Expression of Human hsp70 in Rat Fibroblasts Enhances Cell Survival and Facilitates Recovery from Translational and Transcriptional Inhibition following Heat Shock

Richard Y. Liu, Xiaochuan Li, Ligeng Li, and Gloria C. Li

Departments of Medical Physics and Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, New York 10021

ABSTRACT

We report here our studies on the inhibitory effect of 45°C heat shock on translational and transcriptional activity and their subsequent recovery at 37°C in Rat-1 cells, thermotolerant Rat-1 cells (TT Rat-1), and Rat-1 cells transfected with human hsp70 gene (HR24, M21). Specifically, we ask whether overexpression of hsp70 protects cells from heat-induced inhibition in RNA and protein synthesis, and/or facilitates cells' ability to recover from translational or transcriptional inhibition after heat shock treatment. Our data demonstrate that the constitutive expression of human hsp70, by itself, confers thermal resistance as expressed in enhanced survival and translational tolerance, but not transcriptional tolerance. In addition, the expression of human hsp70 in Rat-1 cells facilitates cells' ability to recover from heat-induced inhibition in protein and RNA synthesis. After heating at 45°C for 25 min, the time required for RNA and protein synthesis to recover is considerably shorter in HR24, M21, and TT Rat-1 cells than in control Rat-1 cells.

These results provide strong evidence for a direct link between the expression of a functional form of mammalian hsp70, and cells' translational and transcriptional tolerance, as well as their ability to recover from translational and transcriptional inhibition after heat shock.

INTRODUCTION

Mammalian cells when exposed to a nonlethal heat shock have the ability to acquire transient resistance to subsequent, lethal heat-shock challenges (1, 2). This phenomenon, termed thermotolerance, has been extensively studied at the level of cell survival, and appears to be correlated with the production of the hsps (3, 4). Qualitative evidence exists for a causal relationship between hsps synthesis and thermotolerance (5-8). While some quantitative studies on thermotolerance and permanent heat resistance strongly suggest the involvement of hsp70 (6-11), other experiments support the notion that the small hsps are important in the acquisition of thermotolerance (12).

Heat shock causes dramatic alterations in gene expression (13). It inhibits normal RNA and protein synthesis, while activating the transcription of a specific set of heat shock genes, and resulting in the preferential synthesis of hsps. This heat-induced inhibition in translational and transcriptional activity is reversible; activity recovers gradually when heated cells are returned to 37°C incubation. The recovery kinetics of RNA and protein synthesis after various heat treatments in nontolerant and thermotolerant cells has been compared (14-18). It was found that cells first made thermotolerant (by a treatment at 43°C for 90 min and followed by recovery at 37°C), and then challenged with a 45°C, 30-min heat shock, exhibited considerably less translational inhibition (17). This phenomenon has been termed translational tolerance. As thermotolerance developed, more cells survived the second heat challenge, and the time required for the recovery of RNA and protein synthesis decreased (15). Phenomenologically, the acquisition and duration of translational tolerance have been correlated with the expression and the accumulation of the major hsps of M, 70,000 and 71,000 (the hsp70 family) in thermotolerant cells. However, it has not been established whether hsp70 is directly responsible for translational tolerance and thermotolerance, or whether this translational tolerance is merely a reflection of the thermotolerant state.

By using a DNA-mediated gene transfer technique, we have established transfected rat cell lines stably and constitutively expressing a cloned human hsp70 gene (19). The expression of this human hsp70 confers heat resistance to the rat cells (19). This result provides direct support to the hypothesis that one of the functions of hsp70 is to protect cells from thermal damage.

In this study, we have performed experiments to examine whether the overexpression of hsp70 will protect cells from heat-induced inhibition in RNA and protein synthesis, and/or facilitate cells' ability to recover from translational or transcriptional inhibition after heat shock treatments. Three types of cells were chosen for our study: (a) the Rat-1 cells that stably and constitutively express an exogenous human hsp70; (b) TT Rat-1 cells that express elevated levels of constitutive and inducible forms of rat hsp70s and other hsps; and (c) the wild type nontolerant Rat-1 cells that express the constitutive form of rat hsp70 at 37°C.

MATERIALS AND METHODS

Cells and Culture Conditions. Rat-1 and TT Rat-1 cells were grown in Dulbecco's modified medium (Gibco, Grand Island, NY) supplemented with 10% fetal calf serum. The transfected Rat-1 cells (HR24, M21), which constitutively express the exogenous human hsp70, were routinely maintained in Dulbecco's modified medium supplemented with 10% fetal calf serum and antibiotic G418 (200 μg/ml; Sigma Chemical Co., St. Louis, MO) (19). The construction of plasmids containing human hsp70 and the procedures for DNA-mediated transfection were as described previously (19, 20). Briefly, the exponentially growing Rat-1 cells were co-transfected with appropriate plasmids containing the human hsp70 gene and genes conferring neomycin resistance by the calcium phosphate precipitation method (21). Neomycin-resistant cells were selected in medium containing G418 (400 μg/ml), and colonies were subsequently isolated. All cell lines (e.g., HR24, M21) used in this study are stable and derived from individual colonies.

Heat Shock Treatment. Monolayers of cells were heated at 45°C for different times in hot water baths in specially designed incubators (6). Cell survival studies were performed as described previously (19). Surviving fractions were always normalized by the plating efficiency of the unheated controls.
Rat-1 cells were made thermotolerant (TT Rat-1) by heating at 45°C for 15 min, and subsequently incubating at 37°C for 16 h. Labeling with [3H]Uridine and [35S]Leucine. To study the effects of heat shock on RNA and protein synthesis, and to follow the recovery kinetics of translational and transcriptional activity after heat shock, monolayers of cells were heat-shocked at 45°C for 5 to 30 min and returned to 37°C incubation for various times. The cells were then dual-labeled in uridine-free medium with [3H]Uridine (specific activity, >42 Ci/mmol; New England Nuclear, Boston, MA) and 0.5 μCi/ml of [35S]Leucine (New England Nuclear; specific activity, >300 mCi/mmol) for 10 min at 37°C. After labeling, the radioactive medium was removed and the cells were washed 3 times with cold phosphate-buffered saline. The cellular proteins were precipitated directly in the dish by adding 1 ml of ice-cold 5% trichloroacetic acid. After 10 min at 4°C, the samples were washed twice with cold 5% trichloroacetic acid. The precipitates were dissolved in 0.5 ml of 0.2% NaOH. One aliquot of the sample was used to measure the protein concentration. The rest of the sample was neutralized with 2% HCl, and its radioactive contents were determined using an LKB scintillation counter (Wallace 1410). The incorporation of label of each sample was expressed in terms of cpm/μg proteins. For each experiment, incorporation of label was determined in duplicate samples and was expressed as averages (SE, <10%). The relative rate of incorporation after each heat shock treatment was calculated by taking the ratio of cpm/μg protein of the heated group to that of the unheated control group. For TT Rat-1 cells, the relative rate of incorporation of TT Rat-1 cells after the second heat shock treatment was always normalized to the value of control TT Rat-1 cells without receiving the second heat shock treatment. All experiments were done at least twice with similar results. Some of our data presented here were also compared with those obtained from the standard protocol using filter filtration (15). Both methods yielded consistent results. However, the method presented here generated less fluctuation between duplicate samples.

We also performed experiments to study the recovery kinetics of transcriptional and translational activity after heat shock in the presence of protein or RNA synthesis inhibitors. To examine the effects of heat shock on the preexisting RNA and their subsequent recovery at 37°C, and to determine whether hsp70 may be involved in facilitating this recovery process, 0.04 μg/ml of Act-D was used to inhibit the production of newly synthesized RNA during and after heat shock treatment (15). In experiments designed to study the effects of heat shock on the preexisting proteins and their relationship with transcriptional recovery, protein synthesis inhibitors such as puromycin or cycloheximide were used to inhibit new protein synthesis during and after heat shock treatment.

Gel Electrophoresis and ImmunobLOTS. Cellular proteins were analyzed by one-dimensional PAGE and immunoblot analysis. Monolayers of cells were heated at 45°C for 25 min and returned to 37°C incubation for 0–6 h. At 0, 2, 4, and 6 h after heating, cells were labeled with [35S]methionine (specific activity, 1000 Ci/mmol; New England Nuclear) at concentrations of 20–40 μCi/ml for 1 h at 37°C. After labeling, cells were washed twice with ice-cold phosphate-buffered saline and then lysed in 1× sodium dodecyl sulfate lysis buffer. Equal amounts of protein were analyzed by one-dimensional sodium dodecyl sulfate-PAGE as described (6, 8, 9, 19). For immunoblot analysis of cellular proteins, Rat-1, TT Rat-1, M21, and HR24 cells were grown at 37°C and lysed in Nonidet P-40 lysis buffer or isoelectric focusing lysis buffer as described previously (19). Equal amounts of cellular proteins were separated by one-dimensional PAGE or isoelectric focusing slab gel, transferred to nitrocellulose membrane, and probed with monoclonal antibodies against hsp70 (N27F3-4). The detailed experimental procedures were described previously (19).

RESULTS

Expression of Human hsp70 Gene in Rat-1 Cells Confers Thermal Resistance. Monolayers of exponentially growing Rat-1, TT Rat-1, HR24, and M21 cells were exposed to 45°C for 0–90 min and the survival was determined by colony formation assay. Fig. 1a shows that when the surviving fractions were plotted as a function of heating time at 45°C, TT Rat-1, HR24, and M21 cells were more thermally resistant than control nontolerant Rat-1 cells. Western blot analysis using monoclonal antibody (N27F3-4) specifically against hsp70 (both the constitutive and the inducible hsp70) revealed that, at 37°C the HR24 and M21 cells expressed the constitutive form of rat hsp70 and the exogenous human hsp70, TT Rat-1 cells expressed both the constitutive rat hsp70 and the heat-inducible rat hsp70, and the nontolerant Rat-1 cells expressed only the constitutive rat hsp70 (Fig. 1, a and c).

Effect of Heat Shock on Transcriptional and Translational Activity in Rat-1, Thermotolerant Rat-1, and Rat-1 Cells Expressing the Human hsp70 Gene. Monolayers of Rat-1, TT Rat-1, HR24, and M21 cells were exposed to 45°C for 0–30 min, and labeled for 10 min at 37°C immediately after the heat shock treatment. In Fig. 2, it is clearly shown that both the translational and transcriptional activity were inhibited after the 45°C heat shock treatment. The degree of inhibition depended on the severity of the heat dose. There was no significant difference in the rate of RNA synthesis among different cell lines after the
45°C heat shock treatment (Fig. 2a). However, the translational inhibition after the 45°C heat shock treatment in HR24, M21, and TT Rat-1 cells appeared to be much less than that in the control nontolerant Rat-1 cells. For example, after exposure of cells to 45°C for 5 min, the protein synthesis in Rat-1 cells was reduced to 10% of the control level, while the protein synthesis in TT Rat-1, HR24, and M21 cells was at 68, 35, and 35% of their control levels, respectively (Fig. 2b).

Expression of Human hsp70 Gene in Rat-1 Cells Facilitates the Translational and Transcriptional Recovery after Heat Shock. To study the recovery kinetics of translational and transcriptional activity after heat shock in Rat-1 cells, TT Rat-1 cells, and Rat-1 cells expressing the human hsp70 gene, monolayers of Rat-1, TT Rat-1, HR24, and M21 cells were first exposed to 45°C for 10 or 25 min. After this heat treatment, cells were returned to 37°C for various times and pulse-labeled for 10 min at 37°C with [3H]uridine and [14C]leucine. Protein and RNA synthesis as estimated by the relative rates of incorporation of [14C]leucine or [3H]uridine, each normalized to their relative rates of incorporation of label after the 45°C heat treatment and that of the corresponding controls. The data represent an average of 4 independent sets of experiments, and the variation is within 15%. Open symbols, relative rate of RNA synthesis; solid symbols, relative rate of protein synthesis. O O and •¿ •¿, Rat-1 cells; O and •¿, TT Rat-1; △ and △, M21 cells; □ and □, HR24 cells.

Effect of Cycloheximide on the Recovery of RNA Synthesis after Heat Shock. We studied the effect of cycloheximide, a protein synthesis inhibitor, on the recovery of RNA synthesis after a 45°C heat shock treatment. Monolayers of Rat-1, TT Rat-1, and HR24 cells were exposed to 45°C for 10 min and returned to 37°C incubation for various times in the presence or absence of cycloheximide (5 µg/ml). These cells were then pulse-labeled for 10 min at 37°C with [3H]uridine and [14C]leucine, and the relative rates of incorporation were determined (Fig. 6). The effects of cycloheximide alone on the RNA and protein synthesis of Rat-1, TT Rat-1, and HR24 cells are shown in Fig. 6a. After 2-h exposure of 5 µg/ml cycloheximide, the RNA synthesis in unheated cells remained at about 65% of the control level. When HR24 and TT Rat-1 cells were exposed to

20 µCi/ml [35S]methionine. Equal amounts of cellular proteins were analyzed by one-dimensional PAGE and autoradiography. It is clearly shown in Fig. 3c that protein synthesis in all cells was inhibited significantly right after the 45°C, 25-min heat shock treatment, but recovered gradually when the cells were incubated at 37°C. The time required for protein synthesis to recover, again, was considerably shorter in TT Rat-1, HR24, and M21 cells than that in Rat-1 cells (Fig. 3c).

Similar results were obtained when the recovery kinetics of RNA synthesis after the 45°C heat treatment were examined. For each cell line, recovery from heat-induced inhibition in RNA synthesis after a 45°C, 10-min heat treatment was sooner than that after a 45°C, 25-min treatment. When the recovery kinetics between different cell lines were compared, the time required for RNA synthesis to recover was considerably shorter in HR24, M21, and TT Rat-1 cells than that in Rat-1 cells (Fig. 4, a and b). When the recovery time between RNA and protein synthesis was compared, a longer delay was seen in the transcriptional recovery than in the translational recovery. For example, after 45°C, 10-min heat treatment, the RNA synthesis in Rat-1 cells remained at a low level of 20%, while the protein synthesis recovered to 50% of the control value for Rat-1 cells. However, for HR24 and TT Rat-1 cells, this difference was much less noticeable.

Effect of Act-D on Translational and Transcriptional Recovery after Heat Shock. We have examined the effect of Act-D (0.04 µg/ml), a rRNA synthesis inhibitor at this concentration (15), on the recovery kinetics of protein and RNA synthesis after a 45°C heat shock treatment. Fig. 5a shows the effect of Act-D alone on RNA and protein synthesis in Rat-1, TT Rat-1, and HR24 cells. When these cells were exposed to 0.04 µg/ml of Act-D at 37°C for 1–8 h, the RNA synthesis was significantly inhibited, while the protein synthesis was affected to a much lesser degree. For example, after 8-h exposure of Act-D at 37°C, the RNA synthesis was reduced to 20–30%, while the protein synthesis remained about 70% of the control value. In separate experiments, when 0.04 µg/ml Act-D was used to inhibit the synthesis of RNA synthesis during and after the 45°C, 25-min heat shock treatment, we found that the RNA synthesis was severely inhibited up to 8 h. However, this inhibition in RNA synthesis had little or no effect on the recovery kinetics of protein synthesis in all 3 cell lines (Fig. 5b). When these data were normalized to that of the control groups treated with Act-D alone (data from Fig. 5b divided by that from Fig. 5a), the recovery kinetics of protein synthesis was almost identical to those presented in Fig. 3b. Therefore, our data suggest that recovery of protein synthesis after heat shock does not require newly synthesized rRNA, but involves the preexisting rRNA.
cycloheximide, during and after the 45°C, 10-min heat shock treatment, their RNA synthesis did not recover after 2-h incubation at 37°C (Fig. 6a). On the other hand, in parallel experiments, when cycloheximide was not present, the RNA synthesis recovered to 60–80% of their control level (compare Fig. 4a and Fig. 6b). Based on these data, we argue that newly synthesized proteins may be important for the recovery of RNA synthesis after the 45°C heat shock treatment.

Similar conclusions can be drawn in separate experiments in which cells were first exposed to 45°C for 25 min, and allowed to recover at 37°C for various times in the presence of 5 μg/ml cycloheximide (or 20 μg/ml puromycin) (data not shown).

DISCUSSION

The ability of thermotolerant cells to transcribe messages and to translate proteins following a second heat challenge has been investigated (14, 15, 17, 22, 23). In general, cells first made thermotolerant exhibited considerably less translational inhibition, a phenomenon termed translational tolerance (14, 15, 17). It has long been proposed that hsp70 is responsible for thermotolerance, and ample evidence has been accumulated to support this hypothesis. On the other hand, the body of evidence for the role of hsp70 in translational tolerance is largely circumstantial and rests on a few correlation studies using thermotolerant cells (15, 17). Overexpression of hsp70 in these studies has been achieved only by experimental manipulations that could potentially alter other cellular components, which in turn may be responsible for thermotolerance as well as translational tolerance. Similarly, the correlation of intrinsic translational tolerance with elevated levels of hsp70 expression in different cell lines naturally expressing various levels of hsp70 may be
overexpression of hsp70 will protect cells from heat-induced cell death (19, 20). In this study, we have performed experiments, using these transfected Rat-1 cells, to examine whether the overexpression of hsp70 will protect cells from heat-induced inhibition in RNA and protein synthesis, and/or facilitate cells’ ability to recover from translational or transcriptional inhibition after heat shock treatment.

First, we examined the effect of 45°C heat shock on protein synthesis. Similar to observations of others (14, 15, 17), our results showed that 45°C heat shock inhibited protein synthesis, and the degree of translational inhibition appeared to be less in thermotolerant Rat-1 cells. When the effect of 45°C on protein synthesis in transfected Rat-1 cells was determined, we found that there was less translational inhibition in HR24 or M21 cells than that in Rat-1 cells. Although the mechanism for this observation is unknown, our data suggest that either the translational machinery and/or some translational factors are more heat-resistant in HR24, M21, or TT Rat-1 cells as compared to control Rat-1 cells. Since the difference between Rat-1 and HR24 or M21 cells is only the overexpression of human hsp70, we argue that the presence of hsp70 protects the translational integrity of cells from thermal stress. On the other hand, our data do not rule out a possible protective role for other hsps. The difference between TT Rat-1 and HR24 cells seen in Fig. 2b may be due to other heat-induced modifications in TT Rat-1 cells, and may represent the collective effects of different hsps and/or other factors on translational tolerance. Second, we examined the recovery kinetics of RNA and protein synthesis after 45°C heat shock in Rat-1, TT Rat-1, HR24, and M21 cells. Protein and RNA synthesis in all cell lines were inhibited after the 45°C heat shock treatment (Fig. 2). When these cells were returned to 37°C incubation, their RNA and protein synthesis gradually recovered (Figs. 3 and 4). The time required for recovery depended on the severity of the heat dose. The higher the heat dose, the longer the time required for the recovery of translational and transcriptional activity (Figs. 3 and 4). For a given heat shock treatment (e.g., 45°C, 25 min), the TT Rat-1 cells and the transfected HR24 and M21 cells exhibited faster recovery of translational and transcriptional activity as compared with the control nontolerant Rat-1 cells. Numerous reports have shown that the recovery of RNA and protein synthesis after heat shock required less time for thermotolerant cells than for nontolerant cells. Here we observed the same phenomenon in transfected Rat-1 cells expressing a cloned human hsp70 gene. Our data provided strong evidence for a direct relationship between hsp70 expression and the faster recovery from translational and transcriptional inhibition after 45°C heat shock treatment. To rule out the possibility that the process of gene transfer, or expression of neomycin-resistance gene, may confer enhanced thermal survival and translational tolerance, we performed experiments in parallel using Rat-1 cells transfected with plasmids containing only the neomycin resistance genes. The results with these cells were indistinguishable from those obtained using nontolerant Rat-1 cells (data not shown). Taken together, our data show that the presence of hsp70 not only confers heat resistance and trans-
lational tolerance, but also facilitates the recovery of protein and RNA synthesis after the 45°C heat shock treatment.

To determine whether newly synthesized RNA or proteins are involved in these recovery processes, the effects of actinomycin D or cycloheximide during and after heat shock treatment were examined. When 0.04 μg/ml Act-D, a dose mainly inhibiting rRNA synthesis (26-28), was present during and after a 45°C, 25-min heat shock treatment, we found that the severe inhibition in RNA synthesis has little or no significant effect on the recovery kinetics of protein synthesis for all cell lines. These data suggest that the recovery of translational activity after heat shock involves the preexisting rRNA, but not the newly synthesized rRNA, at least during the initial period of the recovery. Black and Subjeck (15) also reported similar findings in CHO cells. The fact that less time was required for protein synthesis to recover in HR24 and TT Rat-1 cells than that in Rat-1 cells (Fig. 5, b and c) suggests that one function of hsp70 may be to stabilize the translational machinery and/or to facilitate the reassembly of damaged preribosomes, polyribosomes, and/or other ribonucleoproteins after heat shock. It is intriguing to observe that: (a) there was a longer delay in transcriptional recovery than the translational recovery (compare Figs. 3 and 4); and (b) inhibition of protein synthesis by cycloheximide also interrupted the recovery of transcriptional activity (Fig. 6). Perhaps the enhanced recovery of protein synthesis in cells subsequently facilitated the recovery of heat-induced inhibition on transcription.

Heat shock causes a transient import of cytoplasmic hsp70 into nucleus/nucleoli (17, 19, 29, 30). Recently, we have examined the cellular localization of human hsp70 in transfected Rat-1 cells at normal growth temperature or after heat shock (19). At 37°C, human hsp70 was found exclusively in the cytoplasm of HR24 cells. After 10-min heating at 45°C, the protein rapidly moved into the nucleus and became associated with nucleoli. It has been shown that nucleoli were transiently damaged by heat shock: their morphology changed, and assembly and export of ribosome were blocked for several hours. When high levels of Drosophila hsp70 were produced in unstressed COS cells by transfecting them with an expression plasmid, such cells showed a more rapid recovery of nucleolar morphology following a heat shock than did the untransfected COS cells (29). Furthermore, the ribosome export also appeared to recover more rapidly when presynthesized hsp70 was present (29). Based on these observations, Pelham (29) hypothesized that hsp70 bound to the damaged ribonucleoproteins and catalyzed their orderly reassembly. Welch and Suhan (30) have examined various cellular and biochemical events in rat fibroblasts after heat shock and during recovery from thermal stress. They found that in the initial period of recovery, the major inducible form of hsp70 (M, 70,000) accumulated within the altered nucleoli in close association with the preribosomal-containing granular region. During the later times of recovery from heat shock, the nucleoli began to regain a normal morphology and showed a corresponding loss of the M, 70,000 protein, and the majority of this protein began to accumulate within the cytoplasm (30). In addition, they have shown that much of the perinuclear and cell perimeter-distributed M, 70,000 protein coincided with the distribution of the cytoplasmic ribosomes. These observations further support the notion that the M, 70,000 protein may be involved in rescuing or maintaining cells’ translational activity.

Yost and Lindquist (31) have demonstrated that a brief but severe heat shock treatment in Drosophila cells resulted in a block of mRNA processing. On the other hand, a mild heat shock treatment before the more severe heat shock treatment rescued the ability of cells to correctly process new mRNA transcripts. Similar to translational tolerance, thermotolerant Drosophila cells apparently maintained their ability to process mRNA transcripts (31).

The studies presented here provided strong evidence for a link between the expression of a functional form of mammalian hsp70 and cells’ ability to recover from translational and transcriptional inhibition following heat shock. We have demonstrated that the constitutive expression of human hsp70, by itself, confers thermal resistance and translational tolerance. In addition, the expression of human hsp70 facilitates cells’ ability to recover from heat-induced inhibition in RNA and protein synthesis. The production of hsp70 is only part of the program of new protein biosynthesis that is initiated after heat shock, and it is reasonable to expect that other components of this response also enhance the recovery of translational and transcriptional activity. However, an attractive hypothesis is that hsp70, because of its abundance and its ability to hydrolyze ATP, may function to restore, maintain, and/or stabilize multi-protein complexes, such as the transcriptional and translational machinery, whose functions are sensitive to thermal stress. It is plausible that hsp70 can bind to cellular protein complexes such as ribonucleoproteins and prevent their aggregation at elevated temperature. ATP binding and/or hydrolysis may be utilized to enable hsp70 to dissociate from its substrates and to facilitate the dissociation of these aggregated protein complexes to restore their functional integrity.

The availability of rat cell lines, stably and constitutively expressing an exogenous human hsp70 protein, provides us with a means to accurately assess transcriptional and translational activation parameters, as well as to further dissect the determinants in hsp70 that are responsible in the protection of cells’ transcriptional and translational integrity against thermal stress.

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