Differential Induction of Hsp70-encoding Genes in Human Hematopoietic Cells*

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The rapid transcriptional activation of heat shock genes in response to stress is crucial for the cellular survival and the development of thermotolerance. Although heat shock response is a widespread phenomenon, certain cells exhibit a diminished induction of heat shock gene expression upon stress stimuli. Here we have analyzed the development of thermotolerance and induction of distinct Hsp70 encoding genes in three cell lines representing different hematopoietic cell types. We show that in response to heat shock, cell survival and induction of thermotolerance are impaired in Raji and HL60 cells, as compared with K562 cells. Accordingly, transcriptional induction of the hsp70 gene is diminished in Raji and HL60 cells. This appears to be due to inability of transcription factors, including HSF1 to bind to the hsp70.1 promoter in vivo. Consistent with the genomic footprint, analysis of hsp70.1 mRNA expression using a specific 3′-untranslated region probe reveals that induction of the hsp70.1 gene upon heat shock is completely abolished in Raji and HL60 cells. The suppression of the hsp70.1 promoter is not caused by impaired function of HSF1, since HSF1 is equally activated in all cell types and occupies another heat-inducible promoter, hsp90a. Furthermore, among distinct inducible hsp70 genes, suppression seems to be specific for the hsp70.1 gene, since heat shock results in induction of hsp70.2 and hsp70B′ mRNA expression in all cell lines. Taken together, our results demonstrate that distinct Hsp70-encoding genes contribute to the heat shock response in a cell type-dependent manner.

A common cellular response to environmental or other forms of stress, called the heat shock response, is characterized by a rapid induction of heat shock protein expression. The most abundant and best known heat shock proteins belong to the Hsp70 family. Under normal physiological conditions, members of this family function as molecular chaperones facilitating proper folding and preventing misfolding of newly synthesized polypeptides. A subset of the Hsp70 proteins are expressed constitutively and are not significantly stress-inducible, whereas a prominent induction of Hsp70 expression in response to stress serves as a defense mechanism to protect the cells from protein aggregation that would occur when preexisting proteins unfold upon exposure of cells to stress (1–4). In addition, the inducible Hsp70 plays an important role in the development of thermotolerance (5). The cells, which have been subjected to mild heat treatment sufficient to induce heat shock protein expression, develop a resistance to stress-induced cell death upon subsequent insult. This response, called thermotolerance, is also acquired by overexpressing Hsp70 exogenously (6–11). Conversely, the lack of thermotolerance correlates with reduced induction of Hsp70 expression. Of particular interest are certain human leukemic cell lines, which show impaired thermotolerance in comparison with other cell lines in culture (12–14). Although it is well established that in these cell lines the inducibility of heat shock proteins, especially Hsp70, is diminished, the molecular basis for this has not been established.

Induction of Hsp70 expression in response to stress is primarily regulated at the transcriptional level (15, 16). The transcriptional activation of heat shock genes is dependent on a positive regulatory DNA motif, the heat shock element (HSE), present in the 5′-flanking region of heat shock genes. HSE serves as a binding site for heat shock transcription factors (HSFs), whose activation is essential for the transcriptional regulation of heat shock genes. Although three distinct HSFs have been identified in mammalian cells (HSF1, HSF2, and HSF4), only one of them, HSF1, is activated in response to stress stimuli (Refs. 17–20; reviewed in Ref. 21). Upon activation, HSF1, which is constitutively expressed in most cell types, undergoes trimerization and hyperphosphorylation, localizes in the nucleus, where it interacts with HSEs of the heat shock gene promoters, and induces transcription of the target genes (22–24). Interestingly, the cells that lack HSF1 cannot develop thermotolerance and are thus sensitized to heat-induced apoptosis (25). In addition to rapid transcriptional induction of hsp70 gene expression upon stress stimuli, subsequent mRNA stabilization and enhanced translation contribute to elevated Hsp70 protein levels (26–28).

The existence of multiple distinct Hsp70-encoding genes further extends the complex regulation of inducible Hsp70 expression. Of the three stress-inducible hsp70 genes in humans (hsp70.1, hsp70.2, and hsp70B′) whose expression has been detected at the protein level, hsp70.1 and hsp70.2 code for an
identical protein, the major inducible Hsp70 (29). Although the exact contribution of these gene products to protein expression is difficult to ascertain in vivo, their divergent 3′-UTR sequences allow the analysis of hsp70.1 and hsp70.2 mRNA separately. Accordingly, analysis of steady-state mRNA expression has shown that at least in heat-shocked HeLa cells, both mRNAs are strongly induced (29). The third inducible hsp70 gene, hsp70B, encodes a closely related but a more basic 70-kDa protein (30). In contrast to hsp70.1 and hsp70.2, expression of hsp70B mRNA has been shown to be inducible only at extreme temperatures (30). To date, however, the analysis of these genes has been limited to few cell lines showing normal stress response, and it is not known whether differential regulation of these genes could contribute to differences in Hsp70 expression patterns.

To investigate the molecular basis for impaired induction of heat shock gene expression upon exposure of certain hematopoietic cells to heat stress, we have performed studies on three distinct hematopoietic cell types. In response to heat stress, transcriptional induction of the hsp70 gene, cell survival, and development of thermotolerance are shown to be impaired in Raji Burkitt’s lymphoma and HL60 promyelocytic leukemia cells as compared with K562 erythroleukemia cells. Although HSF1 is equally activated in all cell lines exposed to heat shock in vitro, in vivo genomics footprinting reveals that the hsp70.1 promoter is occupied only in K562 cells and not in Raji and HL60 cells. By using specific 3′-UTR probes for the distinct hsp70 genes, we demonstrate that due to the inaccessibility of the hsp70.1 promoter, the induction of hsp70.1 transcription is completely abolished in Raji and HL60 cells. We further show that the suppression is specific for the hsp70.1 gene, since exposure to heat shock clearly results in increased hsp70.2 and hsp70B mRNA accumulation. Our results indicate that distinct inducible Hsp70-encoding genes contribute to the heat shock response in a cell type-specific manner.

 EXPERIMENTAL PROCEDURES

Cell Culture—K562 (human erythroleukemia) and HL60 (human promyelocytic leukemia) cells were cultured in a humidified 5% CO2 atmosphere at 37 °C in RPMI 1640 supplemented with 10% fetal calf serum. Raji (Burkitt’s lymphoma) cells were maintained in Dulbecco’s modified Eagle’s medium containing 10% fetal calf serum. Cells were heat-shocked at 42 °C (moderate temperature) or 45 °C (high temperature) water baths.

Analysis of Cell Death—Heat-induced apoptotic cell death was measured as previously described (31). Briefly, the cells were stained with propidium iodine in a hypotonic buffer and DNA fluorescence was analyzed by FACScan flow cytometer. A sub-G1 DNA fraction, representing apoptotic nuclei, which show lower DNA content due to leakage of nucleosome-sized DNA fragments from the nuclei, was quantitated with CELLQuest software (Becton Dickinson).

Western Blot Analysis—Whole cell extracts were prepared as described (32). Samples containing 10–20 μg of protein were separated on an 8% SDS-polyacrylamide gel and transferred to nitrocellulose filter using a semidy transfer apparatus (Bio-Rad). Western blotting was performed using mAb 3a3 (Affinity Bioreagents, Inc.) that recognizes both constitutive and inducible forms of Hsp70 (33). Hsp90 was detected by mAb SPA-835 (StressGen). Horseradish peroxidase-conjugated secondary antibodies were purchased from Promega and Amersham Pharmacia Biotech. The blots were developed with an enhanced chemiluminescence method (ECL; Amersham Pharmacia Biotech).

RNA Analysis—Total cellular RNA was isolated using the single step method (34). 15 μg of RNA was fractionated on a 1% agarose-formaldehyde gel, transferred to Hybond-N membrane (Amersham Pharmacia Biotech), and hybridized to [α-32P]dCTP-labeled cDNAs coding for human hsp90α (36), human β-actin (38), and rat GAPDH (37). Bluescript (Stratagene) was used as a vector control. The hybridization and washing conditions were as described (39). Quantitation was performed using a phosphor imager (Bio-Rad).

In Vivo Genomic Footprinting—Cells were harvested and treated with 0.2% dimethyl sulfate for 5 min at room temperature. DNA was isolated, digested with EcoRI, and cleaved with piperidine. Genomic footprinting was performed by using a ligation-mediated polymerase chain reaction method (40). The primers used for footprinting of the HSE regions of hsp70.1 and hsp90α promoters have been described earlier (41, 42). γ-32P-labeled polymerase chain reaction products were resolved on a 6% sequencing gel.

Gel Mobility Shift Assay—A gel mobility shift analysis of protein–DNA complexes was performed by incubating whole cell extracts with a γ-32P-labeled oligonucleotide representing the proximal HSE of the human hsp70.1 promoter (32). Protein–DNA complexes were resolved on a 4% nondenaturing polyacrylamide gel. For antibody purification assays, dilutions of immunoserum specific for HSF1 and HSF2 were preincubated with whole cell extracts prior to assays for DNA binding (24).

RESULTS

Cell Survival, Development of Thermotolerance, and Induction of Heat Shock Gene Expression Vary between K562, Raji, and HL60 Cell Lines—To determine whether distinct hematopoietic cell types respond to heat stress differently, we compared the cellular survival of K562, HL60, and Raji cells after heat shock. K562 cells represent erythroleukemia cells, HL60 cells represent promyelocytic leukemia cells, and Raji is a Burkitt’s lymphoma cell line. All cell types were preconditioned with a moderate, sublethal heat shock (42 °C for 30 min), and the cells were allowed to recover (37 °C for 4 h) before a subsequent severe heat shock (45 °C for 45 min). Cell survival and apoptosis were assessed quantitatively using flow cytometric analysis (31). Fig. 1A shows typical histograms of propidium iodine-stained nuclei 24 h after moderate and severe heat shock. The results are quantitated in Fig. 1B. Exposure of K562 cells to severe heat shock did not affect the viability of these cells. In contrast, in Raji and HL60 cells, severe heat shock led to a prominent loss of cell survival and increased apoptosis (28% and 39% survival as compared with untreated cells, respectively). Pretreatment at 42 °C increased the survival of HL60 cells (65% survival). In Raji cells, the protective effect was less apparent (41% survival). It is also worth of noting that Raji cells had a higher spontaneous rate of apoptosis, since the number of cells containing hypodiploid DNA was greater in untreated Raji cells in comparison with K562 and HL60 cells. Taken together, the results indicate that K562 cells are the most resistant and Raji cells the most sensitive to heat-induced cell death.

As pointed out in the Introduction, reduced cell survival and impaired development of thermotolerance of hematopoietic cells may be consequences of reduced induction of Hsp70 expression in response to heat shock (12–14). To compare the accumulation of inducible Hsp70 in K562, Raji, and HL60 cells, we performed immunoblot analysis (Fig. 2A). Under nonstressful conditions, high and intermediate expression levels of inducible Hsp70 were detected in K562 and Raji cells, respectively, which is typical of most human cells in culture. In contrast, Hsp70 was hardly detectable in untreated HL60 cells. Upon exposure to heat shock, Hsp70 levels were increased in all cell types, although the most prominent increase was observed in K562 cells. Similar results were obtained when Hsp70 synthesis was analyzed by metabolic labeling followed by immunoprecipitation (data not shown). In comparison, the amounts of Hsc70, the constitutively expressed member of the Hsp70 family, remained unaltered in K562 and Raji cells and...
were slightly induced in HL60 cells. Moreover, heat shock did not affect Hsp90 levels in any cell types (Fig. 2A).

Next we examined induction of total hsp70 mRNA expression in response to heat shock (Fig. 2, B and C). Northern blot analysis and subsequent quantification showed that upon heat shock the strongest increase in hsp70 mRNA expression was observed in K562 cells (450-fold). Both in HL60 and Raji cells, hsp70 mRNA induction was considerably weaker, being 2- and 3-fold less than in K562 cells, respectively (Fig. 2C). In comparison, we analyzed the steady-state levels of hsp90α mRNA. Unlike hsp70 mRNA, hsp90α mRNA was detected in all cell lines under nonstressful conditions, and a small but similar increase (2–4-fold) was observed in all cells exposed to heat shock (Fig. 2C).

To examine if the differences in hsp70 mRNA expression between the cell lines were due to differences in transcriptional efficiency, we analyzed the transcription rates by nuclear run-on assay (Fig. 3A). In previous studies, it was shown that transcription of two classical heat shock genes, hsp70 and hsp90α, was coordinately induced upon exposure of cells to various forms of stress, although hsp70 was more strikingly induced than hsp90α (39, 41, 43, 44). Consistent with these studies, transcriptional induction of hsp70 in K562 cells exposed to heat shock was more prominent (67-fold) than that of hsp90α (10-fold) (Fig. 3B). In contrast, both in Raji and HL60 cells, the induction of hsp70 transcription was more moderate and comparable with that of hsp90α. Raji cells responded to heat shock by equally inducing transcription of hsp70 (19-fold) and hsp90α (18-fold), whereas in HL60 cells the induction of hsp70 (17-fold) was 2-fold more than hsp90α (9-fold) (Fig. 3B). We conclude that decreased cell survival and development of thermotolerance in response to heat stress correlate with reduced transcriptional induction of hsp70 but not hsp90α gene expression in HL60 and Raji cells.
hsp70.1 Promoter Is Devoid of HSF1 upon Heat Shock in Raji and HL60 Cells—To gain further insight into the weaker transcriptional induction of the hsp70.1 gene in Raji and HL60 cells, we compared HSF-HSE interactions in the hsp70.1 promoter in unstressed and heat-shocked cells in vivo (Fig. 4). In addition to the sequences of CCAAT box, GC box, Gn element, and TATA box, the human hsp70.1 promoter contains proximal and distal HSEs that consist of five and six 5'-NGAAN-3' sites (39, 41, 45). The genomic footprint of the hsp70.1 promoter from K562 cells indicated occupancy of HSEs only upon heat shock, since protected and hypermethylated G residues were observed in earlier reported positions in the HSE sequences (39, 41) (Fig. 4). Moreover, heat shock did not affect the constitutive binding to the GC box representing the binding site for Sp1 factor and Gn sequences for CBF. In contrast, both Raji and HL60 cells failed to show a heat-inducible genomic footprint of the hsp70.1 promoter. In addition, the Sp1-binding site and Gn sequence showed only slight changes in the methylation patterns both in unstressed and heat-shocked Raji and HL60 cells when compared with the in vitro methylated DNA. Taken together, the results in Fig. 4 indicate that in Raji and HL60 cells, HSF1 is not bound to the hsp70.1 promoter, and also the binding of constitutive factors is severely impaired. To exclude the possibility that HSF1 was not properly activated in Raji and HL60 cells, HSF DNA binding activity was analyzed from unstressed and heat-shocked cells using a gel mobility shift assay (Fig. 5A). In untreated K562 and HL60 cells, HSE binding activity was undetectable, whereas a slight HSE binding activity was consistently detected in unstressed Raji cells. The protein-DNA complex was completely neutralized by the HSF2 antiserum, and the HSF1 antiserum did not have any effect on the complex formation in unstressed Raji cells (Fig. 5B). Therefore, our results suggest that the constitutive HSE binding activity in Raji cells consists predominantly of HSF2, which is refractory to classical stress stimuli. Heat treatment induced prominent HSF1 DNA binding activity in all three cell lines (Fig. 5A), indicating that despite transcriptional silencing of the hsp70.1 promoter, HSF1 appears to be functional in Raji and HL60 cells.

hsp90α Promoter Is Accessible to HSF1 upon Heat Shock in K562, Raji, and HL60 Cell Lines—Induction of hsp90α transcription in heat-shocked Raji and HL60 cells suggested that the hsp90α promoter is a target for HSF1 in these cells. To directly test whether HSF1 interacts with HSE within the hsp90α promoter in vivo, we analyzed the hsp90α promoter by genomic footprinting (Fig. 6). The human hsp90α promoter contains one HSE that is composed of six inverted 5'-NGAAN-3' sites (36). It was previously shown that in HeLa cells and in glioblastoma-like cell lines, T98G and Y79, all sites within HSE were free under normal conditions but became occupied following heat shock (42). Likewise, our analysis of the methylation patterns of the HSE region from untreated cells revealed that K562 and HL60 cells were fully devoid of HSF-HSE interactions on the hsp90α promoter, but heat shock resulted in prominent HSF-HSE interactions (Fig. 6). In Raji cells, HSEs were occupied also under nonstressful conditions, verifying the constitutively observed HSF2 DNA binding activity shown in Fig. 5. Following heat shock, a slight enhancement of dimethyl sulfate reactivity was observed at protected G residues in Raji cells.

hsp70.2 and hsp70B' Genes Are Induced in Raji and HL60 Cells—The findings that the hsp70.1 promoter was silent in Raji and HL60 cells (Fig. 4) but that transcriptional induction and mRNA accumulation of hsp70 were not completely suppressed (Figs. 2 and 3) prompted us to examine whether another inducible hsp70-encoding gene, hsp70.2, contributes to Hsp70 expression in Raji and HL60 cells. Although hsp70.1 and hsp70.2 genes contain almost identical open reading frames, and identical amino acid sequences, their 3'-UTRs are...
completely divergent. Thus, it is possible to distinguish between hsp70.1 and hsp70.2 mRNAs using oligonucleotide probes corresponding to the specific regions within 3’UTRs.

The cells were exposed to moderate (42 °C) or high (45 °C) temperatures for 60 and 30 min, respectively, and the accumulation of hsp70 mRNAs was followed up to 3 h at 37 °C (Fig. 7).

In agreement with the genomic footprint of the hsp70.1 promoter (Fig. 4), hsp70.1 mRNA was induced at moderate temperature in K562 cells, and during the recovery at 37 °C markedly elevated levels of hsp70.1 mRNA were observed. At high temperature, no induction was observed during a 30-min heat shock, but further incubation at 37 °C resulted in elevated hsp70.1 mRNA levels, which were lower than during the recovery from a 42 °C heat shock. In contrast to K562 cells, hsp70.1 mRNA was not induced in Raji cells at either temperature, and it was barely detectable in HL60 cells after a 42 °C heat shock (Fig. 7). Comparison of hsp70.2 mRNA accumulation after a 42 °C heat shock indicated that hsp70.2 mRNA was strongly induced in K562 and HL60 cells and also slightly in Raji cells. Whereas the hsp70.2 mRNA levels remained elevated in K562 cells during recovery at 37 °C, a decrease in hsp70.2 mRNA amounts was detected in Raji or HL60 cells. Therefore, it is likely that the turnover of hsp70.2 mRNA is more rapid in Raji and HL60 cells. Similarly to hsp70.1 mRNA, hsp70.2 mRNA was not induced in any cell types after a 30-min heat shock at 45 °C, but during a recovery at 37 °C a prominent increase in hsp70.2 mRNA levels was detected in K562 cells, and the expression of hsp70.2 mRNA was also slightly enhanced in Raji and HL60 cells. We conclude that hsp70.1 and hsp70.2 mRNAs contribute to the overall hsp70 mRNA levels in a cell type-specific manner; the weaker induction of hsp70 mRNA levels in Raji and HL60 cells, as compared with K562...
Induction of hsp70.1, hsp70.2, and hsp70B’ Genes

Cells were exposed to heat shock at 42 °C for 30 min (1) or at 45 °C for 30 min (15) followed by incubation at 37 °C for 3 h (3). Total RNA was extracted from control (C) and heat-shocked (HS) cells, and the samples (15 μg) were analyzed by Northern blotting using 32P-labeled oligonucleotide probes for hsp70.1, hsp70.2, hsp70B’, and a cDNA probe for GAPDH.

In K562, Raji, and HL60 cells upon heat shock turned out to be that the hsp70.1 promoter is inaccessible to HSF1 as well as to other transcription factors. The finding that the hsp90α promoter is fully functional upon heat shock confirms that the lack of detectable factor interactions on the hsp70.1 promoter is a locus-specific phenomenon and likely to be related to chromatin structure. Although the changes in chromatin structure that have caused the inability of transcription factors to bind hsp70.1 promoter are not currently known, we speculate that the loss of hsp70.1 promoter occupancy may be associated with an increased methylation state of the hsp70.1 promoter. Relevant to this suggestion is that impaired hsp70 transcription has been shown to correlate with increased methylation state of the hsp70.1 promoter in several mouse cell lines (47).

Our results comprise the second report in which the inaccessibility of hsp70.1 promoter has been identified in human cells. Previously, Mathur et al. (42) have demonstrated that in Y79 retinoblastoma cells, reduced transcriptional induction of the hsp70 gene is caused by a failure of transcription factors, including HSF1, to bind to the hsp70.1 promoter. Similarly to the previous study, we have found that the relationship between hsp70 expression and hsp70.1 promoter accessibility is not perfect; no transcription factor binding can be detected on the hsp70.1 promoter in Raji and HL60 cells, yet both cell types express detectable levels of hsp70 mRNA. Since hsp70.1 and hsp70.2 genes contain almost identical reading frames (29), it is plausible to suggest that the hsp70.2 gene contributes to the detected hsp70 expression levels. The utilization of hsp70.1- and hsp70.2-specific probes demonstrates that the hsp70.1 promoter is indeed silent in Raji and HL60 cells, and hsp70.2 mRNA is expressed in Raji and HL60 cells, thereby providing a molecular basis for the disparity between promoter analyses and hsp70 expression profiles.

The hsp70.1 and hsp70.2 genes contain identical amino acid sequences, similar but distinct promoters, and completely divergent 3’-UTRs (29). This type of gene duplication provides a possibility to regulate gene expression at multiple levels. So far, however, the data comparing the regulation of these genes in human cells have remained rather elusive, and no differences in the expression profiles of hsp70.1 and hsp70.2 mRNAs have been reported. In previous reports, induction of human hsp70.1 and hsp70.2 mRNA expression has been shown to vary in a heterogeneous manner, a fraction of cells always remaining unresponsive to heat shock (48, 49). Our results suggest that in addition to the cell type-dependent lack of hsp70.1 transcription upon heat shock, the turnover rates of hsp70.1 and hsp70.2 mRNAs are likely to be different. This is based on the observation that during the recovery of K562 cells from the heat shock, hsp70.1 mRNA levels are increased, while the levels of hsp70.2 mRNA remain unchanged. In line with our results, it has been shown that induction of hsp70 expression in response to various stresses involves stabilization of hsp70 mRNA (27, 28). Although the mechanisms underlying the stabilization of hsp70 mRNAs are not known, it is well established that AU-rich 3’-UTRs in various mRNAs function as instability determinants (50). Whether the distinct sequences in the 3’-UTRs of hsp70.1 and hsp70.2 mRNAs have a regulatory significance remains to be determined.

In addition to the hsp70.2 gene, we have analyzed the expression of another Hsp70-encoding gene, hsp70B’, which has been shown to be induced only at higher temperatures (30). As previously shown using human fibroblasts and HeLa cells (30), hsp70B’ mRNA is prominently induced in response to a severe heat shock in Raji and HL60 cells and weakly in K562 cells. Unlike in the previous study (30), hsp70B’ mRNA is also strongly induced at a moderate temperature in Raji and HL60...
cells, indicating that at least in certain hematopoietic cell types hsp70B' expression is not restricted to extreme stress conditions. The finding that the loss of hsp70.1 expression in Raji and HL60 cells is associated with induction of hsp70B' expression suggests that the cells have adopted compensatory mechanisms to better survive stressful conditions. However, induction of hsp70B' expression appears not to correlate directly with the development of thermotolerance. The comparison of the protein sequences reveals that inducible Hsp70 proteins are very similar in their N-terminal regions. The divergence in the C terminus of the Hsp70B' in comparison with Hsp70.1 and Hsp70.2 may contribute to a selective function of this protein, as has been shown for Grp78 (51).

In conclusion, our data show the importance of an active hsp70.1 gene in the development of thermotolerance. However, the lack of hsp70.1 transcription in response to heat stress can be partially compensated by the expression of hsp70.2 and hsp70B' mRNAs, which are expressed in a cell type-dependent manner. The differential expression of the inducible hsp70-encoding genes provides multiple regulatory pathways for cells to respond rapidly and precisely to stressful challenges.

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