Heat Shock Protein 90 Inhibitor Induces Apoptosis and Attenuates Activation of Hepatic Stellate Cells

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ABSTRACT

Activated hepatic stellate cells (HSCs) are major participants in hepatic fibrosis; thus, the induction of HSC apoptosis has been proposed as an antifibrotic treatment strategy. Heat shock protein (Hsp) 90 is a molecular chaperone that stabilizes major signal transduction proteins, and its inhibitors have antitumor activity. In this study, the susceptibility of HSCs to an Hsp90 inhibitor was evaluated. LX-2 cells, an immortalized human HSC line, 17-(allylamino)-17-demethoxygeldanamycin (17AAG), an Hsp90 inhibitor, and monensin, an acidic sphingomyelinase inhibitor, were used in this study. Cellular apoptosis was quantified by 4',6-diamidino-2-phenylindole dihydrochloride staining, and signaling cascades were explored using immunoblotting and immunoprecipitation techniques. Nuclear factor (NF) \( \beta \) activities were evaluated by immunofluorescent microscopy and enzyme-linked immunosorbent assay. Collagen \( \alpha 1 \) and \( \alpha \)-smooth muscle actin expression levels in HSCs before inducing apoptosis. These results demonstrate that the Hsp90 inhibitor induces HSC apoptosis via a sphingomyelinase- and NF\( \beta \)-dependent mechanism. Because this inhibitor also reduces HSC activation before apoptosis, Hsp90 inhibitor treatment might be therapeutically useful as an antifibrotic strategy in a variety of liver diseases.

Hepatic fibrosis is caused by a wound-healing response to chronic liver injuries, such as persistent viral infection, alcohol or drug exposure, and a hereditary metal overload (Friedman, 2000; Pinzani and Marra, 2001). This process leads to the progressive accumulation of extracellular matrix components, such as collagen types I and III in liver parenchyma, and ultimately results in liver cirrhosis complicated by portal hypertension and hepatocellular dysfunction (Friedman, 2000). Activated hepatic stellate cells (HSCs) are the most important source of extracellular matrix proteins during this fibrotic process (Wells, 2005). Under basal conditions, HSCs are quiescent, have low mitotic activity, and primarily store retinoids (Sato et al., 2003). However, on activation, HSCs transform into myofibroblast-like cells and express \( \alpha \)-smooth muscle actin (Carpino et al., 2005). In addition, activated HSCs migrate to the portal area, proliferate, and produce extracellular matrix components, such as collagen, glycoproteins, and proteoglycans (Hui and Friedman, 2003). Therefore, the majority of antifibrotic therapies are designed to inhibit the activation and proliferation of HSCs and their abilities to synthesize fibrosis-associated protein products. More recently, tumor necrosis factor-related apoptosis-inducing ligand, which selectively induces HSC apoptosis, has been proposed as an antifibrotic treatment (Taimr et al., 2003).

Heat shock proteins (HSPs) are cellular chaperone proteins that are required for essential housekeeping functions, such as protein folding, assembly, and transportation across different cell compartments. In particular, HSPs promote cell survival by maintaining the structural and functional integrity of several client proteins that regulate cell survival,
proliferation, and apoptosis (Lanneau et al., 2008). Furthermore, although HSPs are expressed in normal cells, they are frequently overexpressed in cancer cells, which suggests that they have a role in maintaining malignant transformation.

Hsp90 is the most abundant protein in eukaryotic cells and is required for the stabilities and functions of a number of conditionally activated and/or expressed signaling proteins. However, it also performs the same functions for many mutated, chimeric, or overexpressed signaling proteins that promote cancer cell growth and/or survival (Cullinan and Whitehall, 2006). Hsp90 is known to function in an ATP-dependent manner in cooperation with other molecular chaperones, such as Cdc37 and FKBP52. The small-molecule 17-(α-lamino)-17-demethoxygeldanamycin (17AAG) is a geldanamycin analog that specifically inhibits the ATPase activity of Hsp90. Thus, treatment of cells with 17AAG results in the inactivation, destabilization, and degradation of Hsp90 client proteins. Moreover, because Hsp90 client proteins play important regulatory roles in the cell cycle, cell growth, cell survival, apoptosis, and oncosgenesis, 17AAG obstructs cancer cell proliferation and exhibits anticancer activity in experimental animals. Recently, a phase I clinical trial on 17AAG was completed, and several phase II trials were initiated. Hsp90 inhibitors are unique in that, although they are directed toward a specific molecular target, they simultaneously inhibit multiple signaling pathways that frequently interact to promote cancer cell survival. However, although Hsp90 is an attractive target for cancer therapy, the roles that Hsp90 plays in HSC survival and activation have not been elucidated. In the present study, we evaluated the susceptibilities of HSCs to an Hsp90 inhibitor (17AAG) by investigating whether it induces HSC apoptosis and attenuates HSC activation. The results presented in this study demonstrate that 17AAG induces HSC apoptosis and suppresses HSC activation before inducing apoptosis. Our findings suggest that inhibition of this signaling by 17AAG may be therapeutically efficacious in the treatment of hepatic fibrosis.

Materials and Methods

Cell Culture and Reagents. LX-2 cells, an immortalized human HSC line, were used in this study, and were cultured in Dulbecco’s modified Eagle’s medium supplemented with 10% fetal bovine serum, 100,000 U/l penicillin, 100 mg/l streptomycin, and 100 nM insulin. 17AAG (an Hsp 90 inhibitor) was obtained from Alexis Laboratories (San Diego, CA), and monensin (an acidic sphingomyelinase inhibitor) was from Sigma-Aldrich (St. Louis, MO). TGF-β and lipopolysaccharide (LPS) were also purchased from Sigma-Aldrich. Nitric oxide (NO) donors sodium nitroprusside (SNP) and 3-morpholinosydnonimine (SIN) were obtained from Sigma-Aldrich and Merck (Darmstadt, Germany), respectively.

Cell Proliferation. Cell proliferation was measured using the CellTiter 96 Aqueous One Solution cell proliferation assay (Promega, Madison, WI), on the basis of the cellular conversion of the colorimetric reagent 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt into soluble formazan by dehydrogenase enzymes found only in metabolically active, proliferating cells. After each treatment, 20 ml of dye solution was added into each well in a 96-well plate and incubated for 2 h.

Subsequently, absorbance was recorded at 490-nm wavelength using an ELISA plate reader (Molecular Devices, Sunnyvale, CA).

Apoptosis. Apoptosis was assessed by examining characteristic nuclear changes (i.e., chromatin condensation and nuclear fragmentation) using the nuclear binding dye 4′,6-diamidino-2-phenylindole dihydrochloride by fluorescence microscopy (Carl Zeiss GmbH, Jena, Germany).

ELISA. NFκB activity was evaluated using ELISA. Cells were plated at 5 × 10⁴ cells/well in 1 ml of media or 10⁵ cells in 5 ml of media in a six-well plate or a 100-mm culture dish, respectively, and treated with or without 17AAG. Cytosolic and nuclear extracts were collected, and NFκB concentrations (p50/p65) in fractions were determined using TransFactor NFκB p50/p65 Chemiluminescent Kits (Clontech, Mountain View, CA).

Immunofluorescent Microscopy. NFκB activities were evaluated by immunofluorescent microscopy. In brief, cells were plated at 10⁵ cells in 5 ml of media in a 100-mm culture dish and treated with or without 17AAG. After 20 h of incubation, cells were treated with LPS for 1 h and stained with rabbit anti-NFκB p65 (Santa Cruz Biotechnology Inc., Santa Cruz, CA). They were then incubated with Cy3-conjugated AffiniPure goat anti-rabbit IgG from Jackson ImmunoResearch Laboratories Inc. (West Grove, PA). The immunostained samples were examined under a fluorescence microscope (Carl Zeiss GmbH).

Immunoblotting. Cells were lysed for 20 min on ice using lysis buffer (50 mM Tris-HCl, pH 7.4; 1% Nonidet P-40; 0.25% sodium deoxycholate; 150 mM NaCl; 1 mM EDTA; 1 mM phenylmethylsulfonyl fluoride; 1 μg/ml aprotinin, leupeptin, and pepstatin; 1 mM Na3VO4; and 1 mM NaF) and were then centrifuged at 14,000 g for 10 min at 4°C. Samples were resolved by SDS-polyacrylamide gel electrophoresis, transferred to nitrocellulose membranes, and blotted with appropriate primary antibodies. Blots were then incubated with peroxidase-conjugated secondary antibodies (BioSource International, Camarillo, CA). Bound antibodies were visualized using a chemiluminescent substrate (ECL, GE Healthcare, Chalfont St. Giles, UK) and exposed to Kodak X-OMAT film (Eastman Kodak, Rochester, NY). The primary antibodies used were: rabbit anti-caspase 9 from Cell Signaling Technology Inc. (Danvers, MA); rabbit anti-caspase 8, mouse anti-cytokine c, and rabbit anti-caspase 3 from BD Biosciences Pharmingen (San Diego, CA); rabbit anti-NFκB p50/p65 was from Santa Cruz Biotechnology, Inc.; mouse anti-α-smooth muscle actin was from Biogenex (San Ramon, CA); and mouse anti-cellular FLICE-like inhibitory protein (cFLIP) was from Santa Cruz Biotechnology, Inc.

Immunoprecipitation Analysis. Cytosolic extracts were mixed with anti-sera for the glucocorticoid receptor (RfK D Systems, Minneapolis, MN) and incubated overnight at 4°C. Immune complexes were immunoprecipitated with protein A/G PLUS-Agarose (Santa Cruz Biotechnology, Inc.) and washed for 5 × 10 min with 1 ml of washing buffer. After washing, polypeptides were resolved by boiling with Laemmli sample buffer and then immunoblotted for NFκB p50/p65.

Real-Time PCR. Total RNA was extracted from cells using TRizol Reagent (Invitrogen, Carlsbad, CA). cDNA templates were prepared using oligo(dT) random primers and Moloney murine leukemia virus reverse transcriptase. Collagen α1 mRNA was quantified by real-time PCR using the following primers: forward, 5′-aacatacaggacaaacaaaagt-3′; and reverse, 5′-cattgcttgtccttcttg-3′. Universal 18S primers (Ambion, Austin, TX) were used to control for RNA integrity. Real-time PCR (LightCycler; Roche Diagnostics, Mannheim, Germany) was used for quantification purposes, and SYBR green was used as the fluorophore (Invitrogen, Carlsbad, CA).

Collagen Assay. After collection of media, cells were washed three times with phosphate-buffered saline, and then cell lysates were prepared as described above for immunoblot analysis. Concentrations of type I collagen in culture media were measured using Procollagen type I C-peptide (PIP) EIA Kits (Precoated) (Takara, Kyoto, Japan). In brief, standards and samples were assayed in triplicate, and the resulting standard curve was used to calculate collagen concentrations as micromgroms per milligram of total cellular protein for each experimental condition.

Statistical Analysis. Statistical analysis was performed using the SPSS (version 11.5) statistical package (SPSS Inc., Chicago).
Illinois). Differences between two groups were analyzed using the two-tailed Student’s *t* test or the Mann-Whitney *U* test. *p* Values < 0.05 were taken to indicate that differences were statistically significant.

**Results**

**Hsp90 Inhibitor Induced HSC Apoptosis.** When LX-2 cells were treated with 17AAG, the number of apoptotic cells increased significantly versus untreated controls (Fig. 1). Furthermore, 17AAG induced the activation of caspase 8 (an initiation caspase) and, subsequently, that of caspase 9 (Fig. 2). Because sphingomyelinase-dependent ceramide generation is known to induce apoptosis by activating initiation caspases (Obeid and Hannun, 1995), we next evaluated whether this sphingomyelinase signaling is involved in 17AAG-induced HSC apoptosis. As shown by 17AAG in Fig. 2, when cells were pretreated with monensin (an acidic sphingomyelinase inhibitor), caspase 8 and 9 activations by 17AAG were effectively prevented. These observations indicate that Hsp90 inhibition triggers HSC apoptosis via sphingomyelinase-dependent signaling.

**Hsp90 Inhibitor Prevented NFκB Activation.** Because NFκB activation is crucial for HSC survival (Oakley et al., 2005), we next evaluated whether Hsp90 inhibition alters NFκB activation status. In resting HSCs, NFκB was located in the cytosol, whereas when cells were treated with LPS, it translocated into the nucleus (Fig. 3A). This nuclear translocation was effectively suppressed with 17AAG (Fig. 3, A and B), and NFκB (p50/65) activity was inhibited in 17AAG-treated cells (Fig. 3C).

We next investigated how 17AAG inhibits NFκB activity and its nuclear translocation. Glucocorticoid receptor (GR) is a binding partner of Hsp90 and NFκB (Tago et al., 2004); therefore, we hypothesized that GR binding to NFκB prevents NFκB translocation and activation and that binding between Hsp90 and GR liberates NFκB, thereby facilitating its translocation to the nucleus. To prove this hypothesis, we immunoprecipitated GR from the cytosol and then immunoblotted these precipitates with NFκB. As shown in Fig. 4, GR complexed NFκB (p50/65), and 17AAG enhanced this complex formation. This finding implies that Hsp90 inhibition prevents NFκB translocation and activation by facilitating GR to NFκB binding. Because Akt is a client protein of Hsp90 and when activated up-regulates the kinase activity of IKK complex, which leads to NFκB activation, we also investigated whether Akt activation is influenced by 17AAG treatment. As shown in Fig. 5, Akt activation was partially inhibited at 2 h and completely inhibited at 4 h after 17AAG treatment. These observations indicate that Hsp90 inhibition prevents NFκB activation by inducing GR complex formation with NFκB and also by deactivating Akt.

Next, we evaluated whether NFκB-dependent antiapoptotic protein expression is down-regulated by Hsp90 inhibition. As shown in Fig. 6, the expression of cFLIP, one of the NFκB-dependent downstream antiapoptotic molecules (Kreuz et al., 2001), was found to be down-regulated by 17AAG. Thus, these observations collectively indicate that the Hsp90 inhibitor triggers HSC apoptosis by activatinginitiation caspase via a sphingomyelinase-dependent signaling and that this is augmented by simultaneous NFκB inhibition and cFLIP down-regulation.

**Enhanced Hsp90 Inhibitor-Induced Apoptosis in Activated HSCs.** Because LX-2 cells have a culture-dependent activation phenotype (Arthur et al., 1999), 17AAG-induced apoptosis was compared in HSCs culture-activated for 3 or 10 days. As shown in Fig. 7, 17AAG induced apoptosis more efficiently in HSCs cultured for 10 days, which suggested that Hsp90 plays a greater survival role in activated HSCs.

We then examined whether Hsp90 expression levels were increased with HSC activation, but we found that they were not (Fig. 8) and followed this by investigating the role played by Hsp90 activity in NFκB activation in activated HSCs. As shown in Fig. 9, GR binding with NFκB was lower in culture- and TGF-β-activated HSCs, and this was restored in these activated cells by 17AAG. Because Hsp90 expression and binding with the GR complex were unaffected by HSC activation or 17AAG (Fig. 9), it appeared that Hsp90 activity per se is crucial for NFκB activation in activated HSCs because it prevents NFκB-to-GR complex binding.

**Enhancement of Hsp90 Inhibitor-Induced Apoptosis by NO Donors.** The concentration of 17AAG used in this study was 10 μM, which is relatively higher compared with those used in other studies (up to 2 μM) (Jeon et al., 2007; Al Shaer et al., 2008; Meyer et al., 2008), although this is consistent with the relative resistance of HSCs to apoptotic stimuli (Novo et al., 2006; Hannivoort et al., 2008). We then attempted to sensitize HSCs to 17AAG-induced apoptosis. Because a recent study suggests that NO may promote HSC apoptosis (Langer et al., 2008), we evaluated whether NO donors may also augment 17AAG-induced HSC apoptosis. 17AAG-induced growth suppression (Fig. 10A), and caspase activation (Fig. 10B) were enhanced in the presence of NO donors (SNP and SIN). This finding implies that relatively apoptosis-resistant HSCs may become susceptible to a lower concentration of the Hsp90 inhibitor in the presence of NO.

**Hsp90 Inhibitor Suppressed HSC Activation.** Because NFκB activation is also essential for HSC activation (Mann
and Smart, 2002), we finally evaluated whether Hsp90 inhibition suppresses HSC activation. As shown in Fig. 11, 17AAG treatment reduced \( \beta \)-smooth muscle actin expression before the induction of HSC apoptosis. Furthermore, both LPS- and TGF-\( \beta \)-induced collagen syntheses were suppressed by 17AAG (Fig. 12). Therefore, these observations imply that Hsp90 also participates in HSC activation in addition to HSC survival by regulating NF\( \kappa \)B activation.

**Discussion**

The principal findings of this study relate to the ability of 17AAG (an Hsp90 inhibitor) to modulate HSC survival and activation as a potential antifibrotic strategy for the treatment of liver fibrosis. Our findings demonstrate that 17AAG induced HSC apoptosis via sphingomyelinase- and NF\( \kappa \)B-dependent signaling. In addition, 17AAG was found to suppress HSC activation before inducing apoptosis.

Excessive accumulation of extracellular matrix in liver fibrosis is a dynamic process, which is mainly regulated by activated HSCs (Friedman, 2000). Therefore, these cells are the primary targets of antifibrotic therapies, and considerable efforts have been made to discover drugs that selectively inhibiting Hsp90.
induce the apoptosis in these activated cells (Iredale, 2001; Desmet and Roskams, 2004; Desmet, 2005; Elsharkawy et al., 2005). However, HSCs generally are regarded as resistant to apoptotic stimuli (Kawada, 2006; Novo et al., 2006). The molecular chaperone Hsp90 is an exciting oncologic target (Goetz et al., 2003). Hsp90 facilitates the correct conformation and localization and stabilizes client proteins, many of which are involved in tumor progression. Tumor cells overexpress Hsp90 and its client proteins, and in tumors, Hsp90 is present in multichaperone complexes and has high ATPase activity, whereas Hsp90 in normal tissues is present in a latent, uncomplexed state (Goetz et al., 2003). These findings support the tumor selectivities of Hsp90 inhibitors. In this study, 17AAG was found to induce HSC apoptosis, and this induction was greater in more activated cells. We explain this activation-dependent selectivity as follows. Diverse cellular stresses generated by surrounding inflammation lead to HSC activation, and these cells become dependent on chaperones to overcome these stresses. In particular, it is known that many proteins expressed in response to cellular stresses need Hsp90 for stability and activity (Neckers and Ivy, 2003). Thus, these activated cells are more likely to be susceptible to Hsp90 inhibitors than quiescent cells. However, in the present study, Hsp90 expression levels were not found to increase in activated cells (Fig. 8); thus, it is likely that changes in the expression levels of cochaperones, such as Hsp70, Hop, p23, and AHA1 (an activator of Hsp90 ATPase), may be responsible for the enhanced efficacy of 17AAG observed in activated cells. For example, changes in AHA1 expression, which increase the ATPase activity of Hsp90 (Panaretou et al., 2002), may influence the activities of client proteins and/or cellular response to Hsp90 inhibitor treatment. This suggestion is supported by the recent observation that silencing of AHA1 expression can reduce client protein activation and increase sensitivity to the Hsp90 inhibitor (Holmes et al., 2008).

In the present study, 17AAG-induced HSC apoptosis was found to be sphingomyelinase-dependent. Sphingolipids were formerly considered to serve only as structural components but are now being viewed as an important group of signaling molecules that are involved in many cellular events, including cell growth, senescence, and cell death (Yang et al., 2004). Sphingolipids also have been associated with functions, such as inflammation and response to heat shock and genotoxic stress (Kolesnick and Fuks, 2003), and the best studied sphingolipid, ceramide, is an important mediator in many cellular signaling pathways (Obeid and Hannun, 1995). Because sphingomyelinase-dependent ceramide generation is known to induce apoptosis by activating initiation caspases (Obeid and Hannun, 1995; Lin et al., 2004), sphingomyelinase-dependent HSC apoptosis by 17AAG observed in this study is most likely to be initiated by ceramide generation and subsequent caspase 8 activation. In addition, the present study also showed that 17AAG prevented NFκB activation in HSCs. It has been demonstrated previously that the NFκB inhibition reversed liver fibrosis by inducing activated HSC apoptosis in vitro and in vivo (Oakley et al., 2005; Watson et al., 2008) and, furthermore, that the inhibition of the IKK/NFκB pathway was sufficient to increase the rate at which activated HSCs undergo apoptosis (Oakley et al., 2005). Therefore, these findings collectively indicate that 17AAG initiates HSC apoptosis via a sphingomyelinase-dependent

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**Fig. 6.** 17AAG down-regulated cFLIP expression. LX-2 cells were treated with 17AAG for the indicated times. Cells were then lysed and immunoblotted for cFLIP and β-actin.

**Fig. 7.** 17AAG induced the apoptosis of quiescent and activated HSCs. 17AAG-induced apoptosis was compared in HSCs cultured for 3 and 10 days. *p < 0.05.

**Fig. 8.** Hsp90 expression levels at different cell activation statuses. LX-2 cells were cultured for 2, 4, 8, or 10 days, lysed, and immunoblotted for Hsp90.

**Fig. 9.** 17AAG modulated NFκB activation in HSCs. LX-2 cells were treated with 17AAG (10 μM) for 20 h and then treated with TGF-β. GR was immunoprecipitated from whole-cell lysates, and these immunoprecipitates were immunoblotted for NFκB (p50 and p65).
mechanism and that 17AAG-induced apoptosis is subsequently augmented by the inhibition of NFκB activation.

The chaperone complex Hsp90-Cdc37 has previously been suggested to associate with IKK and to have an important regulatory effect on NFκB signaling (Chen et al., 2002). Given that IKK activity is required for NFκB activation, the inhibition of the Hsp90-Cdc37-IKK-NFκB pathway is likely to be a mechanism of 17AAG-induced NFκB inhibition in HSCs. In addition, we demonstrate in this study that binding between Hsp90 and GR liberates NFκB, thereby facilitating its translocation to the nucleus and that 17AAG-induced GR binding to NFκB prevents NFκB translocation and activation. Furthermore, in addition to this Hsp90-GR-NFκB pathway, we show that the inhibition of Hsp90-Akt-IKK-NFκB pathway is also responsible for 17AAG-induced NFκB inhibition in HSCs. Although 17AAG-induced NFκB-dependent cFLIP down-regulation was suggested as one possible mechanism of apoptosis augmentation, it is also likely that down-regulation of a variety of NFκB- and Akt-dependent survival signals may play a crucial role in 17AAG-induced HSC apoptosis.

The present study also showed that NO donors augmented 17AAG-induced HSC apoptosis, indicating that we may use 17AAG at lower concentrations, especially in the presence of NO. This is also clinically applicable because statins are potent stimuli for NO production in sinusoidal endothelial cells (Deleve et al., 2008; Tokunaga et al., 2008), and adjacent HSCs are likely to be exposed to high concentrations of NO. Therefore, in vivo evaluation of 17AAG/statin combination is anticipated as an antifibrotic strategy.

NFκB is also known to participate in HSC activation (Nieto, 2007). Collagen is a heterodimeric protein composed of two α1 chains and one α2 chain encoded by the COL1A1 and COL1A2 genes, and it has been reported that the COL1A2 promoter contains at least two putative NFκB binding sites (Büttner et al., 2004). Oxidative stress and other inflammatory signals are major inducers of IκB phosphorylation, which then releases NFκB that is translocated to the nucleus to activate the transcriptions of target genes (Viatour et al., 2005). The present study showed that 17AAG reduced α-smooth muscle actin expression in HSCs before the induction of apoptosis and, furthermore, that both LPS- and TGF-β-induced collagen synthesis was suppressed by 17AAG. Therefore, these observations imply that Hsp90 also partic-

![Fig. 10. NO donors enhanced 17AAG-induced HSC apoptosis. A, LX2 cells preincubated in the presence or absence of NO donor (250 μM SNP or 250 μM SIN) were treated with 17AAG (10 μM) for 16 h. Cell viability was compared using 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt assay. Data are expressed as the means ± S.D. of three separate experiments. *p < 0.05. B, LX2 cells preincubated in the presence or absence of the NO donor (250 μM SNP or 250 μM SIN) were treated with 17AAG (10 μM) for indicated times. Cells were then lysed and immunoblotted for caspase 9, caspase 7, and β-actin.](image)

![Fig. 11. Hsp90 participated in HSC activation. α-Smooth muscle actin expression was found to be suppressed by 17AAG. LX-2 cells were treated with 17AAG for the indicated times. Cells were then lysed and immunoblotted for α-smooth muscle actin and β-actin.](image)
ipates in HSC activation in addition to HSC survival by regulating NFκB activation.

In conclusion, this study provides firm support for the notion that Hsp90 functions to activate and promote the survival of HSCs and that HSCs in the activated state are more dependent on Hsp90 for survival. Our findings suggest that the Hsp90 inhibitor may be therapeutically useful in hepatic fibrosis.

References


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