Heat Shock Protein 72 Modulates Pathways of Stress-induced Apoptosis*

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The resistance to stress-induced apoptosis conferred by the thermotolerant state or by exogenous expression of HSP72 was measured in mouse embryo fibroblasts. The induction of thermotolerance protects cells from heat, tumor necrosis factor α (TNFα), and ceramide-induced apoptosis but not from ionizing radiation. Because the development of thermotolerance is associated with increased levels of heat shock proteins, we determined whether constitutive expression of one of the major inducible heat shock proteins, HSP72, could also protect cells from stress-induced apoptosis. Cells expressing constitutive HSP72 were shown to have significantly reduced levels of apoptosis after heat, TNFα, and ceramide but not after ionizing radiation. Activation of stress-activated protein kinase/c-Jun N-terminal kinase (SAPK/JNK) was found to be strongly inhibited in thermotolerant cells after heat shock but not after other stresses. Cells that constitutively express HSP72 did not demonstrate decreased SAPK/JNK activation after any of these stresses. Thus, factors other than HSP72 that are induced in the thermotolerant state are able to reduce activation of SAPK/JNK after heat stress. Notably, the level of activation of SAPK/JNK did not correlate with the amount of apoptosis detected after different stresses. Constitutive HSP72 expression inhibited poly-(ADP-ribose) polymerase cleavage in cells after heat shock and TNFα but not after ceramide or ionizing radiation. The results suggest either that SAPK/JNK activation is not required for apoptosis in mouse embryo fibroblasts or that HSP72 acts downstream of SAPK/JNK. Furthermore, the data support the concept that caspase activity, which can be down-regulated by HSP72, is a crucial step in stress-induced apoptosis. Based on data presented here and elsewhere, we propose that the heat shock protein family can be classified as a class of anti-apoptotic genes, in addition to the Bcl-2 and inhibitor of apoptosis protein families of genes.

The regulation of normal development involves a combination of cell division, differentiation, and death. Although much emphasis was previously placed on mechanisms of cell cycle progression, mechanisms of cell death have only recently begun to be understood. Programmed cell death, or apoptosis, is an active process resulting in characteristic morphological changes to the cell including condensed regions of nuclear material, internucleosomal DNA cleavage, and membrane blebbing (1). The fragmented chromatin, still membrane-bound, is phagocytosed by neighboring cells, thus avoiding an inflammatory response. Apoptosis is responsible for the removal of unwanted cells of many lineages and is thought to be an important safeguard against hyperplasia, which can be an early event in neoplasia (2).

Environmental stresses such as heat, radiation, and hypoxia; growth factors and ligands for surface receptors; and many drugs or chemical agents can induce apoptosis. Nevertheless, cells undergoing apoptosis exhibit a similar morphology, suggesting that these divergent apoptotic stimuli converge to trigger a common pathway of cell death. The common pathway involves a family of proteases known as the interleukin-1β-converting enzyme (ICE)-like proteases or caspases, which are activated in a proteolytic cascade to cleave specific substrates (3, 4). More recently, it has become evident that the transmission of signals from external stresses is accompanied by the activation of two families of kinases, the stress-activated protein kinase families (SAPKs), also known as the c-Jun N-terminal kinases (JNKs), and the p38/HOG-1 kinases (5). Another possible signaling molecule in apoptotic pathways is the second messenger, ceramide. Increases in ceramide levels mediated by the activation of sphingomyelinase and consequent hydrolysis of sphingomyelin have been observed after exposure of cells to heat, radiation, TNFα, and peroxide (6). In addition, exogenously added ceramide induces apoptosis (7). Thus, whereas the early signals appear to be specific to a particular stress or group of stresses, the subsequent events, such as the activation of the caspases and possibly the SAPKs and ceramide, are common events.

Heat shock proteins (HSPs) are a group of inducible proteins, some of which are constitutively expressed and increase in response to stress, whereas others are expressed only after stress (8). The constitutively expressed proteins act as chaperones for other cellular proteins, binding to nascent polypeptides to prevent premature folding and to translocate proteins into organelles (9). The induction of increased levels of the stress proteins is associated with development of thermotolerance, a transient resistance to heat induced by prior exposure to mild heat or other stress agents (10, 11). It is apparent that induced stress proteins can act to protect cells from stress-induced damage by preventing protein denaturation and/or by repairing such damage (12). One major group of HSP is the HSP70 family that comprises a multi-gene family with at least 11 genes in humans (13) and...
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8 identified so far in the mouse (14). We and others have shown previously that induction of thermotolerance with a parallel induction of HSP inhibits heat-induced apoptosis in several cell lines (15, 16). The consequences of exogenous expression of HSP72 in cells have been investigated by several groups. Expression of human HSP72 protects cells from heat stress (17–19), from some drugs (20), from the cytotoxic effects of TNFα (21), from monocyte killing (22), and from nitric oxide (23). In some of these studies, however, it was not demonstrated whether the cells died by apoptosis after these stresses.

As part of our investigation of pathways of stress-induced apoptosis, we have measured the effects of either induction of thermotolerance or constitutive expression of HSP72 in blocking apoptosis induced by external stresses. The protection provided by HSP72 against diverse apoptosis-inducing stresses that we have reported here and other data in the literature lead us to propose that the heat shock gene family represents another class of apoptosis-inhibiting genes.

**EXPERIMENTAL PROCEDURES**

**Cell Cultures**—Mouse embryo fibroblasts (MEF) derived from Balb/c mice were minimally transformed with E1A and Ras as described previously (24). To generate cells with constitutive HSP72 expression, clones were infected with the pMVH/human HSP72 proviral vector previously (24). To generate cells with constitutive HSP72 expression, we have used a kind gift from Dr. S. Kaufmann, which recognizes both the poly(ADP-ribose) polymerase (PARP) from a 116-kDa protein to an 85-kDa fragment. Samples containing equal C-2–10 (a kind gift from Dr. W. Welch) or with an antibody that detects both human and mouse HSP72 (SPA-810, StressGen Biotechnologies). The cleavage of PARP was measured by PhosphorImager analysis (Molecular Dynamics).

**RESULTS**

**Thermotolerance Protects Cells from Apoptosis after Heat Shock, Ceramide, and TNFα but Not after Ionizing Radiation**—MEF were treated with a mild heat shock (44 °C for 10 min) to induce thermotolerance and allowed to recover at 37 °C for 6 h before being subjected to more severe heat shock, ceramide, TNFα, or ionizing radiation. Cells were scored for apoptotic morphology under a fluorescence microscope following permeabilization and staining with propidium iodide. As shown in Fig. 1A, cells in a thermotolerant state showed significant decreases in apoptosis after heat shock, ceramide, and TNFα but not after ionizing radiation. The thermotolerant state protected cells from apoptosis after a range of heat doses (Fig. 1B) or TNFα doses (Fig. 1C). The induction of thermotolerance induces high levels of HSP72 (Fig. 2).

**Constitutive Expression of HSP72 Protects Cells from Apoptosis after Heat Shock, Ceramide, and TNFα but Not after Ionizing Radiation**—Because the development of thermotolerance closely correlates with the induction of HSP72, it was decided to investigate whether constitutive expression of HSP72 alone could protect MEF from stress-induced apoptosis. MEF were infected with HSP72 and single cell cloned, and a number of clones expressing human HSP72 were isolated. The highest HSP72 expressing clone, clone 2, has less HSP72 than the highest HSP72 expressing clone, clone 3 (Fig. 2). Control and HSP72 expressing cells were treated either with heat shock, ceramide, TNFα, or ionizing radiation as described above, stained with propidium iodide, and scored for apoptotic morphology. As shown in Fig. 3, cells expressing constitutive HSP72 are protected from heat shock-, ceramide-, and TNFα-induced apoptosis but not from ionizing radiation. Although we found that HSP72 does protect the cells from heat stress, we found greater protection from TNFα- and ceramide-induced apoptosis. Also shown in Fig. 3 is the response of clone 2 cells to heat or TNFα after the induction of thermotolerance. The level of HSP72 increases further after induction of thermotolerance in clone 2 but is similar to the levels measured in the parental MEF (Fig. 2). Cells expressing both high levels of HSP72 and thermotolerance are more resistant to heat stress than those expressing HSP72 alone (Fig. 3A), whereas the response to TNFα (Fig. 3B) is similar to that of HSP72 expressing cells. Thus the protection from heat-induced apoptosis afforded by the thermotolerant state cannot be attributed solely to the induction of HSP72, whereas protection against apoptosis provided by HSP72 protects the cells from heat stress but not from ionizing radiation.
Heat, TNF

The strong protection against TNFα-induced apoptosis afforded by the expression of HSP72 led us to consider other members of the TNF receptor superfamily. To check whether the p55 or p75 TNF receptor was active in MEF, we measured the extent of apoptosis induced by human TNFα. MEF were sensitive to human TNFα, and the toxicity was blocked by HSP72 (Fig. 3E). This indicates that apoptosis is mediated through the p55 TNF receptor since the p75 TNF receptor does not bind human TNFα. We also tested for sensitivity of MEF to apoptosis induced by binding of antibody or ligand to Fas or binding of Trail to the Trail receptor, other receptors in the TNF receptor family. MEF do not express Fas in amounts detectable by antibody binding, nor do they show signs of toxicity after incubation in either anti-Fas antibody, Fas ligand, or Trail ligand (data not shown).

**Thermotolerance Reduces SAPK/JNK Activity after Heat Shock but Not after Ceramide, TNFα, or Ionizing Radiation**—The activation of the SAPK/JNK cascade detected after a number of cytotoxic insults has been proposed to be required for apoptosis (6). To determine whether the thermotolerant state was protecting MEF from stress-induced apoptosis through the inhibition of this pathway, SAPK/JNK activity was measured by an *in vitro* kinase assay using a GST-c-Jun (1–141) fusion protein as a substrate. Time courses were performed after each stress to determine optimum times for detecting SAPK/JNK activity. Maximal activity was detected at 30 min after heat shock and TNFα. MEF show a 10–15-fold activation of SAPK/JNK after heat shock and 2–3-fold activation after TNFα. Data shown for ceramide and ionizing radiation were obtained 1 h after stress; however, little SAPK/JNK activation was detected in MEF after ceramide and ionizing radiation over a 24-h period. Using these conditions, SAPK/JNK activity was measured in control and thermotolerant cells. Significant reduction of SAPK/JNK activity in thermotolerant cells after heat shock was observed, but no changes in activity were detected after other stresses (Fig. 4A).

** Constitutive Expression of HSP72 Does Not Reduce SAPK/JNK Activation after Stress**—Because the thermotolerant state was shown to reduce SAPK/JNK activation after heat shock but not after other stresses, the effect of HSP72 expression on SAPK/JNK activity was measured. Control and HSP72 expressing cells were subjected to heat shock, ceramide, TNFα, or ionizing radiation and SAPK/JNK activity measured. As shown in Fig. 4B, HSP72 did not reduce SAPK/JNK activation after any of these stresses, despite protecting the cells from apoptosis.

**Thermotolerance Inhibits PARP Cleavage in Cells after Heat Shock, TNFα, and Ceramide But Not after Ionizing Radiation**—A common event in the apoptotic pathway is the activation of a caspase cascade. PARP, a DNA repair enzyme, has been identified as a substrate for caspase-3. Caspase-3 activity was measured by following the cleavage of PARP from a 116-kDa protein to an 85-kDa fragment. PARP cleavage is first from TNFα-induced apoptosis in thermotolerant cells can be fully accounted for by the expression of HSP72.

The level of expression of HSP72 determined the extent of resistance to apoptosis. As shown in Fig. 3 (A and B), clone 3, which expresses less HSP72 than clone 2 (Fig. 2), has less resistance to heat- and TNFα-induced apoptosis. In other retrovirally infected clones expressing less HSP72 than seen in clone 3, no protection against stress-induced apoptosis was detected (data not shown). In summary, protection was only seen in cells expressing moderate to high levels of HSP72, indicating that the process of infection with the retrovirus alone has not altered the response of the cells to stress.
detected in MEF cells 6 h after stress but is more extensive at 16 h after heat, ceramide, and TNFα or 24 h after ionizing radiation (data not shown). We examined the possibility that the thermotolerant state may inhibit PARP cleavage either directly or by regulating some upstream event in the caspase cascade. MEF were treated with heat shock, ceramide, TNFα, or ionizing radiation and allowed to recover for 16 or 24 h. Cell extracts were subjected to immunoblotting with a PARP-specific antibody that recognizes both the 116- and 85-kDa fragments. As shown in Fig. 5A, the induction of thermotolerance can reduce PARP cleavage after heat shock, TNFα, and ceramide but not after ionizing radiation. Measurement of α-tubulin levels demonstrates equal protein loading in each lane.

**DISCUSSION**

Many forms of cellular stress lead to the activation of two related signaling pathways mediated by the stress-activated...
protein kinases, SAPK/JNK and p38/HOG-1 (5). The SAPK/JNKs, which are activated by a kinase known as Sek1, comprise a family of eight or more isoforms that phosphorylate the c-Jun and JunD components of the AP1 transcription factor as well as Elk-1 and ATF-2. ATF-2 is also a substrate for p38/HOG-1, as is MAPKAP kinase-2, which in turn phosphorylates the heat shock protein, HSP27, at the same sites at which it is phosphorylated in response to stress (5). Many stresses capable of activating SAPK/JNK, including heat shock, TNFα, ceramide, UV light, ionizing radiation, osmotic stress, and anti-cancer agents, also result in apoptosis (reviewed in Ref. 5). Despite the observation that SAPK/JNK activation and apoptosis are often co-incident, there is strong debate about the requirement of SAPK/JNK activation for apoptosis. Stable transfection of dominant negative mutants of either Sek1 or c-Jun (TAM-67) has been shown to inhibit apoptosis after ionizing radiation, ceramide, UVC light, heat shock, and hydrogen peroxide (6). In contrast, studies performed in Sek1 (+/-) ES cells demonstrated a normal apoptotic response after ionizing radiation, UV light, osmotic stress, serum deprivation, anisomycin, heat shock, dexamethasone, and anti-cancer agents, although thymocytes from Sek1 (-/-) mice showed impaired Fas-induced apoptosis (27). Controversy surrounds the involvement of SAPK/JNK activation in TNFα-induced apoptosis, with studies claiming that a catalytically inactive MAPKKK (ASK1), which no longer activates SAPK/JNK and p38/HOG-1 (28), can inhibit TNFα-induced apoptosis, as can either Sek1 or TAM67 dominant negative mutants (6). In contrast, other studies have shown that SAPK/JNK activation occurs through a pathway that is not required for TNFα-induced apoptosis (29, 30).

In our study, we have shown that the thermotolerant state or constitutive expression of HSP72 can protect cells from apoptosis induced by heat, TNFα, and ceramide but not from ionizing radiation, thus demonstrating the existence of multiple pathways of stress-induced apoptosis. It is interesting to note that HSP72, which is widely believed to protect cells from heat stress, prevents heat-induced apoptosis to a lesser extent than TNFα- or ceramide-induced apoptosis. Further, the protection seen in thermotolerant cells after TNFα and ceramide can be accounted for by the induction of HSP72, whereas the induction of thermotolerance provides a significantly higher level of protection against heat-induced apoptosis than can be accounted for by HSP72 alone. An explanation for this may lie in the fact that heat is a nonspecific stress that causes damage to many proteins and organelles in the cell, and thus multiple targets need to be protected from heat stress. HSP72 may be able to protect some of these targets, but the induction of other stress proteins may be required for more complete protection. In contrast, TNFα initiates apoptosis through a specific pathway that begins with the activation of TNF receptors. HSP72 could act at one stage of this pathway to minimize the extent to which apoptosis is triggered by TNFα.

The possibility that HSP72 may regulate stress-induced apoptosis through inhibition of the SAPK/JNK pathway was investigated, but expression of HSP72 was found to not alter the extent of activation of SAPK/JNK. In addition, we found that the extent of SAPK/JNK activation after the different stresses did not correlate with the extent of apoptosis observed, possibly indicating that SAPK/JNK activation is not required for the induction of apoptosis in MEF. Alternatively, SAPK/JNK activation may be necessary but is not sufficient for apoptosis to occur. We therefore conclude either that MEF can undergo stress-induced apoptosis using a SAPK/JNK-independent
pathway that can be regulated by HSP72 or that HSP72 acts downstream of SAPK/JNK activation. Interestingly, SAPK/JNK was inhibited in thermotolerant cells after heat shock but not in cells expressing constitutive HSP72. This supports the finding that thermotolerance provides a substantially higher level of protection against heat-induced apoptosis than HSP72 alone, suggesting that factors other than HSP72 that are induced in the thermotolerant state are capable of suppressing SAPK/JNK activation.

An expanding family of cysteine proteases (caspases), of which ICE is the prototype, has been shown to play a key role in mammalian cell apoptosis. The caspases can be divided into three main groups based on sequence similarity: ICE, ICErel 11/Tx/ICH-2 and ICErel 111/Ty; CPP32/Yama/apopain/prICE, ICE-LAP3/MCH3 and MCH2; and finally, Nedd2/ICH-1 (4). Overexpression of any one of these enzymes induces apoptosis in transfected cells (31, 32). Evidence is emerging that multiple caspases may function sequentially after induction of apoptosis in a cell (33). A number of substrates have now been identified, including other caspases, proteins involved in DNA repair (PARP and DNA-protein kinase) and some structural proteins (lamin, actin, and vimentin) (4), but the importance of these substrates in apoptosis is not clear. We investigated the possibility that HSP72 could inhibit stress-induced apoptosis through the regulation of the caspase pathway. Caspase-3 activity can be measured by following the cleavage of PARP from a 116-kDa protein to an 85-kDa fragment. We have shown that constitutive HSP72 expression can prevent PARP cleavage after heat shock or TNFα but not after ceramide or ionizing radiation. The lack of protection of PARP by HSP72 after ceramide exposure is surprising because HSP72 does protect against ceramide-induced apoptosis. The data suggest that HSP72 acts to block the activation or the activity of one of the caspases and/or to protect the substrates of these caspases from proteolytic degradation. The possibility that HSP72 acts as a decoy substrate for the caspases was investigated by Mosser et al. (19), but they found that HSP72 was unable to inhibit the caspase-3-mediated cleavage of PARP in an in vitro assay.

Of interest in this study was the marked protection by HSP72 from TNFα-induced apoptosis, mediated through the p55 TNF receptor. While triggering apoptosis in many cells, TNFα also activates the transcription factor NF-κB that blocks apoptosis (30). How HSP72 may interact with this pathway is unknown, but in WEHI-S cells, the expression of HSP72 does not alter the TNF-induced activation of NF-κB, nor does it alter TNF receptor levels (34). Instead, HSP72 inhibits TNF-induced activation of phospholipase A₂, which releases arachidonic acid from membrane phospholipids (34). It has been shown previously that arachidonic acid is released in response to TNF in sensitive cells but not in TNF-resistant cells (35).

Two other families of genes that block apoptosis have been identified. The inhibitor of apoptosis protein family, first recognized as the candidate gene for spinal muscular atrophy, can block apoptosis induced by a number of stresses (36–38). The best characterized inhibitors of apoptosis are Bcl-2 and several of its homologues, which can block apoptosis in response to a large number of, but not all, stimuli (39). The mechanism by which Bcl-2 and its homologues block apoptosis is not clear; however, it has been suggested that Bcl-X₅ prevents disruption of the mitochondrial membrane potential that otherwise permits the release of apoptosis-inducing proteins into the cytosol (40). Bcl-2 blocks the release of cytochrome c from the mitochondria that occurs following apoptotic stimuli but prior to membrane depolarization. This in turn prevents the interaction between cytochrome c and Apaf-1 and subsequent caspase activation and apoptosis (41, 42). It is feasible that HSP72 may protect cells from apoptosis through a similar mechanism; either through the inhibition of cytochrome c release from the mitochondria, or, more likely, by binding directly to cytosolic cytochrome c and preventing activation of the caspases. HSP72 is known to bind to peptides derived from cytochrome c (43).

Heat shock proteins have been recognized for some years to protect cells from heat damage and more recently from some other cytotoxic insults. As well as the protective effects of HSP72 shown here and in other studies (17–23) the small heat shock protein, HSP27, has been shown to block apoptosis induced by Fas/Apo-1 and staurosporine (44) and by some anticancer drugs (20, 45). Heat shock proteins are often expressed at high levels in tumor cells, leading to suggestions that they can protect cells either from immune attack or from the type of therapy being administered. For example, several recent studies have revealed that tumor specimens from patients whose cancer therapy has resulted in a short disease-free survival contain high levels of one or more of the stress proteins (46–49). Emerging clones of tumor cells would be subjected to host initiated stresses such as TNF and may show prolonged survival if they express high levels of HSP72. Thus, we believe there is evidence to suggest that high levels of heat shock proteins may confer a survival advantage on an emerging or metastasizing clone of neoplastic cells by protecting it from immune surveillance and other host-derived stresses. We therefore propose that the heat shock gene family represents a third class of anti-apoptosis genes.

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