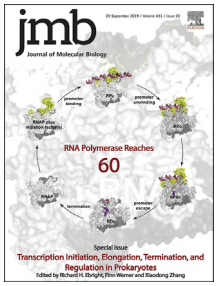

Global Transcriptional Programs in Archaea Share Features with the Eukaryotic Environmental Stress Response

Rylee K. Hackley[1,2] **and Amy K. Schmid**[1,2,3]

*1 - **Department of Biology,** Duke University, Durham, NC 27708, USA*
*2 - **University Program in Genetics and Genomics,** Duke University, Durham, NC 27708, USA*
*3 - **Center for Genomics and Computational Biology,** Duke University, Durham, NC 27708, USA*

Correspondence to Amy K. Schmid: *amy.schmid@duke.edu*
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Abstract

The environmental stress response (ESR), a global transcriptional program originally identified in yeast, is characterized by a rapid and transient transcriptional response composed of large, oppositely regulated gene clusters. Genes induced during the ESR encode core components of stress tolerance, macromolecular repair, and maintenance of homeostasis. In this review, we investigate the possibility for conservation of the ESR across the eukaryotic and archaeal domains of life. We first re-analyze existing transcriptomics data sets to illustrate that a similar transcriptional response is identifiable in *Halobacterium salinarum*, an archaeal model organism. To substantiate the archaeal ESR, we calculated gene-by-gene correlations, gene function enrichment, and comparison of temporal dynamics. We note reported examples of variation in the ESR across fungi, then synthesize high-level trends present in expression data of other archaeal species. In particular, we emphasize the need for additional high-throughput time series expression data to further characterize stress-responsive transcriptional programs in the Archaea. Together, this review explores an open question regarding features of global transcriptional stress response programs shared across domains of life.

Introduction

The ability to maintain homeostasis during fluctuating environmental conditions is an essential and ancient trait. Cells must detect and respond to environmental fluctuations by modifying protein and RNA levels, cell structure, and metabolic processes. Maintaining homeostasis requires the reprogramming of gene expression—transcription factors (TFs) promote or inhibit RNA polymerase to differentially regulate the expression of genes encoding proteins that alter physiology and increase fitness during subsequent stress challenges [1–3]. Transcriptional control, therefore, is a key mediator of organism–environment interactions. Exploring transcriptional changes in response to specific and general stresses has been a fruitful avenue to understand cell physiology, discover gene functions and regulatory hierarchies, and predict evolutionary relationships [4–6].

Studies in microbial eukaryotes and bacteria have assessed genome expression in response to a single stress or across a panel of stresses. Together, the results have contributed to a more holistic understanding of the transcriptome landscape upon exposure to stress [5,7,8]. In a global program such as the environmental stress response (ESR) in budding yeast [9], a large fraction of the transcriptome is rapidly and transiently reprogrammed in response to stress. The ESR is induced in response to a battery of stressful conditions, suggesting a core transcriptional response [9,10].

Characteristics of a core stress response, such as cross-stress protection and adaptation, are observed across other eukaryotes and bacteria [11–13]. For example, cross-stress protection has been reported in response to temperature and osmotic stress in bacterial model organisms such as *Bacillus subtilis* [14], *Listeria monocytogenes* [15], and *Escherichia coli* [16,17]; and adaptive

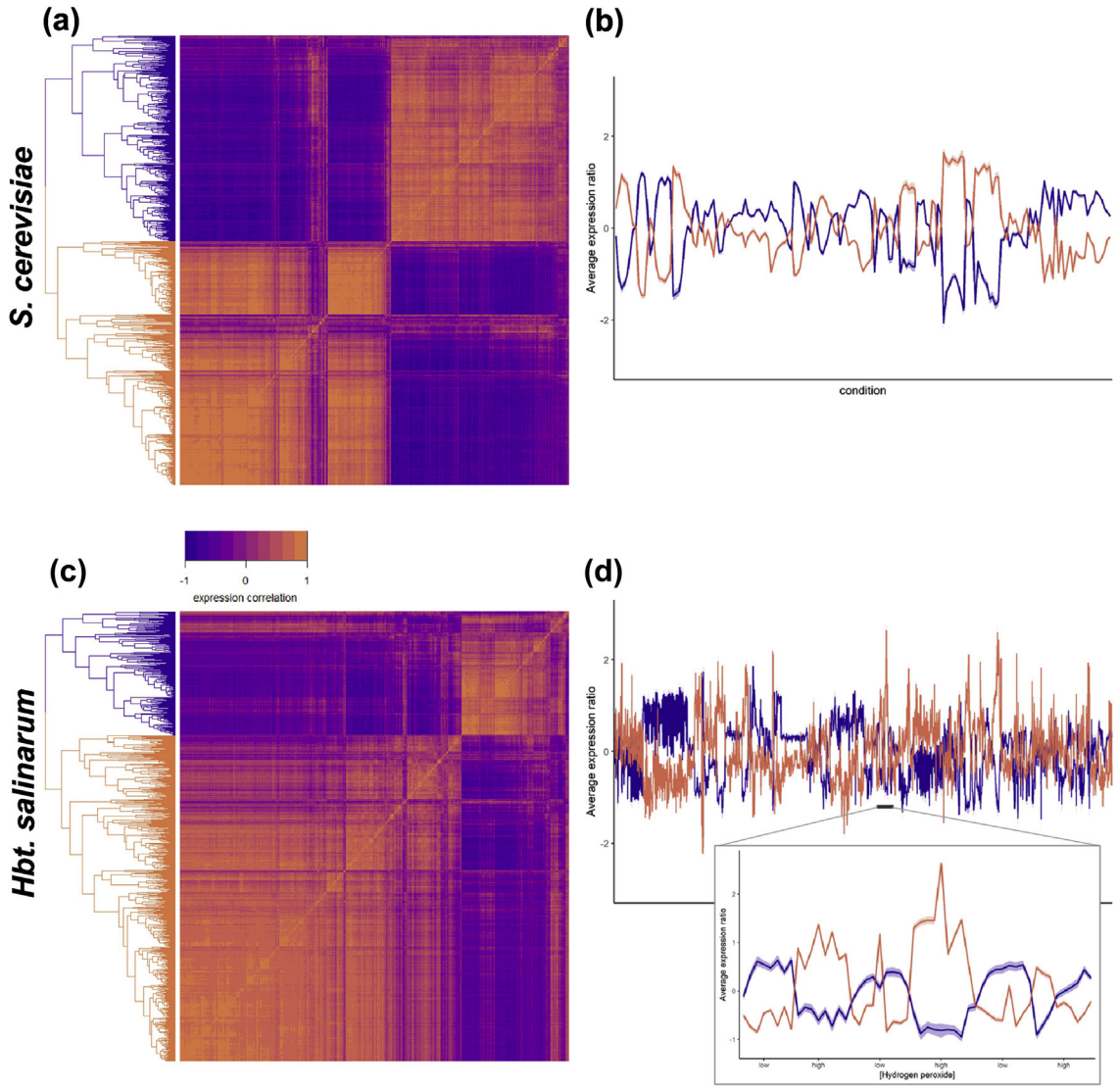

Fig. 1. Similar expression programs occur upon stress exposure in both *S. cerevisiae* and *Hbt. salinarum*. The *S. cerevisiae* ESR (A and B) is characterized by a global expression program consisting of two anti-correlated gene clusters [9]. (A) Gene-by-gene correlation plot of the 1000 most variable genes across 174 transcriptome profiles. Genes were clustered into two groups, which corresponded to repressed (cool colors in heatmap and purple lines on dendrogram) *versus* induced genes (hot colors, orange lines). (B) The average expression of the 543 repressed genes (purple line) and 457 induced genes (orange line) is strongly anti-correlated across conditions. *Hbt. salinarum* exhibits similar genome-wide expression changes upon exposure to diverse stress. (C) Gene-by-gene correlation plot of the 1000 most variable genes in *Hbt. salinarum* responding to 1495 transcriptome profiles [37]. After clustering, genes were split into two clusters. Colors correspond to those in panel A. (D) Mean expression profile for 276 repressed genes (purple line) is strongly anti-correlated with mean expression of 724 induced genes (orange line). The inset depicts the mean expression profiles as they vary over 52 time points corresponding to fluctuating concentrations of hydrogen peroxide. Shaded regions in the line plots (B, D) represent the 95% confidence interval of the average expression across genes in the cluster.

responses to stress have been reported across fungal species (reviewed in Refs. [3,18]). To date, the degree to which these characteristics of a core transcriptional stress response are conserved in archaea remains unexplored.

Archaeal molecular machinery often reflects that of both bacteria and eukaryotes (reviewed in Refs. [19–21]). For instance, the basal transcriptional machinery in archaea, like that of eukaryotes, consists of the general transcription factor B (homologous to TFIIB), TATA binding protein, and an RNA-Pol II-like polymerase. Bacteria, in contrast, use the sigma subunit to recruit RNA-Pol to initiate transcription, with genome-wide transcriptional responses to stress mediated by alternative sigma factors (reviewed in Ref. [22]) and globally acting TFs [23]. Sigma factors

have not been identified in archaeal genomes [24]. However, the TFs that activate and repress gene expression in response to environmental cues in archaea (e.g., stress-responsive TFs) typically resemble those of bacteria [25]. These TFs can bind directly to a signaling ligand (e.g., metal, sugar, metabolite) to activate or repress transcription [19,26–28]. These hybrid mechanisms of transcriptional control, unique environmental interactions, and evolutionary implications make archaeal species excellent models for understanding the basic principles of transcription regulation and fundamental transcriptional programs that may be common to all three domains of life. Together with recent phylogenetic evidence that eukaryotes may have originated from within the archaeal branch of the tree of life [29–33], an investigation of general stress response in archaeal species is central to understanding how such programs may have evolved in eukaryotes.

In this review, we compare previously published, large-scale expression data from representative eukaryotic and archaeal model species. We evaluate archaeal data using criteria that define the eukaryotic ESR [9] to determine if an ESR-like stress responsive transcriptional program is present in archaea. Based on this analysis, we posit that ESR-like features are shared between the two domains. A survey of literature on other species of eukaryotes and archaea synthesizes our current understanding of transcriptional stress response across the two domains, and emphasizes the need for additional expression data across archaeal species.

Characteristic Criteria Defining the ESR

The ESR is a genomic expression program that integrates responses to individual and distinct cellular signals upon environmental change. Four properties defining the ESR, presented in the original paper from Gasch and colleagues [9], are summarized below:

1. Global, stereotypical transcriptional reprogramming: large-scale, rapid, and transient transcriptional changes occur in a "stereotypical manner" [9] upon exposure to diverse stresses. One group of genes is induced in response to stress (iESR), and the other is repressed (rESR). These groups are strongly anti-correlated with one another across time and various stress treatments.
2. Induced and repressed genes are enriched for distinct functions: rESR genes encode functions enriched for growth-related processes, various aspects of translation, RNA metabolism, nucleotide biosynthesis, and other metabolic processes [8,9]. In contrast, iESR genes were enriched for processes involved in protection and repair of stress-related damage, including redox reactions, protein folding and degradation, DNA damage repair, and intracellular signaling [9,10].
3. Duration and magnitude of the transcriptional response is dependent on the intensity of stress: change in transcript levels during the ESR is transient and expression eventually returns to basal levels as homeostasis is re-established. The duration and magnitude of expression changes are dependent upon the severity of stress [9].
4. Induction of the transcriptional response is specific to stress exposure: the large, transient changes in expression characteristic of the ESR are detectable only upon the onset of exposure to environmental stress. Transcriptome behavior reciprocal to the ESR is not observed when environmental stress is lessened or removed [9].

In the following sections, we use each of these criteria to evaluate the transcriptional dynamics observed in *Halobacterium salinarum*, a model archaeal species.

Halobacterium salinarum Exhibits a Eukaryote-like ESR

General methodology and rationale for selected data

For the analysis of focus in this review, we selected transcriptome data sets from a single representative species for each of the archaeal and eukaryotic domains of life. To minimize artifacts due to batch effects and differences in strains and protocols across laboratories, we limited our analysis to published data that were collected within a single laboratory [34–36]. As such, we selected two well-studied species, the mesophilic budding yeast in which the ESR was first reported, *Saccharomyces cerevisiae* [9] and the halophilic archaeon *Hbt. salinarum* NRC-1 [37]. For both species, extensive expression data, comprising hundreds to thousands of transcriptome profiles across a variety of stress conditions, have been collected within single laboratories (see Methods). The collection of expression data for *Hbt. salinarum* far outstrips that of other model organisms in the domain [38], although many smaller-scale data sets are now available for other organisms (example data sets: *Methanococcus maripaludis* [39], *Haloferax volcanii* [41,40], *Thermococcus gammatolerans* [42], *Methanothermobacter thermautotrophicus* [43], *Methanosaeta thermophila* [44], and *Sulfolobus acidocaldarius* [45]). Although

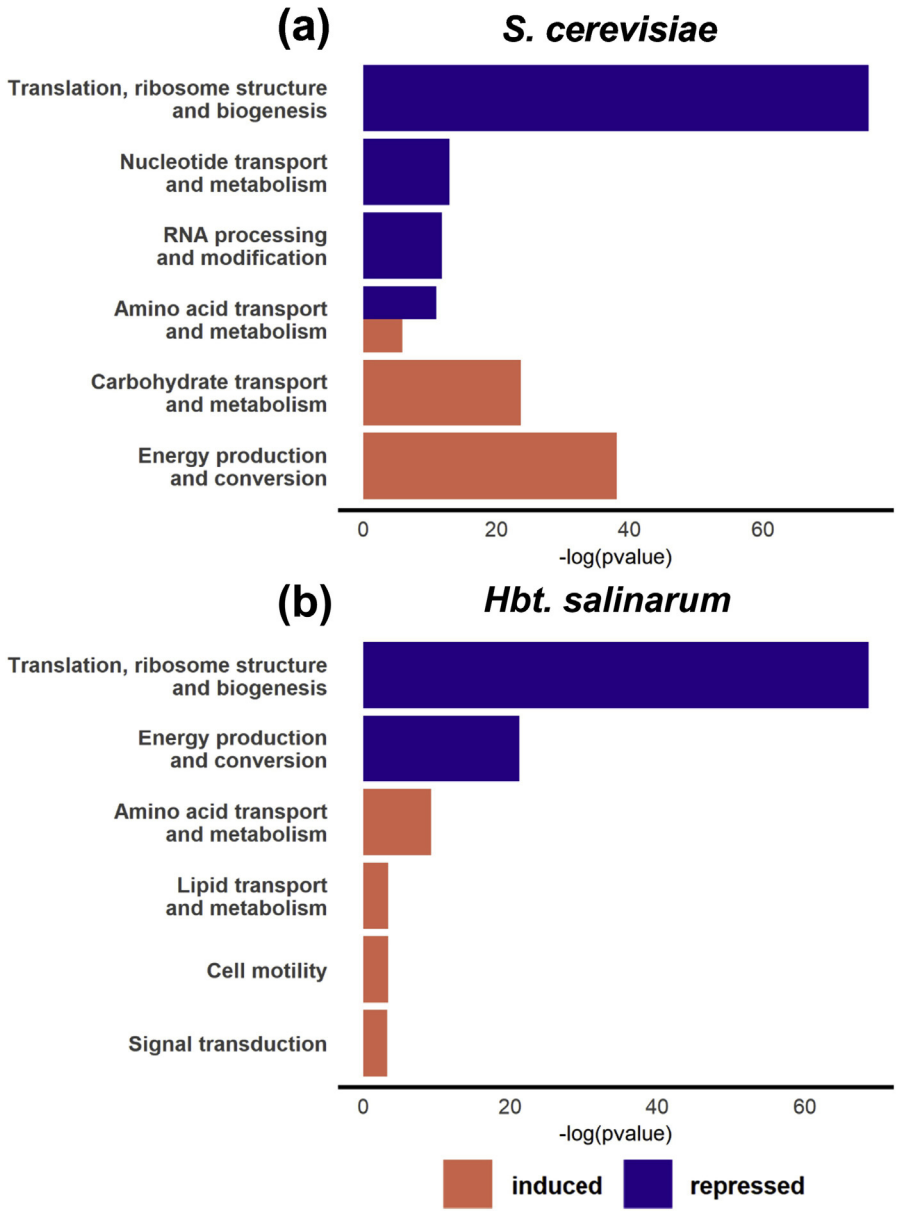

Fig. 2. Repressed genes share functions in *Hbt. salinarum* and *S. cerevisiae*. Degree of functional enrichment in COG categories within induced and repressed gene clusters in *S. cerevisiae* (A) and *Hbt. salinarum* (B). (A–B) Colors are as in Fig. 1: purple depicts genes whose mean expression was repressed, while orange represents the cluster of genes whose mean expression was induced by exposure to stress. In both organisms, translation and ribosome biogenesis was the most strongly repressed upon exposure to stress. Significance was determined by hypergeometric test against the whole genome and corrected for multiple hypothesis testing. Protein sequences were functionally annotated using eggNOG mapper [51].

other data describing the ESR have been collected in *S. cerevisiae* and other yeast species since the ESR was first reported [46–49], we elected to analyze the original expression microarray data from Gasch *et al.* [9] as our eukaryotic benchmark. This way, both the necessity and sufficiency of each criterion can be evaluated as it exists in the third domain (see ensuing sections). Furthermore, both data sets were collected using expression microarrays, limiting any effects of sequencing technology or platform on these data.

As both data sets contain transcriptome profiles from optimal and stressful growth environments, we reasoned that stress-dependent genes would exhibit variable expression patterns. To identify stress-dependent genes, gene-by-gene expression correlations were measured for 1000 genes in each species with highest variance observed across at

Table 1. GO terms significantly enriched in *Hbt. salinarum* by gene cluster

Gene cluster	Function	GO term	Adjusted *p* value
Repressed	Peptide metabolic process	GO:0006518	2.29E−21
Repressed	Peptide biosynthetic process	GO:0043043	2.10E−21
Repressed	Translation	GO:0006412	1.55E−21
Repressed	Macromolecule metabolic process	GO:0043170	5.20E−09
Repressed	Ribosomal large subunit biogenesis	GO:0042273	2.73E−04
Repressed	Ribosomal small subunit assembly	GO:0000028	7.09E−03
Repressed	Ribosomal small subunit biogenesis	GO:0042274	6.98E−03
Repressed	ATP metabolic process	GO:0046034	4.98E−02
Repressed	Regulation of translation	GO:0006417	1.90E−02
Repressed	Ribosomal large subunit assembly	GO:0000027	1.83E−02
Induced	Function unknown		1.87E−03

least 90% of transcriptome profiles tested. Note that 1000 genes corresponds to 16% and 40% of the *S. cerevisiae* and *Hbt. salinarum* genomes, respectively. We chose a more permissive filtering strategy due to substantial variation in the number of genes reported to be involved in the ESR across fungal species (relative to genome size).

Correlations were clustered and resultant dendrograms identified two major gene clusters representing induced and repressed genes. Each cluster was tested for functional enrichment according to Clusters of Orthologous Groups (COG) using eggNOG mapper to assure functional correspondence of gene groups across the two species [50,51].

Criterion 1: Global, stereotypical transcriptional reprogramming

A striking feature of the eukaryotic ESR is the clustering of differentially expressed genes into two anti-correlated groups. Genes within each group exhibit similar expression dynamics across diverse stress conditions [9], including temperature, chemical, and nutrient stressors (Fig. 1A and B). The *S. cerevisiae* ESR is distinct from previously described Msn2/Msn4-dependent general stress response [52–54] because the regulation of ESR genes is dependent on many different signaling systems and regulators [9]. For example, many genes in the ESR are also induced by the high-osmolarity glycerol pathway in response to osmotic stress [55], while transcription factor Mec1 induces ESR genes in response to DNA damage [56]. Thus, the expression of genes in the ESR is regulated by a network of different transcription factors depending on the conditions and the response is governed by multiple upstream signaling pathways.

In *S. cerevisiae*, 868 genes were originally identified by Gasch *et al.* [9] via hierarchical clustering as being involved in the ESR, comprising more than 14% of the genome. Of those genes, 283 were induced and were 585 repressed (iESR and rESR, respectively) [9]. Many of the same genes were confirmed in independent experiments and analyses [46]. Using gene-by-gene correlations, our re-analysis here confirms the striking program of *S. cerevisiae* transcription dynamics in response to stress (Fig. 1A) across nearly all 1000 genes included in our analysis. Upon clustering, we identified a repressed cluster containing 543 genes and an induced cluster containing 457 genes. The average expression value of genes in each of the two clusters is strongly and significantly anti-correlated across the 174 transcriptome profiles (Fig. 1B; $\rho = -0.95$, $p < 2.2 \times 10^{-16}$). Although our analysis differed slightly from the methods used in the original analysis that identified the ESR ([9], Methods), our filtering and clustering strategy recovered ~two-thirds of the 868 genes originally ascribed to the *S. cerevisiae* ESR (Table 3), and maintained the functional enrichment, clustering relationships (Supplemental Fig. 1), and response dynamics originally reported.

To determine if the archaeal transcriptome also exhibits this genome-wide structural reprogramming, the transcriptome experiments for *Hbt. salinarum* [37] were analyzed using the same methodology. A similar pattern of co-expression was detected in the gene-by-gene correlations for the 1000 most variably expressed genes (Fig. 1C). Upon clustering, we identified a repressed cluster containing 276 genes and an induced cluster containing 724 genes. The average expression of these genes (Fig. 1C) is strongly and significantly anti-correlated across the nearly 1500 transcriptome profiles tested (Fig. 1D; $\rho = -0.76$; $p < 2.2 \times 10^{-16}$), suggesting that *Hbt. salinarum* exhibits stereotypical expression changes upon exposure to different stresses. A compelling example of this pattern was observed when transcriptomes were measured over time during treatment and recovery from hydrogen peroxide. There, the cluster of genes that is induced under favorable growth conditions (low oxidative stress) exhibits dramatically reduced expression when exposed to higher concentrations of hydrogen peroxide (Fig. 1D, inset). Such anti-correlation was also observed when transcriptomes were measured over time during a transition from anaerobic to aerobic conditions (61 of the 1500 experiments, [57]). In that case, the rate of induction of ~100

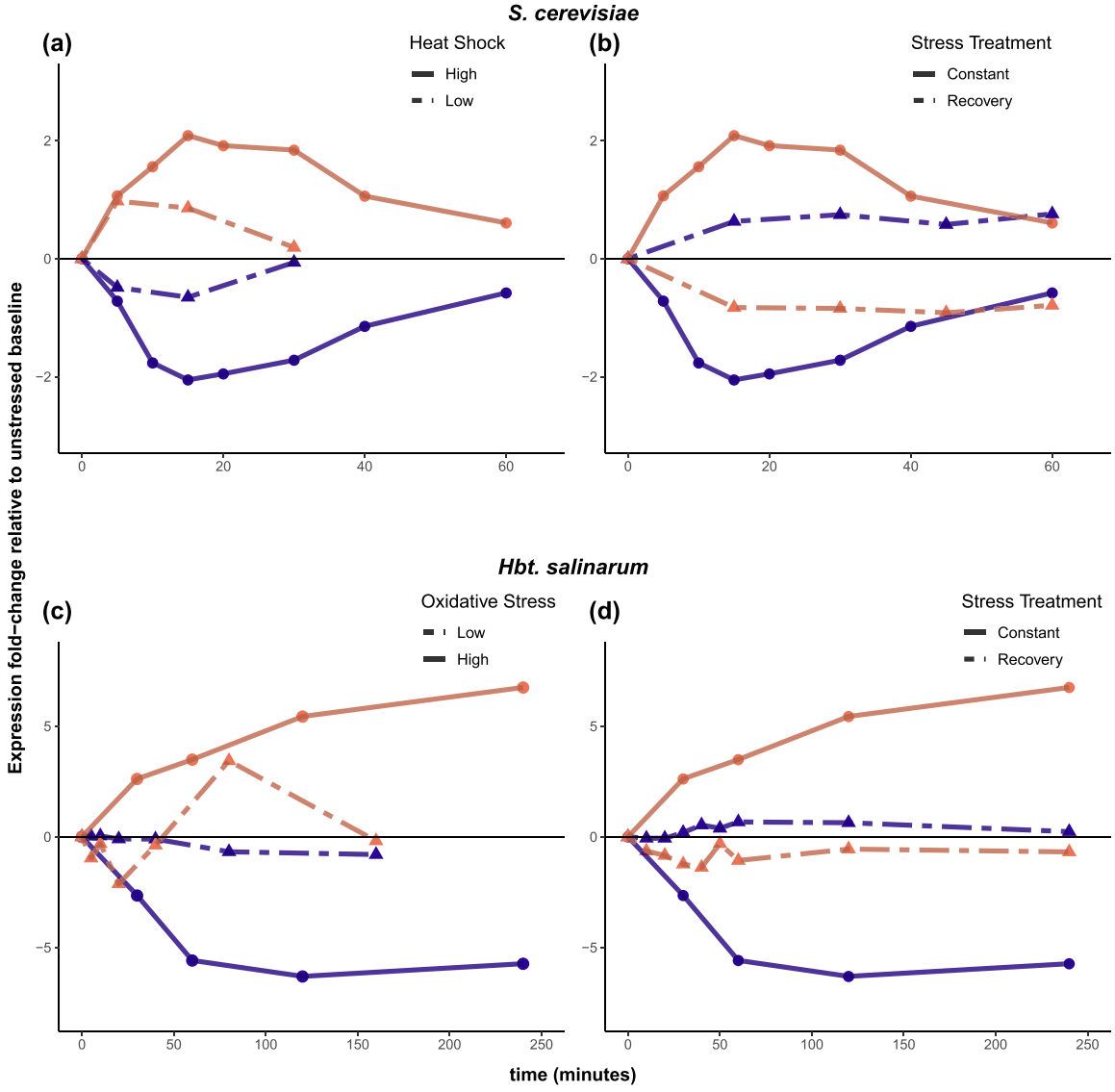

Fig. 3. Response dynamics depend on the directionality and severity of stress in both *S. cerevisiae* and *Hbt. salinarum*. (A) The fold-change relative to baseline expression in un-stressed cultures in *S. cerevisiae* is greater in response to extreme heat shock (temperature shift from 25 ˚ C to 37 ˚ C, solid line) than moderate heat shock (shift from 29 ˚ C to 33 ˚ C, dashed line). (B) The expression response is specific to exposure to stress, not removal. Induced and represed gene clusters in response to extreme heat shock (25 ˚ C to 37 ˚ C, solid line) and recovery from extreme heat shock (37 ˚ C to 25 ˚ C, dashed line). (C) Average expression profiles in *Hbt. salinarum*. Fold-change of the two gene clusters upon exposure to 4 mM paraquat (solid) is greater than the fold-change in response to a lower 0.25 mM challenge (dashed). (D) When cells are removed from 4mM paraquat treatment (dashed line), the expression program is not reciprocal to the expression dynamics of cells exposed to constant 4mM paraquat treatment (solid line). (A−D) Colors are as used in Fig. 1; purple depicts the cluster of genes whose expression was on average repressed by exposure to stress, while orange represents the cluster of genes whose expression was on average induced by exposure to stress.

genes involved in growth under aerobic conditions deviated from each other by only 1.5 min, suggesting a surprising degree of temporal coherence [57]. Conversely, ~100 other genes required for growth under anaerobic conditions were repressed with similar temporal coherence [57]. Taken together, these analyses reveal a pronounced higher-order structure of transcriptome behavior in which a large fraction of the genome exhibits coherent expression patterns across diverse conditions in *Hbt. salinarum* (Fig. 1C-D). This suggests that, like in eukaryotes, large-scale transcriptional coordination of seemingly disparate cellular processes may also be active in archaea.

Criterion 2: Induced and repressed genes are enriched for distinct functions

The two oppositely expressed gene clusters in the yeast ESR are enriched for distinct gene functions [9]. This apparent functional specialization is thought to represent a cellular fitness trade-off between the transcription of genes encoding proteins necessary to withstand stress *versus* the transcription of genes associated with optimum growth [8,58,59]. In *S. cerevisiae*, genes repressed during stress (rESR) are enriched for functions associated with optimal growth, including translation (e.g., ribosome synthesis and processing) and RNA polymerase I- and III-dependent transcription [9]. Genes whose expression are induced during stress (iESR) encode a wide variety of protective and damage repair processes, including carbohydrate metabolism, protein folding and degradation, defense against oxidative stress, intracellular signaling, DNA-damage repair, and other processes [9].

Our re-analysis of the *S. cerevisiae* ESR yielded similar functional enrichments. In this re-analysis, protein sequences corresponding to all genes in each cluster were assigned a COG functional category using eggNOG mapper [51], and tested for over-representation against the whole genome using the hypergeometric test (see Methods). Genes induced upon exposure to stress are enriched for functions involved with energy production and carbohydrate metabolism. In contrast, genes repressed during stress are significantly enriched for genes involved with translation and ribosome biogenesis (Fig. 2A).

In *Hbt. salinarum*, clusters are enriched for distinct functions as determined by COG annotation and hypergeometric tests (see Methods). For the 276 repressed genes, we detected significant enrichment in COG categories for broad functional classifications such as translation, ribosome biogenesis, and energy production and conversion (Fig. 2B). The 724 induced genes were found to be enriched to a lesser extent for functions involved in lipid and amino acid transport and metabolism, cell motility, and signal transduction (Fig. 2B). Interestingly, genes attributed by COG to energy production are co-repressed with translation genes in *Hbt. salinarum*, while those two functions are oppositely expressed in *S. cerevisiae*. This could represent a unique biological feature in *Hbt. salinarum*, but new functional annotations of currently un-annotated *Hbt. salinarum* genes, or more stringent filtering cutoffs may shift the balance.

We also conducted GO term enrichment analysis of iESR and rESR genes for more detailed functional predictions. In *S. cerevisiae*, we detected enrichments similar to what was previously published [9]. In *Hbt. salinarum*, repressed genes were enriched for functions involved in large and small ribosome subunit biogenesis and assembly, peptide biosynthesis, metabolic processes, ATP metabolic process, and regulation of translation (Table 1). For induced genes in *Hbt. salinarum*, only genes without a functional classification were significantly enriched after GO analysis, suggesting a need for further research into the functions of genes induced in response to stress in this organism.

Although the paucity of GO annotations in *Hbt. salinarum* prevents a more detailed discussion comparing the functional roles of individual genes induced upon exposure to stress to those of *S. cerevisiae*, it is important to note that the functions of many iESR genes in *S. cerevisiae* were also uncharacterized at the time the ESR was first reported [9]. This situation has been largely ameliorated by extensive whole-genome annotation efforts in the yeast research community, including deletion collections and subsequent analyses [60–71]; see reviews [72–74]. As genetic and genomic tools advance and become available in archaeal model species [75–81], annotated functions for archaeal-specific genes will improve our ability to make more nuanced comparisons between stress-responsive functions across domains.

In spite of these limitations, certain functional dynamics are similar between *S. cerevisiae* ESR and *Hbt. salinarum* stress-responsive transcriptional programs, most notably the repression of genes involved in ribosome biosynthesis and translation (Fig. 2). This apparent condition-dependent trade-off between stress defense and repair *versus* rapid growth has been reported in other biological contexts, including microbial ecology, host–pathogen interactions, and cancer proliferation ([82], see reviews [83–85]), suggesting an important overarching biological principle.

Criterion 3: Duration and magnitude of the transcriptional response are dependent on the intensity of stress

Notable among the dynamic features of the ESR observed in Gasch *et al.* was that the magnitude and duration of expression change is dependent on the severity of stress. These specific dynamics were explored previously using various temperature shifts [9]. In our analysis, we also qualitatively recapitulated this feature within the *S. cerevisiae* response to heat shock (Fig. 3A; compare with Ref. [9] Fig. 2C–D). Extreme heat shock (25 °C to 37 °C) elicits a greater transcriptional response.

To compare these results from *S. cerevisiae* with dose-responsive expression dynamics in archaea, we used previously published time-course expression data measuring the transcriptional response of *Hbt. salinarum* during exposure to a high (4 mM) and low (0.25 mM) concentration of the redox cycling agent paraquat (Fig. 3C) [37,86]. *Hbt. salinarum* cultures treated with the higher concentration of paraquat mount a higher magnitude change in expression compared to cultures treated with a lower concentration (Fig. 3C). Cultures treated with the higher

concentration of paraquat do not re-establish homeostasis during the course of the experiment (Fig. 3C–D, solid lines), perhaps due to the longer doubling time of *Hbt. salinarum* relative to *S. cerevisiae*. However, gene expression returns to nearly pre-treatment levels after 150 min of exposure to sub-inhibitory concentrations of oxidant (Fig. 3C, dashed lines). These expression features are not unique to paraquat as a condition—analysis of dose-responsive, time-dependent expression in response to zinc [87] yielded similar results (Supplemental Fig. 2).

Criterion 4: Induction of the transcriptional response is specific to stress exposure

In the fourth and final criterion, Gasch *et al.* [9] evaluated transcriptional dynamics upon relief from stress, demonstrating that induction of the ESR is specific to the onset of stress (as opposed to the non-specific result of any major perturbation). In our analysis, we qualitatively recapitulated this characteristic using the *S. cerevisiae* response to heat shock (Fig. 3B; compare with Ref. [9], Fig. 6C). Extreme heat shock (25 ° C to 37 ° C) elicits a distinct transcriptional response from the reciprocal environmental shift (37 ° C to 25 ° C) (Fig. 3B). That is, heat shock elicits the characteristic, transient peak of expression of ESR genes, whereas shifting cultures back to an optimal environment causes a rapid transition to basal expression levels without the peak (Fig. 3B, dashed lines).

Similarly, *Hbt. salinarum* cultures incubated with constant treatment of 4 mM paraquat exhibit a transcriptional response that is distinct from cultures transitioned from 4 mM paraquat to optimum growth conditions (Fig. 3D). Cultures exposed to high concentrations of paraquat experience oxidative stress and exhibit several ESR-like transcriptional characteristics (Fig. 3C). In contrast, cultures recovering from extreme oxidative stress do not exhibit a reciprocal gene expression response. Rather, expression rapidly and uniformly returns to basal expression levels (Fig. 3D, dashed line). Similar, non-reciprocal dynamics are observed upon treatment with hydrogen peroxide [86] (Supplemental Fig. 2).

Summary of ESR criteria

Together these explorations reveal previously undescribed similarities between the eukaryotic ESR and transcriptional changes observed in the representative archaeal species, *Hbt. salinarum*, in response to environmental perturbations. Upon sensing changes in the surrounding environment, *Hbt. salinarum* exhibits transient transcriptional dynamics characterized by the induction and repression of large portions of the genome (criteria 1 and 2). This transcriptional response is specific to stressful conditions and sensitive to the magnitude of stress (criteria 3 and 4). Based on this evidence, we conclude that *Hbt. salinarum* mounts an ESR-like transcriptional program during stress exposure.

Evidence for the ESR in Other Microbial Eukaryotes

Beyond *S. cerevisiae*, genome-wide transcriptional programs have been described in other yeast species, with key similarities and differences. For example, although a significant number of *S. cerevisiae* orthologs were detected in the *Schizosaccharomyces pombe* ESR, control of the *S. pombe* ESR is mediated by two transcription factors, Sty1 and Atf1, which are not homologous to *S. cerevisiae* ESR regulators Msn2 and Msn4 [8,9,52,88]. This provides evidence for variation in regulatory mechanisms despite conservation of ESR effector genes. The opportunistic human pathogen *Candida glabrata* exhibits a strong transcriptional response upon stress, altering expression of over 20% of its genome [89]. Unlike *S. pombe*, *C. glabrata* encodes both *S. cerevisiae* Msn2 and Msn4 orthologs and shares many *S. cerevisiae* Msn2 target genes [89]. In contrast, initial studies in *Candida albicans* reported an absence of the ESR, or only weak induction of *S. cerevisiae* ESR orthologs [90]. Subsequent work has identified components of the ESR that are present in *C. albicans* [8,91–93]; for example, the promoters of iESR orthologs are enriched for *cis*-regulatory sequence elements similar to the *S. cerevisiae* stress response element (STRE) [94]. Furthermore, heterologous expression of the *C. albicans* Msn4 ortholog in *S. cerevisiae* weakly induces STRE-dependent expression [90], and the Msn2 ortholog has been associated with stress tolerance against weak acid stress [95]. Interestingly, in studies in which similar conditions were tested in *S. cerevisiae*, *S. pombe*, *C. albicans*, and *C. glabrata*, a high degree of overlap in stress-responsive gene expression was observed during oxidative and osmotic stress.

Characteristics of the ESR in more ancient yeast species (preceding the whole genome duplication) are less clear. Although putative Msn2 orthologs are present in *Ashbya gossypii* and *Kluyveromyces lactis* [89] and both species exhibit oxidative stress response [96,97], neither organism has been evaluated for ESR-like dynamics. In *Aspergillus nidulans*, only a limited set of ~13 genes was found to respond consistently to different types stress [98]. While *L. kluyveri* undergoes ESR-like transcriptional changes in 33% of genes, only 4 of the 23 STRE genes in the *S. cerevisiae* ESR are conserved in the *L. kluyveri* ESR [48].

Thus, genes induced during environmental stress (iESR), known regulators, and the conditions that induce a response vary across fungi. Such variation

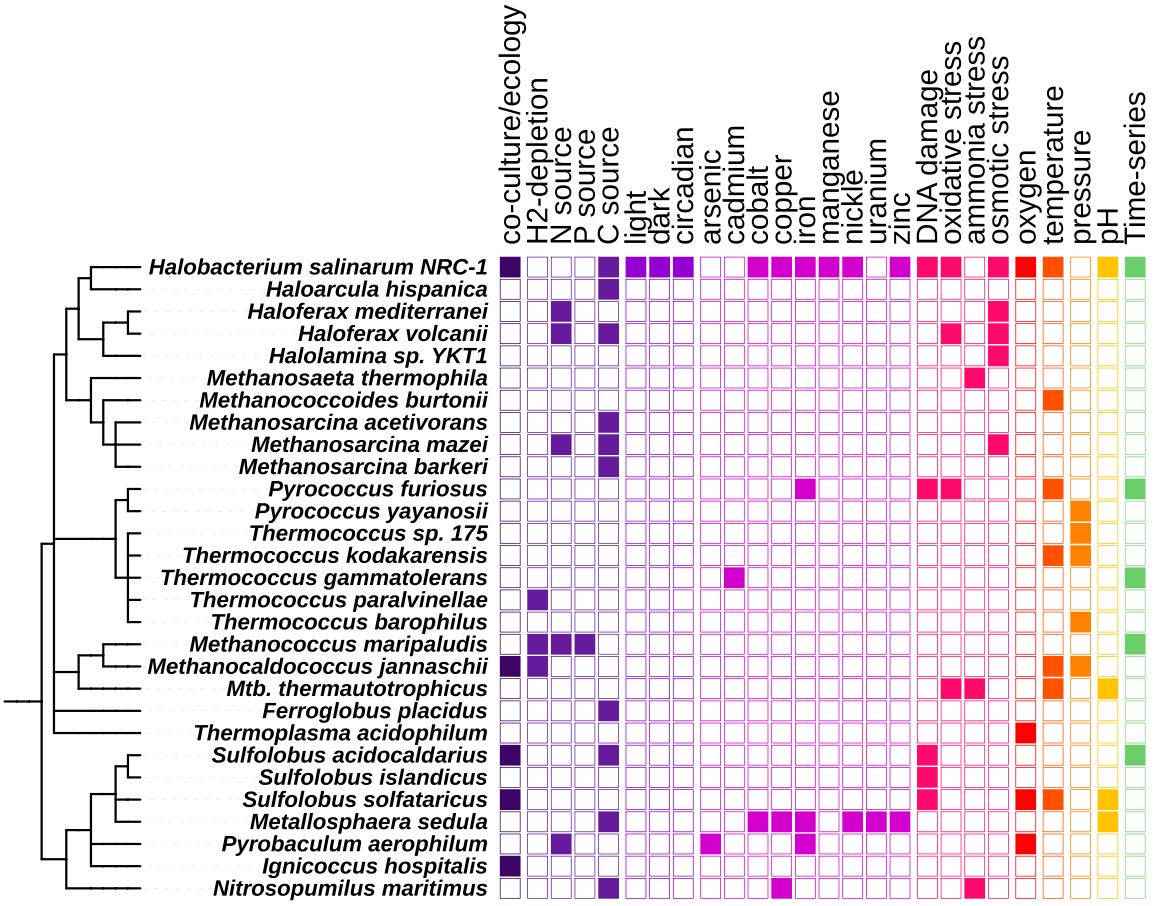

Fig. 4. Available archaeal transcriptome profiles in non-standard conditions. Studies reporting genome-wide expression by species and variable condition. If appropriate, proteomic data are also referenced. **Co-culture/ecology:** *Hbt. salinarum* [37,139]; *Mcc. jannaschii* GSE112986; *S. acidocaldarius* [140]; *S. solfataricus* [141]; *I. hospitalis* [142]. **H_2-depletion:** *Tco. paralvinellae* [143]; *Methanococcus maripaludis* [39,144]; *Mcc. jannaschii* GSE112986. **N source:** *Hfx. mediterranei* [130,145]; *Hfx. volcanii* [146] GSE130934; *Msc. mazei* [147,148]; *Mco. maripaludis* [39,144]; *Pyb. aerophilum* [149]. **P source:** *Mco. maripaludis* [39,144]. **C source:** *Hbt. salinarum* [37,112,113]; *Har. hispanica* [150]; *Hfx. volcanii* [40,151]; *Msc. acetivorans* [152,153]; *Msc. mazei* [154–156]; *Msc. barkeri Fusaro* [157]; *F. placidus* [158]; *S. acidocaldarius* [45,159]; *Metallosphaera sedula* [160,161]; *N. maritimus* [162]. **Light, dark, and circadian:** *Hbt. salinarum* [37,163]. **Metals:** *Hbt. salinarum* [37,87,121,122]; *Pyr. furiosus* [164,165]; *Tco. gammatolerans* [42]; *Metallosphaera sedula* [166–168]; *Pyb. aerophilum* [149]; *N. maritimus* [162]. **DNA damage**: *Hbt. salinarum* [37,169]; *Pyr. furiosus* [170]; *S. acidocaldarius* [171]; *S. islandicus* [172]; *S. solfataricus* [173–175]. **Oxidative stress:** *Hbt. salinarum* [37,116]; *Hfx. volcanii* [41]; *Pyr. furiosus* [165]; *Mtb. thermautotrophicus* [43]. **Ammonia stress:** *Methanosaeta thermophila* [44]; *Mtb. thermautotrophicus* [43]; *N. maritimus* [176]. **Osmotic stress:** *Hbt. salinarum* [177,178]; *Hfx. mediterranei* [179]; *Hfx.volcanii* [127,180]; *Halolamina sp. YTK1* [126]; *Msc. mazei* [181]. **Oxygen:** *Hbt. salinarum* [37,57,182]; *Tpl. acidophilum* [183]; *S. solfataricus* [184]; *Pyb. aerophilum* [149]. **Temperature**: *Hbt. salinarum* [177,185]; *Methanococcoides burtonii* [186]; *Pyr. furiosus* [187,188]; *Tco. kodakarensis* GSE71987; *Mcc. jannaschi* [189,190]; *Mtb. thermautotrophicus* [43]; *S. solfataricus* [192]. **Pressure:** *Pyr. yayanosii* [193]; *Thermococcus sp. 175* GSE70228; *Tco. kodakarensis* [129]; *Tco. barophilus* [129]; *Mcc. jannaschi* [189,194]. **pH:** *Hbt. salinarum* [195]; *Mtb. thermautotrophicus* [43]; *S. solfataricus* [191]; *Metallosphaera sedula* [196].

appears to increase with evolutionary distance. In contrast, genes repressed during stress across yeast species are more similar than genes induced. Taken together, these observations suggest that rESR genes may be under strong purifying selection, whereas the iESR gene identities and their regulatory mechanisms are subject to species- or strain-specific pressures [48,99,100].

What Mechanisms Coordinate and Integrate the ESR?

Regulation of the ESR in eukaryotes

Although the ESR and the function of genes responding to stress have been well studied across

yeast species, it remains unclear how environmental signals are sensed and integrated to enact the global coordination observed for the ESR. Growth rate, cell cycle, and metabolic cycle are intertwined physiologically and also lead to time-dependent transcriptional changes similar to those observed in response to stress [101–105]. For example, in *S. cerevisiae* continuous culture experiments where growth rate was controlled by providing different limiting nutrients, increased expression of ribosomal protein genes correlated with growth rate, while expression of STRE genes decreased [102]. Overall, the majority (~80%) of iESR transcripts also increased upon slower growth [102]. The expression of more than 15% of the genome was dependent on growth rate, independent of nutrient limitation [103,106].

Transcriptional signatures of the yeast cell cycle also share similarities to both growth rate and stress response. Brauer *et al.* [103] found that the proportion of cells in G0/G1 cell cycle phase linearly correlated with growth rate. Yeast metabolic cycling (YMC) [101] has also been argued to underpin the ESR [103,105]. For example, oscillations between high and low oxygen consumption in the YMC correlate with increased resistance to lethal heat shock, which the authors argued could explain both the cross-stress protection and the growth rate dependence of heat shock sensitivity [107]. Upon slow growth, as observed during exposure to stress, *S. cerevisiae* cells accumulate in the G0/G1 phase, where metabolic cycling is most prominent [104,105]. A similar coupling of metabolic cycling, growth rate, and cell-cycle phase was reported in ESR-containing fission yeast *S. pombe*, although these cells accumulate at the G2/M transition [88,105]. Together, these results raised the possibility that much of the ESR could be explained as a general response, or a combination of responses to growth rate, metabolic cycling, and the cell cycle.

Recently, Ho *et al.* [108] addressed these issues by conducting an experiment in which cultures of *S. cerevisiae* were arrested at two points in the cell cycle, then exposed to stress. According to transcriptome, proteome, and polysome profiling evidence, arrested cells mounted a *bona fide* ESR transcriptional program upon exposure to acute stress and changes in expression of ESR genes were independent of cell cycle phase. Together with previous studies, these results suggest that the ESR is not dependent upon cell cycling or growth rate for regulation in *S. cerevisiae*. An interesting question for future research is whether a common regulatory network links the ESR, cell division cycle, and metabolic cycling.

Candidate regulators of the ESR in archaea

Global mechanisms that coordinate the ESR in archaea remain unclear. However, recent progress has characterized the function of archaeal global transcriptional regulators (recently reviewed in Ref. [19]). For example, TrmB family proteins, conserved across archaeal lineages, function as global metabolic regulators, and therefore represent candidates for control of the rESR [109–113].

Other transcriptional regulators have been implicated in the response to stress and therefore represent candidates for regulating the iESR. Archaeal-specific regulators include MsvR in methanogens and RosR in halophiles, each of which regulates genes induced during oxidative stress [114–116]. Surprisingly, the eukaryote-like TFB and TBP proteins have also been implicated in archaeal stress response regulation, including heat shock and nutrient starvation [45,117]. Additional candidate TFs have recently been discovered in *Hbt. salinarum*. For example, 12 of 27 transcription factors analyzed were implicated in fitness under two or more stress conditions [118]. Similar cross-stress regulation has been observed for the Lrp family TFs, where shared targets of the eight paralogs present in the *Hbt. salinarum* genome encode essential cellular functions, whereas independent targets are responsive to specific stressors [119,120]. A set of four paralogous DtxR-family regulators (Idr1, Idr2, SirR, and TroR) cross-regulate each other to form a complex subnetwork in response to cellular iron concentrations [87,121,122].

In spite of our increasing knowledge of transcription factor function in archaea, additional research is required to understand how perturbation of these TFs (or other as-yet-uncharacterized transcription factors) may affect the ESR, the functions of the genes regulated by these TFs, and how these TFs communicate and/or cross-regulate each other.

Toward an Evaluation of ESR-like Programs Across Archaeal Species

To evaluate the possibility of a conserved genome-wide transcriptional stress response program in archaea, we compared the function of genes differentially expressed in response to stress across *Hbt. salinarum* and other archaeal species. In general, the stressors tested in many prior studies were specific to the unique niche of the extremophile of interest, including hypo-osmotic shock for halophiles, temperature extremes for hyperthermophiles, and so on (Fig. 4). As a result, transcriptome responses to a variety of stressors are rarely measured in a given organism, despite the dynamism of extreme environments and the frequency of polyextremophily across archaea [123]. In addition, studies that measure gene expression in archaea over time subsequent to stress shock are rare, with notable exceptions [37,45,124]. Measuring transcription under such experimental designs would

be a fruitful avenue for future investigations into the archaeal ESR. Once such data are collected, the analytical approach described here would provide a clear definition of what constitutes a transcriptional stress response. Leveraging this definition, it would be interesting to test the hypotheses that archaeal extremophiles undergo a *bona fide* stress response when exposed to mesophilic conditions, and have evolved to thrive in environments with low energy availability and under chronic energy stress [125].

Nevertheless, recent transcriptomics studies on archaeal species report a common trend in which genes encoding core cellular processes required for rapid growth are repressed during stress in a similar manner to the ESR of yeast and *Hbt. salinarum* (Fig. 3). Repression during stress of processes such as ribosome biogenesis and translation, DNA replication, and biosynthesis of macromolecules and their building blocks (e.g., nucleotides and amino acids) has been widely reported (Fig. 4). In particular, the repression of translation has been reported across species and stress conditions, including halophiles exposed to suboptimal salt concentrations [127−128]; thermoacidophiles and methanogens under nutrient limitation [45,124]; and hyperthermophiles under varying pressure regimes [129], among others (Fig. 4). However, an evaluation of functional conservation of genes induced during stress across archaeal species awaits experimental characterization of unknown function genes, as well as comparative transcriptomics across species exposed to the same stress.

Also consistent with what has been observed in the ESR for yeast [8,9] and here for *Hbt. salinarum* (Fig. 1), large proportions of archaeal genomes were differentially expressed during stress. For example, in *Halolamina* sp. *YKT1* exposed to sub-optimal salt concentrations, the authors reported that 55% of the genome was up-regulated and 41% was down-regulated [126]. Similarly, nearly half of the genome was differentially expressed at the level of transcription in *S. acidocaldarius* exposed to a time course of nutrient starvation [45]. In summary, the expression trends described here suggest the possibility of genome-wide transcriptional stress response programs in other archaeal organisms, and call for more detailed expression studies.

Concluding Remarks

Here we used the largest collection of expression experiments available for an archaeal species, *Hbt. salinarum*, to explore the existence of a coordinated global transcriptional program in response to stress. We find, based on the genome-wide expression patterns, specific dynamics, and gene functional enrichment, that *Hbt. salinarum* exhibits a genome-wide ESR-like response to stress (Figs. 1, 2, and 3). Studies in *S. cerevisiae* provide a convenient roadmap for experimental design and questions for future exploration. For example, investigating the mechanistic connections between growth rate and archaeal ESR would help identify key drivers of the transcriptional program, including the gene regulatory network and other mechanisms, and will inform investigation into cell division control in this domain. It remains to be seen how additional regulatory mechanisms such as small RNAs or post-translational regulation play a role in the context of a *Hbt. salinarum* stress response [41,130].

By recognizing a transcriptional stress response in archaea, we create a framework to begin comparing transcriptomes, with the goal of identifying conserved features of the ESR across archaeal species and across domains of life. In the future, similar analyses of transcriptomic profiles from bacterial models could reveal whether this response is general to microbes across the tree of life, or if the aspects of the ESR discussed here are specific to eukaryotes and archaea.

As discussed above (Fig. 4), additional data sets that measure expression over time are needed, with a given model organism exposed to a variety conditions. For example, a useful experimental design would measure transcriptome behavior in 5- to 10-min intervals following exposure to a given stress condition until homeostasis is re-established. Such an experiment would be repeated for a wide variety of other stress conditions. The generality of globally coordinated ESR-like stress response programs in archaea could then be evaluated at the level of data analysis, integrating transcriptomic data across these conditions, time points, and species [6,131]. It is important to note that these types of experiments are not limited to archaeal model species with genetic tool kits [38]. As costs continue to fall for high-throughput sequencing, large-scale comparative studies across related species can be an attractive alternative to genetic manipulations. Accordingly, these types of studies will drive the development of new functional annotation, analysis tools, and comparative systems biology approaches. Comparative transcriptomic analyses could then address many important open questions. For example, are certain ESR-like features are specific to monophyletic groups, or do they co-occur with certain physiologies and metabolic capabilities (e.g., thermoacidophily or methanogenesis)? Because physiology and phylogeny are tightly linked in the third domain [125], it is intriguing to speculate that differences in stress-responsive transcriptional programs could group with specific clades and environmental niches. Answering these questions may identify certain groups within archaea whose transcriptional programs resemble those of eukaryotic species, perhaps informing the understanding of eukaryotic origins.

Summary Points

- *Hbt. salinarum* induces a temporally coordinated, genome-wide transcriptional response across diverse stresses. This response shares features with the ESR in *S. cerevisiae* and other eukaryotic microbes. Investigation into a bacterial ESR could reveal universally conserved characteristics of the ESR.
- Functions of genes repressed during stress are conserved between eukaryotes and archaea, whereas genes induced during stress appear to encode niche-specific functions that vary with evolutionary distance. The molecular and evolutionary mechanisms underlying such conservation remain fundamental open questions.
- The diversity of environmental niches inhabited by archaeal species makes this domain an attractive target to explore conserved features of the genome-wide transcriptional stress response.
- Additional high-resolution temporal transcriptome data measured across an array of conditions are needed to elucidate specific stress response dynamics and potential ESR-like programs among archaeal species.

Methods

Data provenance

Microarray data were downloaded and accessed as reported in Table 2. All computer codes associated with the data analysis and figures reported in this study are freely available via the GitHub online repository at GitHub.

Preparation of data for comparative analysis

Expression data were accessed and downloaded as reported in Table 2 and analyzed in the R coding environment. If necessary, data were transposed using a custom function that calls base R and dplyr() tools into a matrix with genes in the columns and transcriptome profiles in the rows [132]. Data were filtered to include only the 1000 most variable genes whose expression was detectable in at least 90% of transcriptome profiles tested (Supplemental Fig. 3).

Table 2. Data provenance

Domain	Conditions	Data URL	Citation
Eukarya	174	www-genome.stanford.edu/yeast_stress	[9]
Archaea	1495	egrin2.systemsbiology.net/downloads/	[37]

Table 3. Number of genes retained after each filtering step

Data set	*S. cerevisiae*	*Hbt. salinarum*	S. *cerevisiae* ESR
Original	6152 (100%)	2400 (100%)	868 (100%)
90% profiles	5584 (90.8%)	2400 (100%)	837 (96.4%)
1000 most variable	1000 (16.2%)	1000 (41%)	570 (65.7%)

Percentages in parentheses represent the fraction retained relative to the original number of genes in top row.

Table 3 displays summary metrics for these filtering steps.

The entire filtered data sets are available via GitHub. For analyses relevant to criteria 3 and 4 (Fig. 3), *Hbt. salinarum* log10 expression values from cultures exposed to paraquat at each time point were normalized relative to those at the start of the time course (time zero, scripts for this analysis can be found in our GitHub repository). Data subject to a similar normalization scheme was already provided in the original publication of the *S. cerevisiae* expression data [9]. As such, for each time point, the *y*-axis represents the fold change in average expression relative to the un-stressed, time-zero sample.

Clustering expression data and heatmaps

Genes within filtered data sets were grouped by expression profile using complete linkage hierarchical clustering using functions in the dendextend() package in the R coding environment [133]. Heatmap visualizations of clustering data were conducted using gplots() [134]. Since the ESR is characterized by two anti-correlated clusters in yeast, resultant dendrograms were split into two clusters using the cutree() function for visualization and subsequent analysis. Resultant gene lists were then subjected to functional enrichment analysis relative to the whole genome.

Functional enrichment

Genome-wide protein sequences and genome annotation files were downloaded from NCBI for reference strains *Hbt. salinarum* GCF_000006805.1 and *S. cerevisiae* GCF_000146045.2 on 2018-11-08. For each organism, protein sequences were used to assign COG functional annotations using eggNOG mapper 4.5 default settings [51]. The proportions of RefSeq proteins for *S. cerevisiae* and *Hbt. salinarum* that were processed using the eggNOG mapper were 98% and 93%, respectively (this includes proteins with "function unknown").

Since eggNOG uses text mining to assign single-letter functional categories in addition to mining KEGG, SMART, Pfam, and GO databases, Non-supervised Orthologous Groups (NOG), missing a functional category assignment (the remaining 2% and 6% of *S. cerevisiae* and *Hbt. salinarum* proteins, respectively), have no informative descriptions in the searched space. As such, we manually assigned genes with a missing functional category to "S," or unknown function, in order to evaluate if missing functions were driving enrichment. Finally, for *Hbt. salinarum* genes, we manually verified that eggNOG assigned functional categories were congruent with previously published functional predictions using the *Hbt. salinarum* NRC-1 reference genome [135,136]. As expected, *Hbt. salinarum* had a high percentage of proteins of unknown function (approximately 30% of the proteome *versus* the 20% of the *S. cerevisiae* proteome), and there was some variation in the distribution of functional categories between the two genomes. However, these differences were not significant by paired *t*-test (see GitHub repository).

Genes in both iESR and rESR clusters were tested for functional enrichment against the respective genomic background for each species using a hypergeometric test. The complete list of genes, their functional categories, and associated *p* values for each cluster are available in our GitHub repository.

GO term enrichment was conducted using the PANTHER 14.0 database [137]. After clustering, gene lists were submitted to the online browser and tested against the *Hbt. salinarum* UniProt Reference Proteome (UP000000554, 2018-04 release). Enrichments were considered significant if the FDR-adjusted *p* value from Fisher's exact test was less than 0.05 (FDR correction was conducted within the PANTHER database). PANTHER enrichments and run details for all 1000 *Hbt. salinarum* genes are available in Supplemental Table 1.

Archaeal phylogeny

The taxonomy tree in Fig. 4 was constructed using NCBI taxa IDs and the phyloT online tool.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmb.2019.07.029.

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Abbreviations used:
ESR, environmental stress response; TF, transcription factor; iESR, induced environmental stress response; rESR, repressed environmental stress response; STRE, stress response element.

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