Activation of the p38 Signaling Pathway by Heat Shock Involves the Dissociation of Glutathione S-Transferase Mu from Ask1*

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Heat shock affects all proteins and structures but nevertheless produces a highly specific stress response aimed at protecting the cells and re-establishing homeostasis. In addition to the well characterized transcriptional activation of the genes coding for heat shock proteins (1–5), within minutes heat shock activates a major signal transduction pathway involving the stress-activated protein kinase p38 and leading to the phosphorylation of heat shock protein 27 (HSP27) (4, 5). Phosphorylation of HSP27 activates a protective function, which may result from the known phosphorylation-modulated function of the protein at the level of the actin microfilaments (6–8) or from other described protective activities, either as a chaperone (9–11) or as an inhibitor of apoptotic processes (12–14). Activation of the p38 pathway and phosphorylation of HSP27 occurs within minutes at elevated temperature and constitutes a very tightly regulated response (15). After a mild heat shock, cells becomes refractory to reinduction of p38 activity by a second heat shock but remained fully responsive to reinduction by other stresses, cytokines, or growth factors (15). The specificity of this desensitization reinforces the existence of a highly specific heat shock-sensing pathway upstream of p38. Despite its importance for cell survival, the signaling components and the molecular mechanism leading to heat shock-induced p38 activation are unknown.

Little is known about the mechanisms of activation of the stress-sensitive pathways. In the case of UV light and hyperosmotic shock, activation of the stress-activated protein kinase JNK2 is triggered by an activation of the receptors for epidermal growth factor, tumor necrosis factor (TNF) α, and interleukin-1 (16). Alterations of receptor conformation by energy absorption or physical perturbation of the cell surface are thought to be the initial triggering events causing the clustering and internalization of these receptors and the subsequent subversion of signaling pathways normally used by growth factors or cytokines (16). In the case of oxidative stress, the sensing mechanism seems to act at the level of Ask1 (apoptosis signal-regulating kinase-1). Ask1 is a MAP kinase kinase that can activate the MAP kinase kinases 3 and 6 leading to the activation of p38, or the MAP kinase kinases 4 and 7 leading to the activation of JNK (17). The redox regulatory protein thioredoxin (Trx) acts as the oxidative stress sensor for this cascade (18). Under normal conditions, Trx in the reduced state binds to and inhibits Ask1. Upon oxidative stress, oxidation of Trx triggers its dissociation from Ask1, allowing the activation of Ask1 and the subsequent activation of downstream kinases.

Here we show that Ask1 is also activated during heat shock and that this activation is responsible for p38 activation. However, heat shock activation of Ask1 does not proceed by a redox-dependent mechanism as shown for oxidative stress. Instead, a new mechanism of Ask1 activation is described involving the heat shock-induced dissociation from Ask1 of a recently identified inhibitor of Ask1, glutathione S-transferase Mu-1 (GSTM1-1) (19). It is concluded that the alternative regulation of Ask1 by the redox-sensitive repressor Trx or the heat-sensitive repressor GSTM1-1 defines the converging point of the heat shock and oxidative stress-sensing pathways leading to p38 activation.

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EXPERIMENTAL PROCEDURES

Materials—[γ-32P]ATP (3000 Ci/mmol) was purchased from PerkinElmer Life Sciences. H2O2, NaHCO3, N-acetyl-l-cysteine (NAC), and myelin basic protein (MBP) were from Sigma. Protein A-Sepharose was from Amersham Biosciences. Chemicals for electrophoresis were obtained from Bio-Rad and Fisher.

Antibodies—HA.11 is a mouse monoclonal antibody recognizing the YPYDVPDYA peptide sequence from human interferon lambda 2 (14). Anti-p38 recognizes the C-terminal sequence PPLIQEEDL of murine p38 (7). Antibody against phosphorlylated p38 was obtained from New England Biolabs (Beverly, MA). Anti-Ask1 is a novel antibody developed for this study. It was raised in rabbits against the C-terminal sequence of human Ask1 protein (KAIDFRNKQT) as described before for anti-p38 (7). Anti-GSTM1-1 is an affinity-purified polyclonal antibody (20).

Cell Culture and Treatments—Chinese hamster CCL39 and human Hela cells were cultivated in Dulbecco’s modified Eagle’s medium containing 2.2 g/l NaHCO3 and 4.5 g/l glucose, and supplemented with 5 or 10 mM Tris-HCl, pH 7.5, containing 250 mM NaCl, 5 mM EGTA, 1% Triton X-100, 0.5% deoxycholate, 20 mM dithiothreitol, and 1 mM phenylmethylsulfonyl fluoride. The extracts were vortexed and centrifuged at 17,000 g for 15 s and washed at least three times with 300 μl of SDS-PAGE loading buffer. Kinase activity in immune complexes using MBP as substrate. Proteins were then separated by SDS-PAGE, and kinase activity was visualized by autoradiography of the 32P-labeled substrate. B, exponentially growing CCL39 cells were co-transfected with 3 μg of pEBGp38-GST together with increasing concentrations of PCDNA3-HA-Ask1(K709M) (Ask1(K709M), 0–17 μg) as indicated. 48 h after transfection, cells were left untreated (Ctrl), exposed at 44 °C for 20 min (HS), or treated with H2O2 (5 μM, 15 min), sorbitol (HOS, 0.3 M, 15 min) or sodium arsenite (Ars, 200 μM, 60 min). After treatments, extracts were prepared and subjected to SDS-PAGE/Western blot analysis (WB) using antibodies specific for phospho-p38 (p38-p, left panels) and total p38 (p38, middle panels). Expression of PCDNA3-HA-Ask1(K709M) was confirmed by immunoblotting with anti-HA antisera (HA, right panels).

Communoprecipitation Assay—After treatments, cells were scraped and extracted in coimmunoprecipitation buffer containing 20 mM Tris-HCl, pH 7.5, 150 mM NaCl, 5 mM EDTA, 1 mM Na3VO4, 10 mM dithiothreitol, and 1 mM phenylmethylsulfonyl fluoride. The extracts were vortexed and centrifuged at 17,000 × g for 12 min at 4 °C. The clarified supernatants were frozen on dry ice and stored at −80 °C. The further steps were carried out at 4 °C. To assay Ask1 activity, an equal volume of Ask1 cell lysate normalized for Ask1 protein was incubated with 10 μl of anti-Ask1 antibody for 1 h and harvested with 15 μl of protein A-Sepharose 50% v/v in lysis buffer. After 30 min, the samples were centrifuged for 15 s and washed twice with 300 μl of 20 mM Tris-HCl, pH 7.5, containing 5 mM EDTA, 1 mM phenylmethylsulfonyl fluoride.

RESULTS

Ask1 Is an Essential Component for Heat Shock-Mediated p38 Activation—Heat shock strongly activates the stress-activated protein kinase p38, but the upstream signaling pathway leading to this activation is not known. The MAP kinase kinase kinase Ask1 has been shown to be an upstream activator of p38. After treatments, extracts were prepared and subjected to SDS-PAGE/Western blot analysis (WB) using antibodies specific for phospho-p38 (p38-p, left panels) and total p38 (p38, middle panels). Expression of PCDNA3-HA-Ask1(K709M) was confirmed by immunoblotting with anti-HA antisera (HA, right panels).

Communoprecipitation Assay—After treatments, cells were scraped and extracted in coimmunoprecipitation buffer containing 20 mM Tris-HCl, pH 7.5, 150 mM NaCl, 5 mM EDTA, 1 mM Na3VO4, 1% Triton X-100, 0.5% deoxycholate, 20 μM ATP, 20 mM MgCl2, and 6.5 μg MBP. Ask1 activity was assayed for 12 min at 30 °C and was stopped by the addition of 10 μl of SDS-PAGE loading buffer. Kinase activity was evaluated by measuring incorporation of the radioactive into MBP after resolution by SDS-PAGE and quantification using a PhosphorImager (Molecular Dynamics).

To assay endogenous or transfected GST-tagged p38 activity, cells were lysed directly in SDS-PAGE loading buffer. MBP fractions were separated by SDS-PAGE on 10% acrylamide gels. Under these conditions, the transfected tagged protein is distinguished from the endogenous protein due to its slower migration. Proteins were then transferred onto nitrocellulose as previously described (6). After reacting the membranes with anti-phospho-p38 antibody, proteins were detected using an enhanced chemiluminescence (ECL) detection kit (Pierce). Equal loading of the kinase on different lanes was verified by immunoblotting with anti-p38 antibody.
 Activation of Ask1 by Heat Shock

GST-tagged p38 and exposed to heat shock or other known activators of p38. p38 activity was measured in transfected cells using a phosphospecific p38 antibody (Fig. 1B, left panels). Western blot analysis confirmed equivalent levels of expression of GST-tagged p38 and increasing levels of expression of HA-Ask1(K709M) (Fig. 1B, middle and right panels). Expression of Ask1(K709M) inhibited heat shock-induced p38 activation in a dose-dependent manner. The inhibitory effect was specific. In agreement with previous reports (18, 21), Ask1(K709M) blocked the activity by heat shock; however, it had no effect on the activation of p38 by hyperosmotic shock (sorbitol) or sodium arsenite. These findings indicate that Ask1 is an essential upstream activator of p38 in response to heat shock. The specificity of the inhibitory effect indicates that Ask1 mediates only a subset of the stimuli that activates p38.

**Activation of Ask1 by H_{2}O_{2} in Heat-desensitized Cells**—We previously reported that following a first heat shock treatment, cells become temporarily desensitized to further p38 activation by heat shock but remain fully responsive to p38 activation by cytokines, growth factors, and stresses (15). This suggests the existence of a specific mechanism for p38 activation by heat shock. We examined whether this homologous heat desensitization process also affected Ask1 activity. Cells were first exposed to a 20-min heat shock at 44°C and then exposed 7 h later to a second heat shock or to a H_{2}O_{2} treatment. Pretreatment with NAC at concentrations higher than 10 mM inhibited H_{2}O_{2} activation of p38 but had no effect on the stimulation induced by heat shock (Fig. 3A). Thus, whereas generation of reactive oxygen metabolites is an essential event upstream of p38 activation in response to H_{2}O_{2}, oxidative stress is not a key triggering element for the induction of p38 in response to heat shock.

Next we investigated if Trx, an endogenous inhibitor of Ask1, could block p38 activation by heat shock. CCL39 cells were transfected with expression vectors encoding GST-tagged p38 and Myc-tagged Trx and exposed to heat shock or H_{2}O_{2} treatments. p38 activity was measured using a phosphospecific p38 antibody (Fig. 3B, upper panel). Equivalent levels of expression of GST-tagged p38 and increasing levels of expression of Myc-tagged Trx were confirmed by Western blot analysis (Fig. 3B, middle and bottom panels). Expression of Trx inhibited H_{2}O_{2} activation of GST-tagged p38 in a dose-dependent manner but had no effect on heat shock activation of GST-tagged p38. We examined the effect of heat shock treatment on the in vivo interaction between Ask1 and Trx. Hela cells were transfected with an expression vector encoding HA-tagged Ask1-WT or with an empty vector and exposed to heat shock or H_{2}O_{2}.
exponentially growing CCL39 cells were co-transfected with pEBGpS8-GST together with increasing concentrations of pH66-GSTM1-1(Y6F) (GSTM1-1 Y6F, 0–17 μg) as indicated. 48 h after transfection, the cells were left untreated (Ct), exposed to a 20-min heat shock at 44 °C (HS), or treated with H2O2 (5 μM, 15 min) or sorbitol (HOS, 0.3 M, 15 min). After treatments, extracts were prepared and subjected to SDS-PAGE/Western blot analysis (WB) using antibodies specific for phospho-p38 (p38-p, left panels) to detect phosphorylated GST-p38 and anti-p38 (p38, middle panels) to detect total GST-p38 expression. Expression of GSTM1-1(Y6F) was verified by immunoblotting with the anti-HA antiserum (HA, right panels). B, CCL39 cells were transfected with 3 μg PCDNA3-HA-Ask1-WT. 48 h after transfection, cells were left untreated (C), exposed to a 20-min heat shock at 44 °C (HS), or treated with H2O2 (P, 5 μM, 15 min). After treatments, cell lysates were immunoprecipitated (IP) with anti-GSTM1-1 antibody, and the immunopellets were subjected to SDS-PAGE/Western blot (WB) analysis using anti-HA antibody to detect the presence of HA-Ask1-WT (upper panel). Expression of PCDNA3-HA-Ask1-WT (middle panel) and endogenous GSTM1-1 (lower panel) in total soluble cell lysates was verified by immunoblotting with anti-HA and anti-GSTM1-1 antiserum, respectively.

Endogenous Trx was immunoprecipitated with monoclonal anti-human Trx antibody, and the immunocomplexes were analyzed by immunoblot with anti-HA antibody (Fig. 3C, upper panel). Western blot analyses confirmed equivalent levels of expression of HA-tagged Ask1-WT and endogenous Trx (Fig. 3C, middle and bottom panels). An association between Trx and Ask1 could be demonstrated under control conditions. H2O2 treatment, but not heat shock, caused a dissociation of Trx from Ask1.

**DISCUSSION**

**Ask1 Is an Obligatory Component of the Specific Heat-sensitive p38 Signaling Pathway**—The stress-activated protein kinase p38 is activated by a number of different stimuli including growth factors and cytokines, but also by many different stress agents or conditions such as exposures to physical or chemical DNA damaging agents, cytoskeleton disrupting drugs, hypo- or hyperosmotic shock, shear stress, reoxygenation following hypoxia, oxidative stress, and heat shock (7, 15, 28–37). The fact that so many different stressors can activate the p38 pathway suggests the existence of distinct sensing pathways that converge on an upstream activator capable of integrating different signals. Using classical desensitization experiments, we recently demonstrated the existence of such a specific heat shock-sensing pathway upstream of p38, distinct from that used by other stresses such as hyperosmotic stress or H2O2 (15). Here we showed that this sensing pathway converges on Ask1, a MAP kinase kinase kinase that also mediates Ask1, enabling the binding of TRAF2 to Ask1 and its activation. During heat shock a dissociation of the complex formed by glutathione S-transferase Mu1-1 (GSTM1-1) and Ask1 occurs, leading to the activation of Ask1 and downstream kinases. The mechanism that leads to this dissociation remains to be determined. It may involve the release of a lipophilic molecule that competes with Ask1 for binding with GSTM1-1 following heat shock. Because of an alternative regulation by distinct repressors, thioredoxin and GSTM1-1, Ask1 constitutes the converging point of the heat shock and oxidative stress-sensing pathways that lead to p38 activation (see text for details).
tion. First, endogenous Ask1 activity was stimulated by a mild heat shock (Fig. 1A). Second, and most important, overexpression of the catalytically inactive mutant of Ask1, Ask1(K709M), inhibited p38 activation by heat shock (Fig. 1B) in a dose-dependent manner. As expected (18, 21), Ask1(K709M) also blocked the activation of p38 by H$_2$O$_2$. However, it did not block the activation by sorbitol or sodium arsenite, two agents that did not activate Ask1, indicating a specific effect of the inhibitor.

Distinct Molecular Mechanisms Mediate Heat Shock and H$_2$O$_2$-induced Activation of Ask1—We recently reported that the signaling elements downstream of Ask1 are desensitized homologously by heat shock (15). Here we showed that a priming heat shock treatment also inhibits the activation of Ask1 by a subsequent heat shock, but does not affect activation of Ask1 by H$_2$O$_2$ (Fig. 2B). This result implied that there exists a heat-specific activation mechanism operating at the level of upstream of Ask1 that is distinct from that used by H$_2$O$_2$. Such distinct mechanisms of Ask1 activation are presented in Fig. 5.

H$_2$O$_2$ activates the Ask1-p38 module by the oxidation of the redox-sensing protein Trx (18). In non-stressed cells Trx binds to Ask1, an association that keeps Ask1 in an inactive form. This interaction is dependent on the redox status of Trx. Oxidation of Trx dissociates the complex, allowing the activation of Ask1 by oligomerization and autophosphorylation (26). Recent evidence also suggests the participation of an unidentified kinase in this process (39). A similar mechanism is involved in TNF-induced activation of Ask1 (38, 40). Reactive oxygen species produced in response to TNF cause the oxidation-mediated dissociation of Trx from Ask1, enabling the binding of TNF receptor-associated factor 2 (TRAF2) to Ask1 and its activation (Fig. 5). Activation of Ask1 could be blocked in both cases with free-radical scavengers, including the overexpression of Trx (38, 40).

In contrast to H$_2$O$_2$-induction, activation of p38 by heat shock was not antagonized by pretreatment with the antioxidant NAC or by overexpression of Trx (Fig. 3A and B). Furthermore, in contrast to H$_2$O$_2$, heat shock did not cause a dissociation of Trx from Ask1 (Fig. 3C). Instead, we found that heat shock-induced activation of Ask1 involves the modulation of GSTM1-1, a potent endogenous inhibitor of Ask1 activity (19). It was previously proposed that GSTM1-1 could inhibit Ask1 activity by binding to the kinase and preventing its oligomerization. The modulation of Ask1 activity by GSTM1-1 was hypothesized to be the results of modulations in the level of expression of GSTM1-1. In particular it was suggested that induction of GSTM1-1 expression after stress could participate in a homeostatic mechanism to block further Ask1 induction, thereby protecting the cells from Ask1-induced apoptosis (19). Our results imply a more direct regulation of GSTM1-1 inhibitory activity by heat shock. We showed that heat shock causes the release of GSTM1-1 from Ask1 (Fig. 4B). The dissociation of GSTM1-1 from Ask1 is not induced by H$_2$O$_2$ treatment suggesting that the dissociation is not a consequence of Ask1 activation. Instead, the dissociation of GSTM1-1 likely triggers Ask1 activation since overexpression of exogenous GSTM1-1 inhibited p38 activation by heat shock in a dose-dependent manner (Fig. 4A).

This heat shock-induced dissociation of GSTM1-1 from Ask1 is reminiscent of H$_2$O$_2$ and TNF-α-induced dissociation of Trx from Ask1 (18, 21, 40). A similar mechanism of activation has also been described for JNK. Association between GST-pi and JNK is disrupted by oxidative stress caused by the formation of GST-GST dimers and multimers, and the dissociation leads to enhanced-JNK activity (41). It is tempting to suggest that similar to Trx, which acts as a redox-sensitive repressor of Ask1, GSTM1-1 acts as a heat-sensitive repressor of Ask1, and its dissociation following heat shock leads to Ask1 activation.

The mechanisms that lead to the dissociation of GSTM1-1 from Ask1 and whether it can also be induced by stresses other than heat shock remain to be determined. The release of GSTM1-1 from Ask1 as well as inhibition of its activity were demonstrated using GSTM1-1(Y6F), a mutant with no glutathione S-transferase activity (19), indicating that this activity was not involved in the regulation of Ask1. GST activity results in the conjugation of glutathione to dangerous electrophilic compounds. In addition to their catalytic activity GST proteins have an ill-defined role as ligandins, being capable of binding a number of small lipophilic molecules such as steroids and their metabolites (42, 43). It is possible that during heat shock such ligandin-binding molecules are released or produced in such a way that they compete with Ask1 for binding to GSTM1-1 (Fig. 5). Like the release of Trx from Ask1 in the case of H$_2$O$_2$, the release of GSTM1-1 during heat shock may then allow subsequent Ask1 activation by oligomerization. However, the release of this inhibitor may not be sufficient for activation of Ask1. In the case of TNF the participation of the activator TRAF2 is required for Ask1 activation (38, 40). Likewise, Ask1 activation by heat shock may necessitate the contribution of a heat-induced activator in addition to its dissociation from GSTM1-1.

Ask1, a Tightly Regulated Kinase Integrating Two Stress-signaling Pathways—As a result of this alternative regulation exerted by Trx and GSTM1-1, Ask1 can constitute the converging point of the heat shock and oxidative stress-sensing pathways leading to p38 activation. The nature of this dual regulation remains to be determined. Since heat shock and H$_2$O$_2$ cause the release of only one of the inhibitors, it could be suggested that neither Trx nor GSTM1-1 can by itself inhibit Ask1 and thus that the release of only one is sufficient for activation. A simpler hypothesis, however, is that both Trx and GSTM1-1 are by themselves fully efficient as inhibitors, but that there exist in the cells different pools of Ask1 at equilibrium, some bound to Trx and responsive to oxidative stress and others bound to GSTM1-1 and responsive to heat shock (Fig. 5). This is possible because both inhibitors bind to the N-terminal region of Ask1 (18, 19) and thus may compete for the same region. Considering the large number of regulatory molecules known to bind Ask1 (18, 19, 25, 38, 40, 44–53), several distinct pools of these regulatory complexes might exist. Indeed, one example already reported in the literature is the existence of a complex composed of Ask1, MKK4, and JNK3 that are held together by the scaffold protein β-arrestin-2. This complex mediates Ask1 and JNK3 activation in response to stimulation of guanine nucleotide-binding protein-coupled receptors (54). The position of Ask1 at the converging point of several sensing pathways might be particularly important in cell physiology in the light of the recently proposed pivotal role of Ask1 in determining cell fate between survival and apoptosis (55).

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