of transcription through Hsf1–HSE binding is regulated via promoter architecture and Hsf1 conformation, which itself is controlled by a number of regulatory domains. The apparent role of Hsf1 in the transcriptional activation of stress response genes is the resolution of repressive chromatin structure. Hsf1, an unusually strong activator, has been repeatedly shown to activate transcription without the normal entourage of transcription factors and coactivators required for general transcription (Apone et al. 1998; Lee and Lis 1998; McNeil et al. 1998; Moqtaderi et al. 1998; Chou et al. 1999). It is possible that by altering chromatin structure, either directly or indirectly, Hsf1 is sufficient for stabilizing TBP binding to the TATA element, thereby decreasing the reliance on cofactors that would otherwise be responsible for such stabilization.

Trimerized yeast Hsf1 constitutively binds to certain HSEs without heat shock or hyperphosphorylation (Sorger and Pelham 1987; Jakobsen and Pelham 1988; Gross et al. 1990). Hsf1 has 4 primary domains that affect activation: C- and N-terminal activation domains (AD) (Nieto-Sotelo et al. 1990; Sorger 1990; Chen and Pederson 1993), a DNA binding domain (Harrison et al. 1994; Hardy and Nelson 2000; Hardy et al. 2000), and a trimerization domain (Sorger and Nelson 1989; Peteranderl and Nelson 1992; Peteranderl et al. 1999). The two activation domains have distinct roles in heat-induced activation and appear to be at least partially regulated via interactions through the DNA binding domain (Bulman et al. 2001). It has been suggested that trimerized Hsf1 can have two conformations: an activated state where the ADs are accessible and an inactivated state where ADs are masked (Nieto-Sotelo et al. 1990; Sorger 1990; Bonner et al. 1992).

Hsf1 in stressed cells can often be found in a hyperphosphorylated state; however, the role of Hsf1 hyperphosphorylation in yeast is not fully understood (Sorger et al. 1987; Sorger and Pelham 1988; Sarge et al. 1993). Recent evidence suggests that hyperphosphorylation of Hsf1 confers a conformation that is necessary to overcome promoter and chromatin repression in a stress-induced and promoter-specific manner (Sorger et al. 1987; Hoj and Jakobsen 1994; Hashikawa and Sakurai 2004). More specifically, studies indicate that hyperphosphorylation is required for the transcription of promoters containing atypical (gapped or stepped) HSEs, while typical HSEs are sufficient to support transcription in the absence of Hsf1 hyperphosphorylation (Hashikawa et al. 2005). Heat-induced phosphorylation of Hsf1 is dependent on the C-terminal modulator (CTM) domain of Hsf1 (Hashikawa and Sakurai 2004). By determining the CTM dependency for an array of Hsf1-regulated genes, Hashikawa et al. demonstrated that only genes containing elements with

greater than 3 HSE sequence repeats (*n*GAA*n*) were induced in a CTM-independent manner (Hashikawa et al. 2005). These studies suggest that the element itself can determine the level of post-translational modification necessary for gene induction. Furthermore, using mutated HSEs at the *HSP82* promoter, Erkine et al. show that cooperative binding occurs between Hsf1 bound at higher and lower affinity HSEs (Erkine et al. 1999).

The interplay between chromatin remodeling and promoter architecture: *HSP82* as a model

The *HSP82* promoter is the most extensively studied Hsf1-regulated promoter in yeast. It is dominantly regulated by Hsf1, as mentioned above. The promoter contains 1 STRE; however, Msn2/Msn4-mediated regulation apparently plays little or no observable role in heat-shock- or osmotic-shock-induced expression of *HSP82* (Erkine et al. 1999). While Hsf1 regulates expression in a gene- and stress-dependent manner, research on this promoter is likely to provide basic paradigms for understanding the regulation of other Hsf1-dependent promoters.

Activation of HSP82

The *HSP82* promoter contains 3 HSEs within 230 bp upstream of a TATA element (Fig. 1C). The HSE most proximal to the TATA box (HSE1) is constitutively bound by Hsf1 and is required for transcription (Gross et al. 1993). The deletion of HSE1 results in a 100-fold reduction in uninduced *HSP82* mRNA levels, and upon the loss of Hsf1–HSE1 binding, 2 stable nucleosomes form over the promoter region (Gross et al. 1993; Venturi et al. 2000). For any Hsf1-regulated gene, the number and strength of the HSEs at the promoter has a great influence on how that promoter is regulated. The close proximity to the TATA box and sequence conservation of HSE1 at the *HSP82* promoter results in strong and efficient Hsf1-activated transcription with little influence from other activators. While most Hsf1-regulated genes do have a predominant HSE, not all of them compare with the strength demonstrated by the *HSP82* HSE1.

The binding of Hsf1 to the promoter region of *HSP82* results in the formation of DNase I-hypersensitive sites (DHSs) (see orange bars in Fig. 1C), suggesting that Hsf1 binding holds chromatin in an open state, permitting transcription (Szent-Gyorgyi et al. 1987; Gross et al. 1993). Studies using a mutated *hsp82* promoter, in which HSE1 is deleted (*hsp82*-ΔHSE1), show that HSE1–Hsf1 binding is critical for the maintenance of DHS sites. The loss of DNase I hypersensitivity is due to the establishment of 2 de novo nucleosomes that are centered over the HSE1 and TATA region of the *HSP82* promoter (Gross et al. 1993). Overexpression of *HSF1* in the *hsp82*–ΔHSE1 strain reinstates the nucleosome-free region, detected by the return of DNase hypersensitivity to the promoter, through Hsf1 interactions with the low-affinity sites HSE2 and HSE3. The mechanism by which Hsf1 excludes nucleosomes is unclear. Activators gain access to promoter sequences via a number of mechanisms, such as recruiting chromatin-remodeling complexes and (or) histone-modification complexes, or binding to the promoter before nucleosome assembly occurs (immediately following DNA replication). Some activators are also capable of binding unaided to their sites in chromatin.

Using the nucleosomal *hsp82*–ΔHSE1 promoter, Venturi et al. demonstrated that Hsf1 binds to nucleosomal HSEs more efficiently in S-phase cells than in cells arrested in G1 by α-factor. However, Hsf1 binding can still occur independently of replication after release from G1 arrest (Venturi et al. 2000). To explain these findings, Venturi and co-workers proposed that, following the release from α-factor arrest, the dinucleosome is remodeled by either histone-modifying enzymes or chromatin remodelers, permitting Hsf1 binding. While these experiments provide general information on Hsf1's binding capabilities, the relevance to the normal regulation of *HSP82* is not clear, given the critical role of HSE1 in the wild-type promoter. However, unpublished results (A. Erkine and D.S. Gross) emphasize the importance of overcoming nucleosomal repression at the *HSP82* promoter, by demonstrating that the nucleosomal state of the mutant promoter also forms over the wild-type promoter in vitro, and that Hsf1 is incapable of binding to even a high-affinity nucleosomal HSE in vitro (Venturi et al. 2000).

Another study investigating the relationship between Hsf1–HSE1 binding and nucleosome accessibility demonstrated that heat shock-induced displacement of histones throughout the promoter, coding region, and 3′-UTR of *HSP82* is Hsf1–HSE1 dependent (Zhao et al. 2005). Displacement of histones is immediately preceded by a short burst of acetylation within the first 45 s of heat shock, supporting the idea that chromatin modification plays an essential role in Hsf1-mediated nucleosome exclusion. In fact, the degree of nucleosome displacement appears to be proportional to the levels of transient histone acetylation, which also appears to vary for different heat shock promoters (A. Erkine, personal communication). This may represent a direct link between Hsf1–HSE binding affinity and the induction of a concerted acetylation/displacement activity. The cofactor(s) responsible for the rapid histone acetylation have not been elucidated, although it appears that Gcn5 is not involved (Zhao et al. 2005).

Stress-response-associated nucleosome displacement may be important for vigorous transcription (Zhao et al. 2005). Presumably, the total loss of nucleosomes would allow much faster and more efficient transcription. Apart from the probable role of histone tail acetylation, the mechanism of displacement remains a mystery (Zhao et al. 2005). Histone displacement has been observed at promoters such as *PHO5*; however, the kinetics of displacement is significantly slower (Barbaric et al. 2003; Reinke and Horz 2003). Interestingly, the histone H2A variant Htz1 associates with repressed *PHO5*, suggesting that it may play a role in *PHO5* activation (Santisteban et al. 2000). Htz1 deposition is also associated with certain patterns of histone acetylation. However, genome-wide studies have not shown Htz1 deposition at the *HSP82* promoter in the presence or absence of a 30 min heat shock (Zhang et al. 2005). This could be explained in two ways: either *HSP82* promoter nucleosomal depletion is Htz1 independent, or Htz1 deposition and subsequent nucleosomal loss occurs at low levels or at such a rapid rate that it was simply missed in the whole-genome analyses. Direct ChIP analysis of Htz1 at *HSP82* may resolve this question.

The role of chromatin-remodeling complexes at the

HSP82 promoter is still unclear; however, there are clues that remodeling complexes are important in *HSP82* regulation. First, Zhao et al. have shown that SWI/SNF is recruited to the activated *HSP82* gene (Zhao et al. 2005). Both *snf2*Δ and *swi1*Δ strains show a 6-fold reduction in *HSP82* expression in response to heat shock; however, histone displacement occurs normally in both strains, indicating that the role of SWI/SNF is not in direct nucleosome displacement.

As stated previously, the RSC subunit Rsc9 associates with stress-response genes (Damelin et al. 2002). Genome-wide localization indicates that Rsc9 associates with *HSP82* during normal environmental conditions and shows a moderate increase in *HSP82* association in response to hydrogen peroxide or rapamycin treatment. Unfortunately, the effect of heat shock on Rsc9 localization was not tested in this study. It is possible that the RSC complex may play a role in *HSP82* regulation, but this needs to be tested directly. Rsc1 and Rsc2, 2 possibly redundant RSC complex subunits, are both required for late sporulation-related genes and their deletion results in decreased sporulation efficiency (Bungard et al. 2004). *HSP82* expression increases during sporulation and has been shown to be regulated by the early meiotic *IME1–IME2* transcriptional cascade (Szent-Gyorgyi 1995), suggesting its role in early meiotic activities. Interestingly, 1 phenotype of *rsc1*Δ and *rsc2*Δ mutant spores is a decreased viability in response to heat shock (Bungard et al. 2004), again suggesting a functional link between RSC and *HSP82* expression.

Repression of HSP82

Szent-Gyorgyi, in a search for regulatory regions of the *HSP82* promoter that are specific for sporulation, demonstrated that URS1 (upstream repression sequence 1) mediated repression is important in *HSP82* regulation (Szent-Gyorgyi 1995). At many repressed genes in yeast, the repressor Ume6 binds to a URS1 element and then recruits the Rpd3 HDAC complex (Kadosh and Struhl 1997). As described above, Rpd3 has been associated with both gene activation and repression. However, Rpd3 recruitment often results in the localized deacetylation of H3 and H4 histone tails, resulting in a repressive state (Kadosh and Struhl 1998*b*).

The role of URS1 in the regulation of *HSP82* has largely not been studied. However, footprinting experiments have shown protein binding at URS1 while *HSP82* is in an uninduced state, and this binding is lost in response to heat shock or when HSE1 is deleted (Erkine et al. 1999; Kurdistani et al. 2002). Strains lacking the URS1 element in the *HSP82* promoter have only a 2-fold higher basal expression rate in the absence of heat shock, suggesting that URS1-mediated regulation is insufficient for total *HSP82* repression (Erkine et al. 1999). Rpd3 is enriched at *HSP82*, as shown in whole-genome studies (Kurdistani et al. 2002), suggesting that URS1 may be responsible for recruiting the deacetylase complex. Rpd3 recruitment has been shown to inhibit recruitment of SWI/SNF, which plays a role in *HSP82* transcription (Zhao et al. 2005), and SAGA, which is also associated with *HSP82* expression (Deckert and Struhl 2002). Also, considering the importance of histone tail acetylation for histone displacement (Zhao et al. 2005; A. Erkine, personal communication), it seems likely that an HDAC, such as Rpd3, could play a vital role in preventing nucleosome displacement.

Fig. 2. Model of heat-induced chromatin alterations at the *HSP82* promoter. Hsf1 is constitutively bound to the perfect heat shock element. Upon heat shock, rapid acetylation of histone tails is followed by the displacement of nucleosomes throughout the *HSP82* locus (Zhao et al. 2005). The binding of RNA polymerase II occurs almost concurrently with the beginning of chromatin modification (A. Erkine, personal communication). Recovery from heat shock results in the re-establishment of nonacetylated nucleosomes. See Fig. 1 for key to promoter elements. The possible roles of remodeling complexes are discussed in the text.

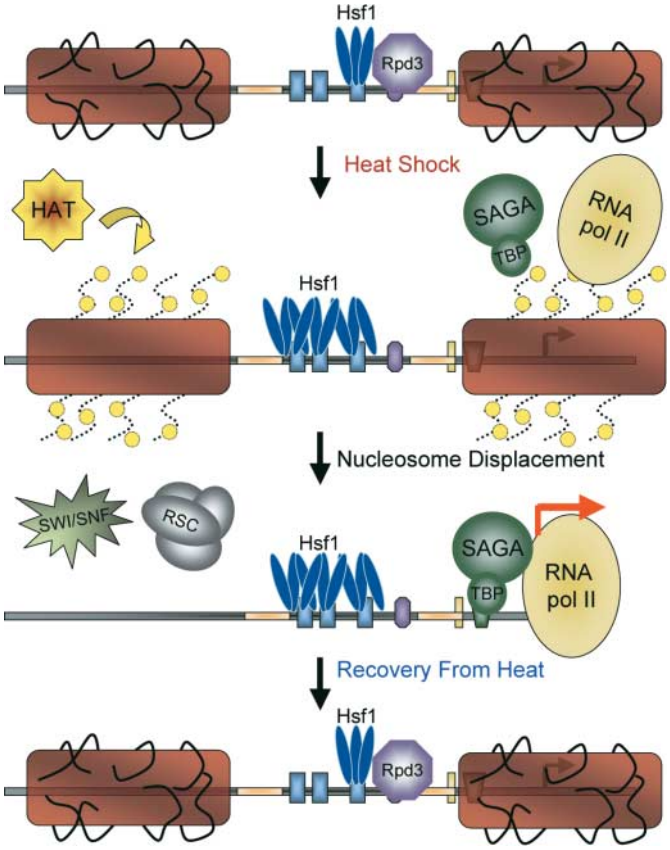


Figure 2 presents a model for how these various factors influence *HSP82* transcription. Within the first minute of heat exposure, an unknown HAT hyperacetylates multiple histone tails, and Pol II becomes associated with the promoter and coding region (Zhao et al. 2005; A. Erkine, personal communication). Immediately thereafter, nucleosome displacement occurs throughout the entire *HSP82* locus, allowing vigorous transcription (Zhao et al. 2005). Also following heat shock, the URS1 element loses its binding factor (possibly Rpd3 or a factor targeting Rpd3), further derepressing the promoter (Erkine et al. 1999; Kurdistani et al. 2002). The precise roles of SWI/SNF and RSC are unknown; however, evidence suggests that they are also involved in *HSP82* regulation (Zhao et al. 2005; Erkine et al. 1999; Kurdistani et al. 2002). While many details are still missing, we are beginning to get a better understanding of how this model stress gene is regulated.

Stress-induced transcriptional regulation: global effects

General stress responses cause global transcription changes that drastically alter the expression patterns of not only stress-response genes, but housekeeping genes as well. Within minutes of encountering stress, cells downregulate nonessential transcription, focusing all transcriptional machinery on a few crucial stress-response genes. It is likely that the downregulation of housekeeping genes and the upregulation of stress-induced genes is initiated by the same stressor, while acting through 2 distinct regulatory pathways. However, a clear mechanism connecting these 2 regulatory pathways has yet to be elucidated.

Transcription of any Pol II-transcribed gene requires recruitment of the TATA binding protein (TBP) to the promoter. It has been suggested that chromatin structure deters TBP from binding on its own, therefore it is highly dependent on transcriptional activators to facilitate its binding (Kuras and Struhl 1999; Li et al. 1999). TBP binding is critical to both stress-induced and nonstress-induced genes; however, it appears that the mechanism for recruiting TBP is different depending on the target gene. There is some evidence to suggest that different factors which facilitate TBP binding may reflect global mechanisms linking the transcription of specific subsets of genes.

The 2 best known complexes that facilitate TBP binding are the SAGA and TFIID multisubunit complexes, both of which can interact directly with TBP to facilitate promoter binding (Grant et al. 1997; Nishikawa et al. 1997). While it has long been believed that SAGA promotes TBP binding by modifying chromatin via histone acetylation by Gcn5, an analogous pathway for the Taf1 HAT in TFIID has been more controversial (Brownell et al. 1996; Mizzen et al. 1996). Recent evidence has shown that Taf1's HAT activity is not sufficient for the high level of acetylation detected at TFIID-mediated promoters (Durant and Pugh 2006), and instead, TFIID is likely to be recruited to previously acetylated promoters via the bromodomain protein Bdf4. Intriguingly, Mot1, which associates with TBP and can have either positive or negative effects on transcription, is specifically present at heat shock promoters under inducing conditions (Geisberg and Struhl 2004).

To investigate the different roles of SAGA and TFIID, Huisinga and Pugh employed a whole-genome strategy to distinguish genes that are regulated predominately by SAGA, TFIID, or both (Huisinga and Pugh 2004). Genome-wide microarray analysis was used to observe changes in expression patterns in strains carrying crucial SAGA or TFIID subunit deletions. These studies indicated that expression of 90% of all genes is dominated by TFIID, while only 10% of gene expression is dominated by the SAGA complex. The SAGA-dominated genes were strongly enriched for stress-responsive genes. However, it is important to note that many genes depend equally on both complexes, and that a promoter dominated by a particular complex may use the other complex to a lesser degree as well.

While all Pol II promoters require TBP, approximately 80% of genes lack a TATA box (Basehoar et al. 2004). Comparing the locations of TATA-containing or TATA-less promoters, Basehoar et al. used chromatin immunoprecipitation (ChIP) to correlate the presence of a TATA box with SAGA-mediated TBP binding and TATA-containing promoters with TFIID-mediated TBP binding. Further investigation using genome-wide microarray analysis suggests that most environmental stress-response genes have TATA-containing promoters and are SAGA dominated, while TATA-less, TFIID-mediated TBP binding tends to regulate housekeeping or stress-inhibited genes (Basehoar et al. 2004; Huisinga and Pugh 2004).

These data suggest that the SAGA complex is predominantly used to mediate stress-induced TBP binding; however, it appears that the complex may use a variety of mechanisms to achieve TBP binding, depending on the gene being expressed and the type of stress encountered. Many studies have demonstrated that SAGA subunits are differentially required for activity of specific genes (Horiuchi et al. 1997; Roberts and Winston 1997; Grant et al. 1998; Natarajan et al. 1998; Sterner et al. 1999; Lee et al. 2000; Bhaumik and Green 2002). Lee et al. have shown that although both Spt3 and Gcn5 are found in the SAGA complex, genome-wide expression data supports the idea that they regulate separate sets of genes (Lee et al. 2000). In addition, Jazwinski speculates that the addition of Rtg2p to the SAGA complex converts SAGA to the SAGA-like SLIK complex, extending the function of this complex to the activation of metabolic genes in addition to stress genes (Jazwinski 2005).

These studies suggest mechanisms for the regulation of global stress responses. The apparent functional separation of SAGA-mediated vs TFIID-mediated transcription allows coordinated yet differing responses to the same environmental cue. Therefore, a given stress response, acting through these 2 global pathways, can modulate drastic transcriptional alterations for large gene sets through the regulated binding of TBP. Of course, regulation of TBP binding is complex and primarily occurs in the context of individual promoters and their varying states of chromatin structure, ensuring that the response is gene appropriate.

While one goal of studying stress-response pathways is to elucidate common mechanisms of transcriptional regulation, research in this field has also uncovered the importance of unique promoter architecture in permitting the fine-tuning of general stress responses. The complex interplay of chromatin-modifying activities with related but nonidentical promoter structures allows great variation in transcriptional output using the same sets of factors and general modes of regulation. This allows global transcriptional responses that are nevertheless uniquely refined in a stress- and gene-dependent manner.

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