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A transcription cofactor required for the heat-shock response

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The Stress-responsive activator of p300 (Strap) is a transcription cofactor that has an important role in the control of DNA damage response through its ability to regulate p53 activity. Here, we report that Strap is inducible by heat shock and stimulates the transcription of heat-shock genes. A chromatin-associated complex involving heat-shock factor 1 (HSF1), Strap and the p300 coactivator assembles on the heat-shock protein 70 (*hsp70*) promoter, and Strap augments HSF1 binding and chromatin acetylation in Hsp genes, most probably through the p300 histone acetyltransferase. Cells depleted of Strap do not survive under heat-shock conditions. These results indicate that Strap is an essential cofactor that acts at the level of chromatin control to regulate heat-shock-responsive transcription.

Keywords: heat shock; transcription; Strap; HSF1; p300

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INTRODUCTION

DNA damage is one form of cellular stress that activates an evolutionarily conserved signalling pathway that culminates in a checkpoint response, usually resulting in DNA repair, cell-cycle arrest and apoptosis (Zhou & Elledge, 2000). The p53 tumour suppressor protein has a crucial role in the DNA damage response through regulating various target genes that instigate the checkpoint response (Bates & Vousden, 1996). The ability of p53 to activate transcription is controlled by coactivator complexes, involving p300/CBP (CBP for CREB-binding protein) proteins, which physically interact with the transcription activation domain (Barlev *et al*, 2001; Espinosa & Emerson, 2001). The histone acetyltransferase (HAT) in p300/CBP acetylates the chromatin of p53-responsive target genes, together with lysine residues in the p53 protein, to augment the p53 response (Gu *et al*, 1997; Ito *et al*, 2001).

p300/CBP proteins interact with various cofactors that influence transcriptional activity (Chan & La Thangue, 2001). JMY (junction-mediating and regulatory protein) and Strap (Stress-responsive activator of p300) are two cofactors that cooperate in regulating p53 activity in a pathway in which Strap is targeted and regulated by DNA damage-responsive kinases (Shikama *et al*, 1999; Demonacos *et al*, 2001; Coutts & La Thangue, 2005; Coutts *et al*, 2007). For example, Strap is phosphorylated by the phosphatidylinositol-3 kinase-like kinase ATM (ataxia-telangiectasia mutated), which enables it to undergo nuclear accumulation (Demonacos *et al*, 2004). As a consequence, Strap forms a p300-dependent coactivator complex that activates p53 transcription (Demonacos *et al*, 2001, 2004). Six tetratricopeptide repeats (TPR), which function as protein-binding modules and facilitate protein assembly, are instrumental in allowing Strap to influence p300 activity (Demonacos *et al*, 2001).

However, DNA damage is only one form of cellular stress and it is possible that certain components of stress response pathways are shared between different types of stress. During the heat-shock response, a group of chaperones—exemplified by heat-shock protein (Hsp)90 and Hsp70—control various cellular processes, including protein folding, assembling multi-component protein complexes, translocation across cellular compartments and targeting protein degradation to the proteasome (Nollen & Morimoto, 2002). As a consequence, the action of chaperones in response to heat shock is believed to maintain the balance between misfolded and native-state proteins.

The expression of *Hsp70* and *Hsp90* genes is regulated through a conserved transcription response involving heat-shock factor 1 (HSF1), which binds to heat-shock elements (HSEs) located in the promoters of target genes (Morimoto, 2002). Activation of HSF1 requires phosphorylation and trimerization, which then allows HSF1 to bind to the HSE (Morimoto, 2002). In turn, chaperone activity is influenced by a group of regulatory proteins, called co-chaperones, which physically bind to the Hsp70/Hsp90 complex (Morimoto, 1998).

To explore the interaction between different stress response pathways, we tested whether Strap participates in the heat-shock response. Here, we describe an unexpected yet crucial role of Strap in the heat-shock response. Under heat-shock conditions, Strap assembles with HSF1 and p300, and activates transcription through the HSE. A heat-inducible chromatin-associated complex involving HSF1, Strap and p300 coincides with enhanced chromatin acetylation in Hsp genes through a mechanism that probably involves the HAT activity of p300. Notably, cells depleted of Strap are compromised in their ability to survive

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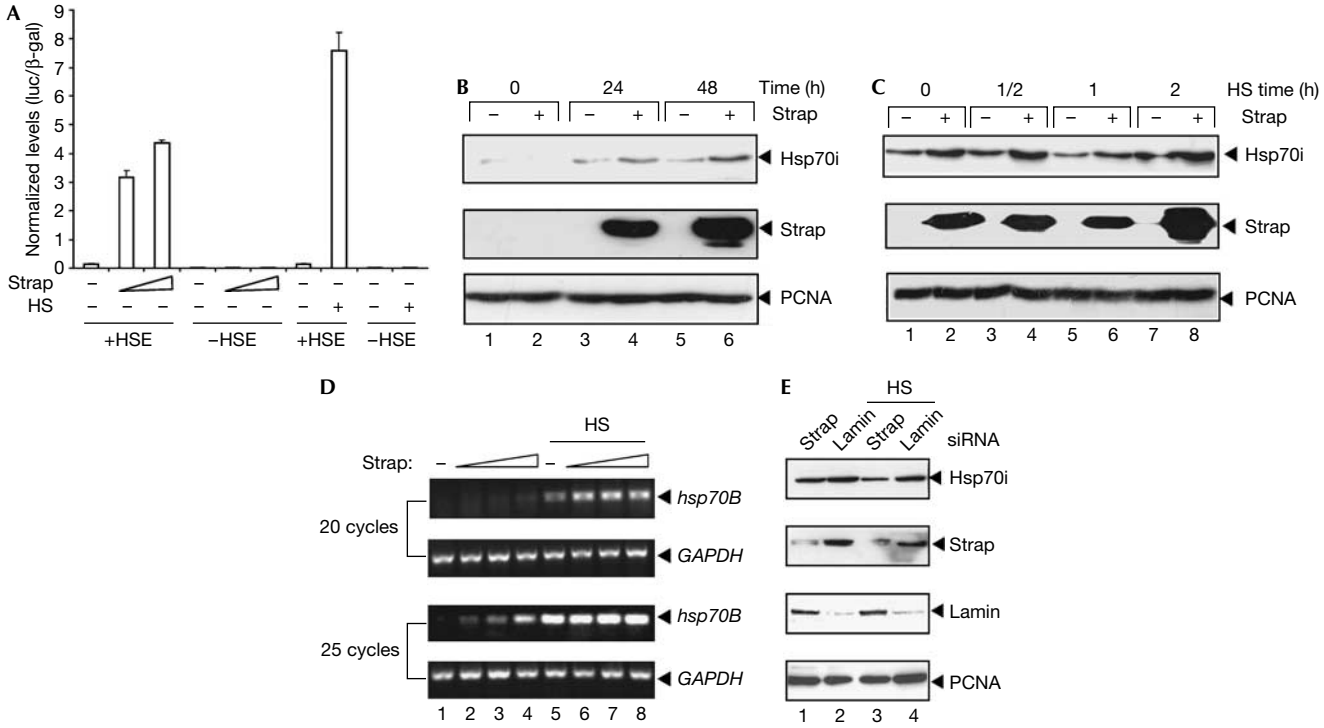


Fig 1 | Strap activates heat-shock protein genes. (**A**) Luciferase reporter assays were performed using a pGL3-luc vector (200 ng) containing *hsp70B* promoter (+HSE) and a control pGL3-luc vector (−HSE). Expression vectors encoding Strap (200 or 500 ng) were co-transfected into U2OS cells with the luciferase reporter (200 ng) and β-galactosidase (β-gal) expression vector (100 ng) as the internal control. After 48 h, cells were collected, and both luciferase and β-gal activities were measured in triplicate. The graph represents the luciferase/β-gal (luc/β-gal) ratio. Heat shock (HS) was at 43 °C for 1 h. (**B**) U2OS cells were transfected with HA-Strap or control vector (2 μg), and collected at 0, 24 and 48 h as indicated. The expression of endogenous inducible Hsp70 (Hsp70i) and HA-Strap (Strap) was detected by immunoblotting as described. Proliferating-cell nuclear antigen (PCNA) was used as the loading control. (**C**) U2OS cells were transfected with HA-Strap or control vector (2 μg) and treated with heat shock at 43 °C for 30 min, 1 h or 2 h. Cell lysates were immunoblotted to detect the Hsp70i and Strap as described above. PCNA was used as the loading control. (**D**) Reverse transcription–PCR was carried out with equal amounts of complementary DNA templates prepared from transfected U2OS cells (control vector or 0.2, 0.5 or 1.0 μg HA-Strap). Heat-shock treatment was at 43 °C for 1 h. The coding region of the genes for Hsp70B or glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was amplified, as described, for the indicated number of PCR cycles (20 or 25). (**E**) U2OS cells were transfected with siRNA targeting Strap or control lamin (100 nM) for 72 h, and left untreated or treated with heat shock at 43 °C for 1 h before being collected. The levels of Hsp70i, Strap, lamin and PCNA were measured by immunoblotting as described. HA, haemagglutinin; HSE, heat-shock element; Hsp, heat-shock protein; siRNA, short interfering RNA; Strap, Stress-responsive activator of p300.

under heat-shock conditions. Thus, Strap is a cofactor that participates in heat-shock-responsive transcription and facilitates cell survival under heat shock.

RESULTS

Strap stimulates the Hsp70 promoter

As Strap is a transcription cofactor, we considered that it might have a wider role in the cellular stress response, for example, in regulating heat-shock-inducible transcription. Therefore, we assessed the effect of Strap on the *hsp70B* promoter, which is heat-shock inducible through several HSEs (Voellmy *et al*, 1985; Wang *et al*, 2000). In a transfection-based reporter assay, Strap efficiently activated transcription driven by the *hsp70B* promoter (Fig 1A). Activation was dependent on the presence of HSEs because a reporter construct lacking the HSE could not be activated (Fig 1A). As expected, heat-shock-dependent activation of the *hsp70B* promoter was mediated through the HSE (Fig 1A).

The ability of Strap to activate the *hsp70B* promoter reflected an increase in endogenous Hsp70-inducible protein and RNA because the expression of Strap increased the level of Hsp70 under heat shock (Fig 1B,C), which was mirrored by a concomitant increase in *hsp70* RNA (Fig 1D). To confirm that endogenous Strap regulates *hsp70* expression, we used a short interfering RNA (siRNA) that specifically depletes endogenous Strap (Fig 1E). Treating cells with Strap siRNA reduced the level of Hsp70, which was most evident in heat-shocked cells (Fig 1E). The effect was specific because lamin siRNA, used as the control siRNA (Coutts *et al*, 2007), did not affect Hsp70 induction (Fig 1E; supplementary Fig 1A online).

Fig 2 | Strap binds to heat-shock factor 1 and undergoes heat-shock-dependent chromatin association. (**A**) Whole-cell lysates from normal or heat-shocked (43 °C, 1 h; HS) U2OS cells transfected with pcDNA3 or haemagglutinin (HA)-Strap (2 μg) were immunoprecipitated (IP) with an HSF1 antibody or a control antibody and the immunocomplexes were immunoblotted (IB) with an HA or HSF1 antibody as indicated. The input levels of HSF1 and Strap are indicated. Quantification is presented in the graph (bottom). (**B**) (i) U2OS cells transfected with expression vectors encoding either HA-Strap or pcDNA3 (2 μg) were left untreated, incubated at 43 °C for 30, 60, 90 or 120 min and recovered at 37 °C for 4–6 h before being collected or treated with 10 μM etoposide (Etop) for 16 h as indicated. Cell extracts were immunoblotted with a Strap 510 antibody. pCMV-β-galactosidase (β-gal) was co-transfected as an internal control and used to normalize protein loading. (ii) Immunoblot depicting the heat-shock-dependent accumulation of endogenous Strap determined by immunoblotting with a Strap 510 antibody in U2OS cells treated as described above. Actin was used as a control for protein loading. (**C**) ChIP assays were performed in U2OS cells treated as described above with or without heat shock at 43 °C for 1 h. Crosslinked chromatin was immunoprecipitated with the indicated antibodies (Ab) followed by semiquantitative PCRs against the promoters of *hsp70B* and *albumin*. (**D**) ChIP assays were performed on endogenous Strap and HSF1 proteins as described above with or without heat shock at 43 °C for 1 h. (**E**) For the sequential ChIP analysis, U2OS cells were treated and collected as in (**C**) and primary (I °) immunocomplexes were eluted using 10 mM dithiothreitol, followed by re-immunoprecipitation with the indicated secondary (II °) antibodies and semiquantitative PCR as described in (**C**). Quantification of the ChIP analysis by real-time PCR is shown in the graph (bottom). (**F**) ChIP assays were performed on endogenous HSF1 as described above in U2OS cells treated with Strap or control lamin siRNA (100 nM) with heat shock as described above, or mock treated as indicated. Quantification of the ChIP analysis by real-time PCR is shown in the graph (bottom). ChIP, chromatin immunoprecipitation; HA, haemagglutinin; HSF1, heat-shock factor 1; Hsp, heat-shock protein; siRNA, short interfering RNA; Strap, Stress-responsive activator of p300.

Strap and HSF1 exist in a heat-inducible complex

To investigate the mechanism by which Strap augments Hsp70 transcription, we tested whether Strap associates with HSF1 under heat-shock conditions and, thereafter, whether Strap exists in a chromatin-bound complex on the *hsp70B* promoter. An interaction was apparent between endogenous HSF1 and Strap (Fig 2A). Although the complex was present in normal cells, the level of Strap bound to HSF1 increased by about threefold on heat shock and, under heat-shock conditions, Strap associated with the heat-inducible phosphorylated form of HSF1 (Fig 2A). The interaction between Strap and HSF1 reflected a time-dependent increase in the steady-state level of Strap protein under heat-shock conditions, as shown by immunoblotting experiments (Fig 2Bi). As expected, DNA-damaging agents caused an induction of Strap (Fig 2Bi; Demonacos *et al*, 2004). To confirm that the regulation of ectopic Strap reflected physiological control, we investigated the response of Strap in several cell types (here the response in U2OS cells is shown). Endogenous Strap behaved similarly to the ectopic protein; the response was maximum after 120–150 min heat-shock treatment and resulted in a 2.5-fold increase in levels of Strap (Fig 2Bii).

Strap and HSF1 are chromatin associated, as both proteins were shown, by chromatin immunoprecipitation (ChIP) analysis, to be present in the chromatin of the *hsp70B* promoter (Fig 2C). Consistent with the interaction between Strap and HSF1, when Strap was expressed ectopically, the increased level of chromatin-bound Strap reflected a concomitant increase in the association of endogenous HSF1 with chromatin (Fig 2C; supplementary Fig 1C online), indicating that Strap augments the DNA-binding activity of HSF1. Endogenous Strap was present on the *hsp70B* promoter, which also increased under heat-shock conditions (Fig 2D).

To clarify whether Strap and HSF1 exist in a complex on chromatin, we performed a sequential ChIP analysis in which chromatin bound to HSF1 was re-immunoprecipitated with a Strap antibody (by using a haemagglutinin (HA) antibody against HA-Strap). Strap and HSF1 were found to coexist in a heat-inducible chromatin-associated complex (Fig 2E). Again, the increased level of Strap that resulted from expressing the ectopic protein correlated with enhanced HSF1 binding. To obtain further evidence that endogenous Strap influenced chromatin-associated HSF1, we performed a ChIP analysis with cells treated with Strap siRNA. Under conditions of Strap depletion (Fig 1E), there was a coincident reduction in chromatin-associated HSF1 (Fig 2F). Thus, the association between Strap and HSF1 is heat inducible, Strap and HSF1 exist in a chromatin-associated complex and Strap regulates the level of chromatin-bound HSF1.

Strap modulates the HAT activity of p300

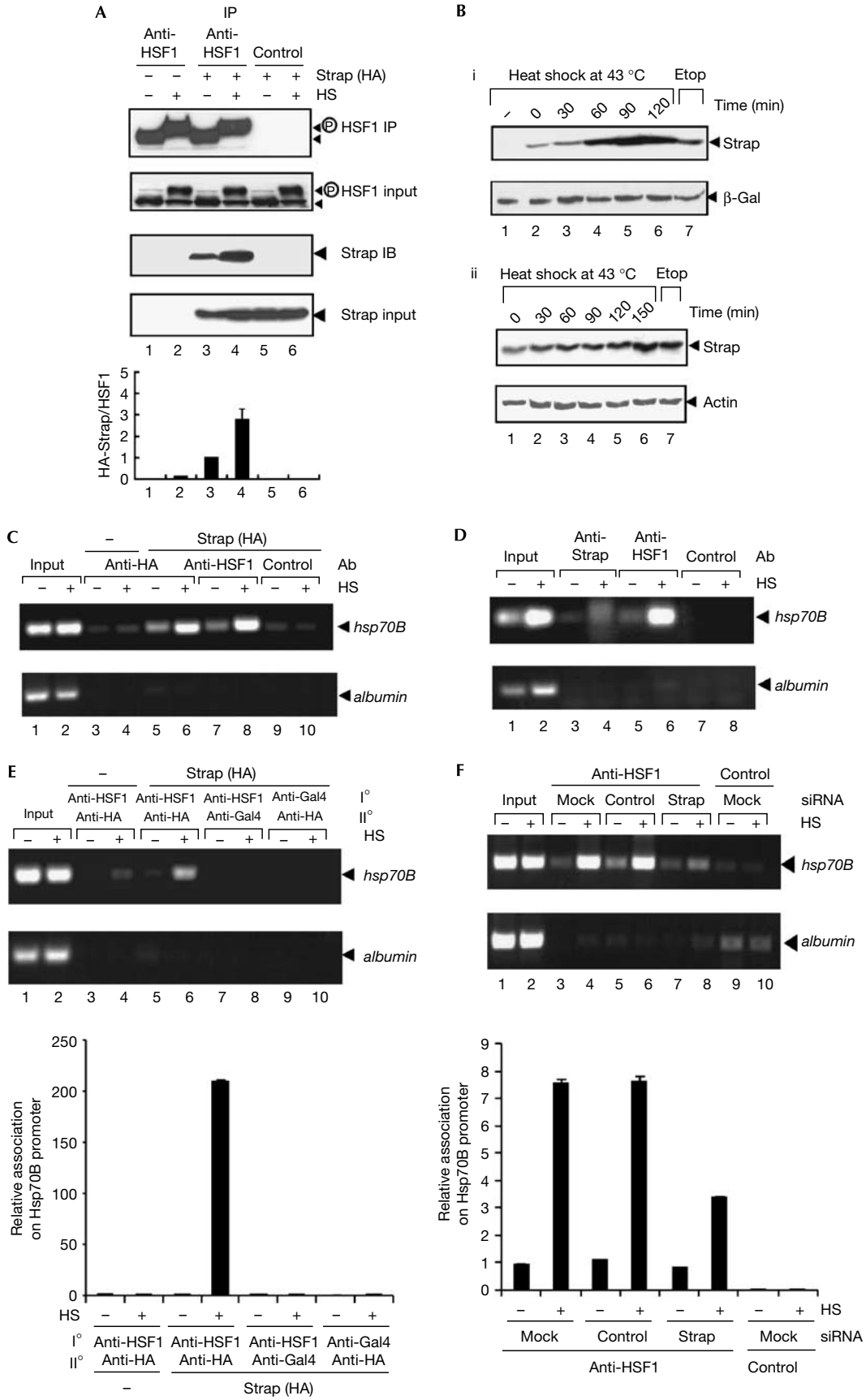
As Strap interacts with p300 coactivators (Demonacos *et al*, 2001), we reasoned that p300 might be involved in heat-shock-dependent transcription. Moreover, as p300 is a HAT and because p300 HAT is required for activation by certain transcription factors (Ito *et al*, 2001), the ability of Strap to activate the *hsp70* gene might involve p300 and altered chromatin acetylation.

Strap was present in p300 immunoprecipitates, and the level of Strap in the p300 complex was higher in heat-shocked cells compared with untreated cells (Fig 3A), which coincided with the presence of HSF1 (supplementary Fig 1B online). Consequently, we assessed whether Strap could affect the HAT activity of p300, by studying p300 in a U2OS cell line in which Strap expression was under conditional control by using the TET-ON expression system (Fig 3B). p300 was immunoprecipitated from cell extracts in the presence of increasing levels of Strap and, thereafter, p300 HAT was measured by monitoring the acetylation of core histones. p300 immunocomplexes showed an increased level of acetyltransferase activity when immunoprecipitated from cell extracts containing induced levels of Strap (Fig 3B,C), suggesting that Strap augments the HAT activity of p300.

Next, we tested whether Strap had a direct influence on p300 HAT by studying the effect of purified Strap on the acetylation of core histones. Wild-type Strap stimulated the HAT activity of recombinant p300 by about twofold (Fig 3D). By contrast, denatured Strap failed to affect p300 HAT and, similarly, a truncated Strap derivative (Demonacos *et al*, 2001) could not stimulate p300 HAT (Fig 3D). These results indicate that Strap can augment the HAT activity of p300.

Strap augments chromatin acetylation in Hsp genes

Given the heat-shock-dependent association between Strap and p300, we investigated whether p300 was present on the *hsp70B*



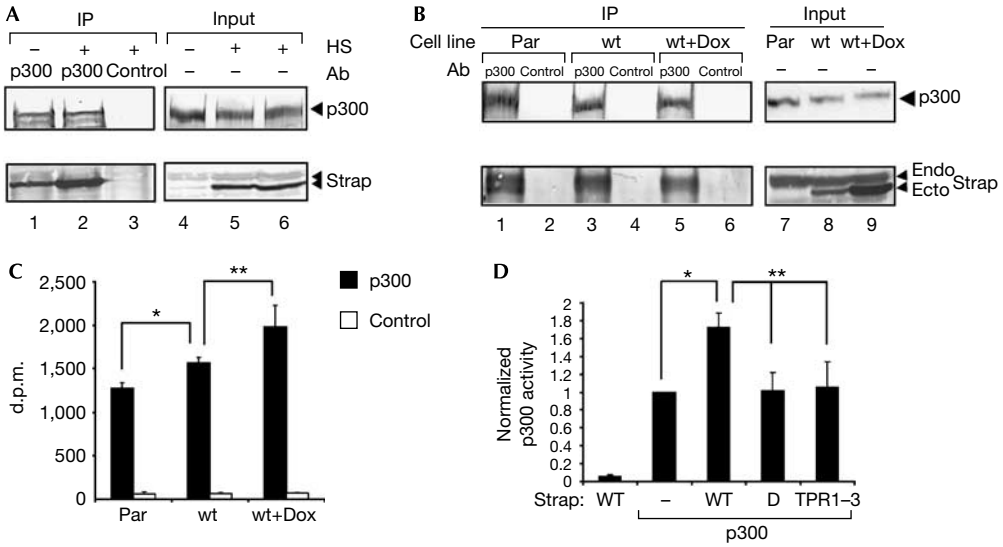


Fig 3 | Strap regulates p300 histone acetyltransferase. (**A**) Immunoprecipitation (IP) was performed in normal or heat-shocked (43 °C, 1 h; HS) U2OS cells that stably express Flag-Strap (Demonacos *et al*, 2004). p300 immunocomplexes were immunoblotted by using a Strap 510 antibody (Ab) as described. (**B**) The TET-ON U2OS parental cell line (Par) and inducible TET-ON Strap stable cell line in the absence (wt) or presence of doxycycline (wt + Dox) were treated as described previously (Demonacos *et al*, 2004). Cell lysates were immunoprecipitated with either a p300 or a control antibody, and immunoblotted with a p300 and a Strap 510 antibody as described. (**C**) The HAT activity in the immunocomplexes collected in (**B**) was measured as described by using core histones as the substrate. *P*-values are indicated (**P* < 0.01; ***P* < 0.01). (**D**) Core histones were used as the substrate for each reaction in the *in vitro* HAT assay. Wild-type Strap (WT), denatured Strap (D) or Strap TPR1–3 (1 μg) was assayed as indicated in the presence or absence of wild-type p300 (1 μg). *P*-values determined by Student's *t*-test are indicated (**P* < 0.01; ***P* < 0.01). d.p.m., disintegrations per minute; HAT, histone acetyltransferase; Strap, Stress-responsive activator of p300; TPR1–3, tetratricopeptide repeats 1–3.

promoter. ChIP analysis showed that the level of chromatin-bound p300 increased under heat shock in a manner that paralleled the increase in HSF1 binding (Fig 4A). We reasoned further that if Strap augments p300 HAT as part of the HSF1 complex, then we might expect that the acetylation of chromatin in heat-shock-responsive genes would increase in a Strap-dependent manner. We investigated this possibility by performing ChIP assays, in which chromatin bound to the *hsp70B* and *hsp90ß* promoters was immunoprecipitated with an acetyl histone H4 antibody in the presence of increasing levels of Strap. The expression of Strap correlated with increased chromatin acetylation in the *hsp70* and *hsp90* promoters in heat-shocked cells (Fig 4B). Trichostatin A, which blocks histone deacetylase, did not enhance acetylation to a similar extent as in the presence of ectopic Strap (Fig 4B), indicating that altered HAT activity—rather than decreased histone deacetylase activity—was responsible for the increased acetylation. The presence of Strap therefore enhances the level of chromatin acetylation in Hsp genes.

Strap is required for cell survival during heat-shock

The results described above indicate that Strap has a crucial role in regulating the transcription programme induced by heat shock. To establish whether this role was functionally important in cell survival during the heat-shock response, we reduced the level of endogenous Strap through siRNA-dependent depletion (Fig 1E) and then measured the level of cell survival under lethal heat-shock conditions (45 °C for 90 min; Shamovsky *et al*, 2006; Westerheide *et al*, 2006). Flow cytometric analysis showed that introducing Strap siRNA into cells growing under normal culture conditions caused an increase in the G2/M population relative to the control siRNA lamin treatment (Fig 5A). As expected from previous reports (Kuhl & Rensing, 2000), heat-shock treatment caused an increase in the G2/M population, and this effect was similar in both the mock and siRNA lamin treatments (Fig 5A). However, Strap siRNA-treated cells that had been subjected to heat shock underwent a significant increase in the level of apoptosis compared with cells that underwent control treatment (Fig 5A). Cells depleted of Strap therefore have impaired survival under heat-shock conditions.

DISCUSSION

Strap influences heat-shock-induced transcription

We have obtained evidence that Strap regulates the transcription of Hsp genes. Specifically, ectopic Strap augmented *hsp70* and *hsp90* expression and, conversely, the depletion of endogenous Strap reduced *hsp70* expression. Moreover, Strap is present in the chromatin of *hsp70* and *hsp90*, activates transcription from the Hsp70 promoter and formed a chromatin-bound protein complex with HSF1. In fact, increased levels of Strap correlated with HSF1 binding and, conversely, depleting Strap caused a coincident reduction in chromatin-associated HSF1. Strap therefore has an important role in regulating HSF1 activity and Hsp gene transcription during heat shock. This is supported by the effect of Strap depletion on cell viability, where Strap is required for cell survival under heat shock.

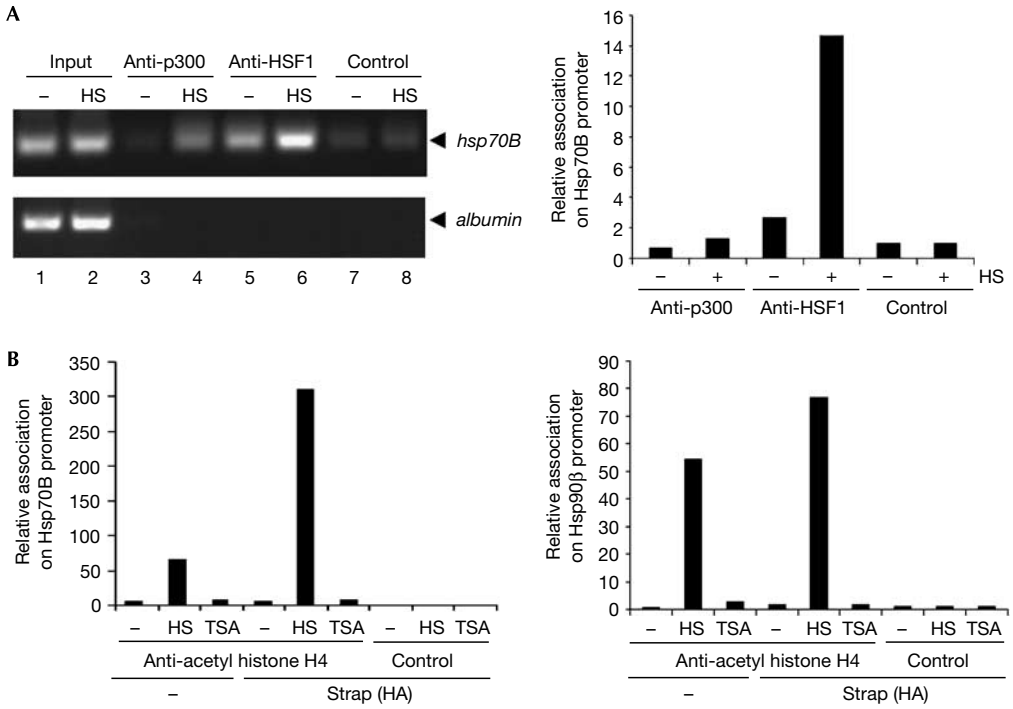


Fig 4 | Strap augments chromatin acetylation in Heat-shock protein genes. (**A**) U2OS cells were treated with or without heat shock (43 °C, 1 h; HS) and aliquots of chromatin were immunoprecipitated with p300, HSF1 or control antibodies. The PCRs were performed against *hsp70B* and *albumin* as described. Quantification of the ChIP by real-time PCR is shown to the right. (**B**) ChIPs were carried out as described in U2OS cells transfected with expression vectors encoding HA-Strap (2 μg) and then treated with heat shock (43 °C, 1 h) or trichostatin A (TSA; 1 μM). Chromatin was immunoprecipitated with acetyl histone H4 or control antibodies and quantified by real-time PCR. ChIP, chromatin immunoprecipitation; HA, haemagglutinin; HSF1, heat-shock factor 1; Hsp, heat-shock protein; Strap, Stress-responsive activator of p300.

At a mechanistic level, Strap enhanced chromatin acetylation of the *Hsp70* and *Hsp90* genes, suggesting a mechanism that might account for the ability of Strap to facilitate transcriptional activation. p300 co-immunoprecipitated with Strap and HSF1, and therefore is a candidate for mediating increased acetylation. Previous reports have suggested an association between Hsp70/Hsp90 and HSF1 (Abravaya *et al*, 1992; Thomson *et al*, 2004), and a role for p300 in the control of Hsp transcription (Li *et al*, 1998), and it has generally been regarded that the Hsp70/Hsp90 chaperone provides a feedback loop involved in downregulating HSF1-dependent transcription (Morimoto, 1998). From these results, it is possible that Strap participates in regulating this feedback loop, perhaps through its ability to recruit p300 and influence HSF1 activity (Fig 5B).

Strap integrates transcription with cellular stress

Strap participates in the cellular response to DNA damage (Demonacos *et al*, 2001, 2004). Under DNA damage, Strap drives the assembly of a coactivator complex containing p300 and several other cofactors (Demonacos *et al*, 2001). In fact, Strap acts to assemble a functionally competent transcription-regulating coactivator complex (Demonacos *et al*, 2001). DNA damage signalling kinases—most notably ATM—regulate Strap activity and, in turn, influence the assembly of the coactivator complex (Demonacos *et al*, 2004).

The studies described here indicate that Strap takes on a similar role during the heat-shock response, by interacting with HSF1 and recruiting p300. Strap therefore has a conserved role in regulating coactivator function during the cellular response to various forms of stress. The different roles assigned to Strap might reflect distinct stress-responsive signalling pathways, and it will be interesting to clarify the nature of the signals that influence Strap during the heat-shock response.

METHODS

Plasmids and expression vectors. pcDNA3, Flag-p300, HA-Strap, pET28 Strap(wt) and the Strap deletion mutant TPR1–3 (1–205) were cloned into either HA-tagged pcDNA3 or pET28 vectors. A firefly luciferase reporter vector containing the *hsp70B* promoter (372 bp containing two HSEs) region was as described previously (Wang *et al*, 2000).

Cell culture and transfection. U2OS cells were maintained in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum at 37 °C with 5% CO_2. Transfections were carried out by using Gene Juice (Novagen, Wisconsin, WI, USA) as described in the protocol. Inducible Strap stable cell lines, which were generated previously by using the TET-ON gene expression system (Demonacos *et al*, 2004), were grown and induced by the addition of doxycyclin (1 μg/ml) for 36 h. Except for Figs 2B,5A, heat-shock treatment was performed at 43 °C for 1 h (Zou *et al*, 1998). In Fig 2B, cells were heat shocked at 43 °C for the indicated periods of time, followed by 4–6 h recovery at 37 °C (Beere *et al*, 2000). In Fig 5A, lethal heat-shock treatment was performed at 45 °C for 90 min, followed by a

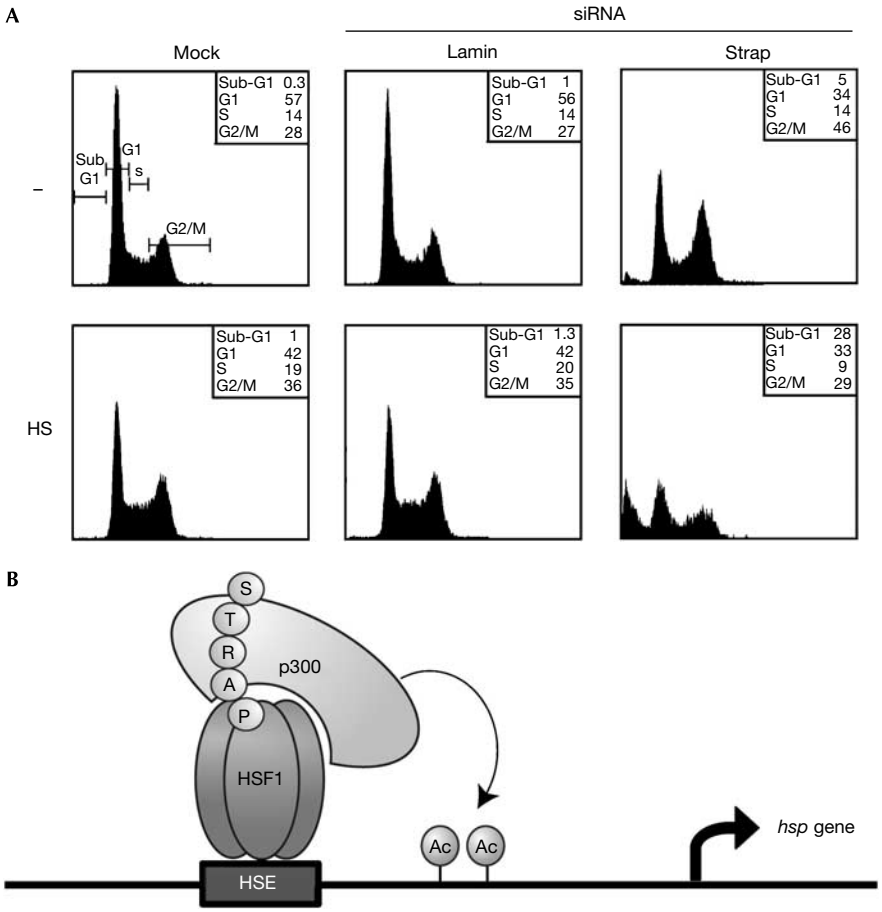


Fig 5 | Strap is required for survival under heat shock. (**A**) U2OS cells were treated with control siRNA lamin, siRNA Strap or mock treated for 72 h and then subjected to lethal heat shock (45 °C, 90 min) and recovered at 37 °C for 16 h before being collected. Flow cytometry was performed as described. The 'gates' for sub-G1-, G1-, S- and G2/M-phase cells are shown in the mock no heat-shock treatment. (**B**) Model for role of Strap in the heat-shock response. Strap is induced after heat shock and recruited to HSEs through interacting with the HSF1/p300 complex. Transcriptional activation is facilitated through increased acetylation of chromatin by an effect of Strap on p300 histone acetyltransferase. HSE, heat-shock element; HSF1, heat-shock factor 1; *hsp*, heat-shock protein gene; siRNA, short interfering RNA; Strap, Stress-responsive activator of p300.

recovery period of 16 h at 37 °C (Shamovsky *et al*, 2006; Westerheide *et al*, 2006).

Supplementary information is available at *EMBO reports* online (http://www.emboreports.org).

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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