Heat shock protein 90 is involved in IL-17-mediated skin inflammation following thermal stimulation

BO-KYUNG KIM[1], MINHWA PARK[1], JI-YON KIM[1], KYUNG-HO LEE[2] and SO-YOUN WOO[1]

[1]Department of Microbiology, School of Medicine, Ewha Womans University, Seoul 158-710; [2]Department of Dermatology, College of Medicine, The Catholic University of Korea, Bucheon, Gyeonggi 420-727, Republic of Korea

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Abstract. The pathogenesis of inflammatory skin diseases involves interactions between immune cells and keratinocytes, including the T helper 17 (Th17)-mediated immune response. Several chemokines [chemokine (C-X-C motif) ligand (CXCL)1, CXCL5 and CXCL8] and antimicrobial peptides [β-defensin 1 (BD1), LL-37, S100A8 and S100A9] were transcriptionally upregulated in the keratinocyte cell line HaCaT upon stimulation with interleukin (IL)-17. Balneotherapy, the treatment of disease by bathing, is an alternative therapy that has frequently been used for the treatment of inflammatory skin diseases. Immersion in pools of thermal mineral water is often considered to have chemical, thermal, mechanical and immunomodulatory benefits. We examined the effect of thermal treatment on IL-17-mediated inflammation in a model of skin disease. As Act1 is required for IL-17 signaling and is a client protein of heat shock protein 90 (HSP90), we evaluated the effect of HSP90 inhibition on IL-17-mediated cytokine and antimicrobial peptide expression in keratinocytes following heat treatment. We found that after thermal stimulation, Act1 binding to HSP90α was significantly increased in the presence of IL-17 (100 ng/ml) and 17-N-allylamino-17-demethoxygeldanamycin (17-AAG, 1 μM). Antimicrobial peptide and chemokine expression generally increased after heat treatment; Act1 knockdown and 17-AAG reversed this effect. These observations demonstrate the possible immunomodulatory effect of heat on keratinocytes during the progression of IL-17-mediated inflammatory skin diseases.

Correspondence to: Professor So-Youn Woo, Department of Microbiology, School of Medicine, Ewha Womans University, 911-1 Mok-Dong, Yang-Chun-Gu, Seoul 158-710, Republic of Korea
E-mail: soyounwoo@ewha.ac.kr

Abbreviations: 17-AAG, 17-N-allylamino-17-demethoxygeldanamycin; HSP90, heat shock protein 90; BD1, β-defensin 1

Key words: heat shock protein 90, thermal effect, inflammatory skin disease, keratinocyte, interleukin-17

Introduction

The pathogenesis of inflammatory skin diseases involves interactions between immune cells and keratinocytes. Keratinocytes perform important functions in the regulation of inflammation and respond to environmental and pro-inflammatory stimuli, including the cytokines interleukin (IL)-17 and IL-22 which are produced by T helper 17 (Th17) cells. IL-17 binds to a heterodimeric receptor complex consisting of IL-17RA and IL-17RC. The adaptor protein Act1 binds to IL-17RA and mediates IL-17-induced signaling pathways. Following stimulation with IL-17, Act1 is recruited to the IL-17 receptor, followed by the activation of the kinase transforming growth factor β-activated kinase 1 (TAK1) and the IκB kinase (IKK) complex, which subsequently activates nuclear factor-κB (NF-κB). Previously, we have observed that IL-17 enhanced skin inflammation by stimulating the secretion of IL-1β by keratinocytes through the NLR family, pyrin domain containing 3 (NLRP3)-caspase-1 pathway (1). It has been reported that Act1 is a client protein of heat shock protein 90 (HSP90), and that HSP90 activity is required for IL-17 signaling (2).

HSP90 functions as a chaperone that facilitates the folding and assembly of its client proteins. Loss of HSP90 chaperone function results in the degradation of its client proteins. HSP90 is constitutively expressed in human keratinocytes and fibroblasts *in vitro* (3) and is focally expressed in epidermal layers *in vivo*. The epidermal expression of HSP90 is upregulated by external stimuli, such as heat (4), chemical stress and tape stripping (5). In addition, increased HSP90 expression in keratinocytes and mast cells from the skin of patients with psoriasis has been reported (6).

Balneotherapy involves immersing the patient in mineral water baths or pools. Inflammatory skin diseases, including psoriasis and atopic dermatitis, are commonly and successfully treated using balneotherapy (7,8). Although the mechanisms through which spa therapy exerts beneficial effects on inflammatory skin diseases have not been fully elucidated, they are likely to involve chemical, thermal, mechanical and immunomodulatory processes (9).

Based on the involvement of HSP90 in IL-17-mediated inflammatory skin diseases, we hypothesized that following stimulation with IL-17, thermal stimulation may affect keratinocyte function through HSP90. Thus, we stimulated the human keratinocyte cell line HaCaT with IL-17 in the presence

or absence of the HSP90 inhibitor, 17-N-allylamino-17-demethoxygeldanamycin (17-AAG). Following thermal stimulation, we compared the expression of antimicrobial peptides and chemokines.

Materials and methods

Cell culture. The human immortal keratinocyte cell line, HaCaT (kindly provided by Dr Tae-Yoon Kim, College of Medicine, The Catholic University of Korea, Bucheon, Korea), was cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and 100 U/ml penicillin/streptomycin (all from Welgene Inc., Dalseogu, Korea). The cells were maintained at 37˚C in a 5% CO_2 incubator. The cells were grown until they were approximately 70-80% confluent and treated for 24 h with 100 ng/ml IL-17 (R&D Systems, Inc., Minneapolis, MN, USA), followed by the addition of 1 μM 17-AAG (Sigma, St. Louis, MO, USA) for 1 h. For thermal stimulation, the cells were incubated at 42˚C for an additional hour after the addition of 17-AAG.

Immunoprecipitation assays. The cells were lysed in lysis buffer [0.5% Triton X-100, 20 mM HEPES (pH 7.4), 150 mM NaCl, 12.5 mM β-glycerophosphate, 1.5 mM $MgCl_2$, 10 mM NaF, 2 mM dithiothreitol, 1 mM sodium orthovanadate (Na_3VO_4)] supplemented with 10 μg protease inhibitor cocktail (P8340; Sigma) and 2 mM Na_3VO_4. The cleared cell lysates were incubated with antibodies (2 μg) and protein G sepharose beads (10 μl of a 50% slurry in lysis buffer). Following incubation on a rotating shaker at 4˚C for 2 h, the protein G sepharose beads were washed twice with lysis buffer. Finally, reducing sample buffer was added prior to performing sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and western blot analysis (also known as immunoblot analysis).

Western blot analysis. The cells were lysed in lysis buffer [1% Triton X-100, 150 mM NaCl, 20 mM Tris (pH 7.5)] supplemented with protease inhibitors, and the proteins (10 μg) were separated via SDS-PAGE on 10% gels. Resolved proteins were transferred to polyvinylidene fluoride (PVDF) membranes (Millipore Corp., Bedford, MA, USA). The membranes were blocked with 5% skim milk in Tris-buffered saline and incubated with the following primary antibodies: anti-HSP90-α (D7a, mouse monoclonal IgG1; Abcam, Cambridge, UK), anti-Act1 (C-16, goat monoclonal IgG; Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA), and anti-β-actin (AC-40, mouse monoclonal; Sigma). After washing, the membranes were incubated with horseradish peroxidase-conjugated anti-mouse, anti-rabbit, or anti-goat IgG secondary antibodies, and the signals were visualized using an enhanced chemiluminescence (ECL) kit (Thermo Fisher Scientific, Waltham, MA, USA) according to the manufacturer's instructions.

Reverse transcription-quantitative polymerase chain reaction (RT-PCR). Total RNA was extracted from the cells using TRIzol (Invitrogen, Carlsbad, CA, USA) in accordance with the manufacturer's instructions. A total of 1 μg RNA was transcribed to cDNA using a reverse transcription system (Promega, Madison, WI, USA). qPCR with SYBR green detection was conducted using a Maxime PCR PreMix kit (Toyobo, Osaka, Japan) and an ABI PRISM 7000 sequence detection system (Applied Biosystems Life Technologies, Foster City, CA, USA). cDNA (50 ng) was amplified using the following primers: 5'-TGA GAT GGC CTC AGG TGG TA-3' and 5'-CGG GCA GGC AGA ATA GAG AC-3' for human β-defensin 1 (BD1; 106 bp); 5'-GGG GCT CCT TTG ACA TCA GT-3' and 5'-TGG GTA CAA GAT TCC GCA AA-3' for human LL-37 (153 bp); 5'-GCC GTC TAC AGG GAT GAC CT-3' and 5'-TTT GTG GCT TTC ATG GC-3' for human S100A8 (204 bp); 5'-CAA AGA GCT GGT GCG AAA AG-3' and 5'-CGA AGC TCA GCT TGT CT-3' for human S100A9 (125 bp); 5'-GCT GCT CCT GCT CCT GGT A-3' and 5'-CTT TCC GCC CAT TCT TGA GT-3' for human chemokine (C-X-C motif) ligand (CXCL)1 (200 bp); 5'-TGC G-TTG CGT TTG TTT ACA G-3' and 5'-GAA AAG GGG CTT CTG GAT CA-3' for human CXCL5 (162 bp); and 5'-GCA GCT CTG TGT GAA GGT GC-3' and 5'-TCT GCA CCC AGT TTT CCT T-G-3' for human CXCL8 (220 bp).

Small interfering RNA (siRNA) silencing of Act1 expression. The HaCaT cells were transfected with siRNA oligonucleotides (80 pmol; sc-29634; Santa Cruz Biotechnology, Inc.) to reduce endogenous Act1 expression. The cells were transfected with either an siRNA oligonucleotide against Act1 or a non-targeted control siRNA oligonucleotide, and maintained at 37˚C under standard tissue culture conditions. Twenty hours after transfection, the cells were treated with IL-17 or IL-22 (100 ng/ml) and maintained for 24 h. Thereafter, the cell lysates and the supernates were harvested for RT-qPCR and western blot analysis. For the detection of Act1 (85 bp) by RT-qPCR in siRNA gene knockdown experiments, we used the following specific primers: 5'-CAC AGA GAG ACT GCT CCT TTC C-3' (forward) and 5'-CCA GGA GCA CCA GCT CTA TTA-3' (reverse). As a control for input, glyceraldehyde 3-phosphate dehydrogenase (GAPDH; 395 bp) was amplified using the following primers: 5'-GTC TTC TCC ACC ATG GAG AAG GCT-3' (forward) and 5'-CAT GCC AGT GAG CTT CCC GTT CA-3' (reverse).

Statistical analysis. Values are expressed as the means ± standard error of the mean (SEM). Non-parametric Mann-Whitney tests or two-way analysis of variance (ANOVA) were conducted to determine significance using GraphPad Prism software (GraphPad Software Inc., San Diego, CA, USA). A P-value <0.05 was considered to indicate a statistically significant difference.

Results

Act1 binding to HSP90α is increased in HaCaT cells after thermal stimulation. Firstly, we examined whether the heat treatment of IL-17-stimulated HaCaT cells affects the outcome of IL-17 receptor-mediated signaling. To analyze signaling in IL-17-stimulated HaCaT cells after heat treatment, we first compared the amount of Act1 binding to HSP90 in the presence or absence of heat. We immunoprecipitated HaCaT cell lysates with the anti-Act1 antibody following IL-17 stimulation, with or without heat stimulation (Fig. 1A). HSP90α expression was decreased after heat treatment when the HSP90α inhibitor, 17-AAG, was added with IL-17 (Fig. 1B). We also found that Act1-bound HSP90α levels were increased after thermal stimulation;

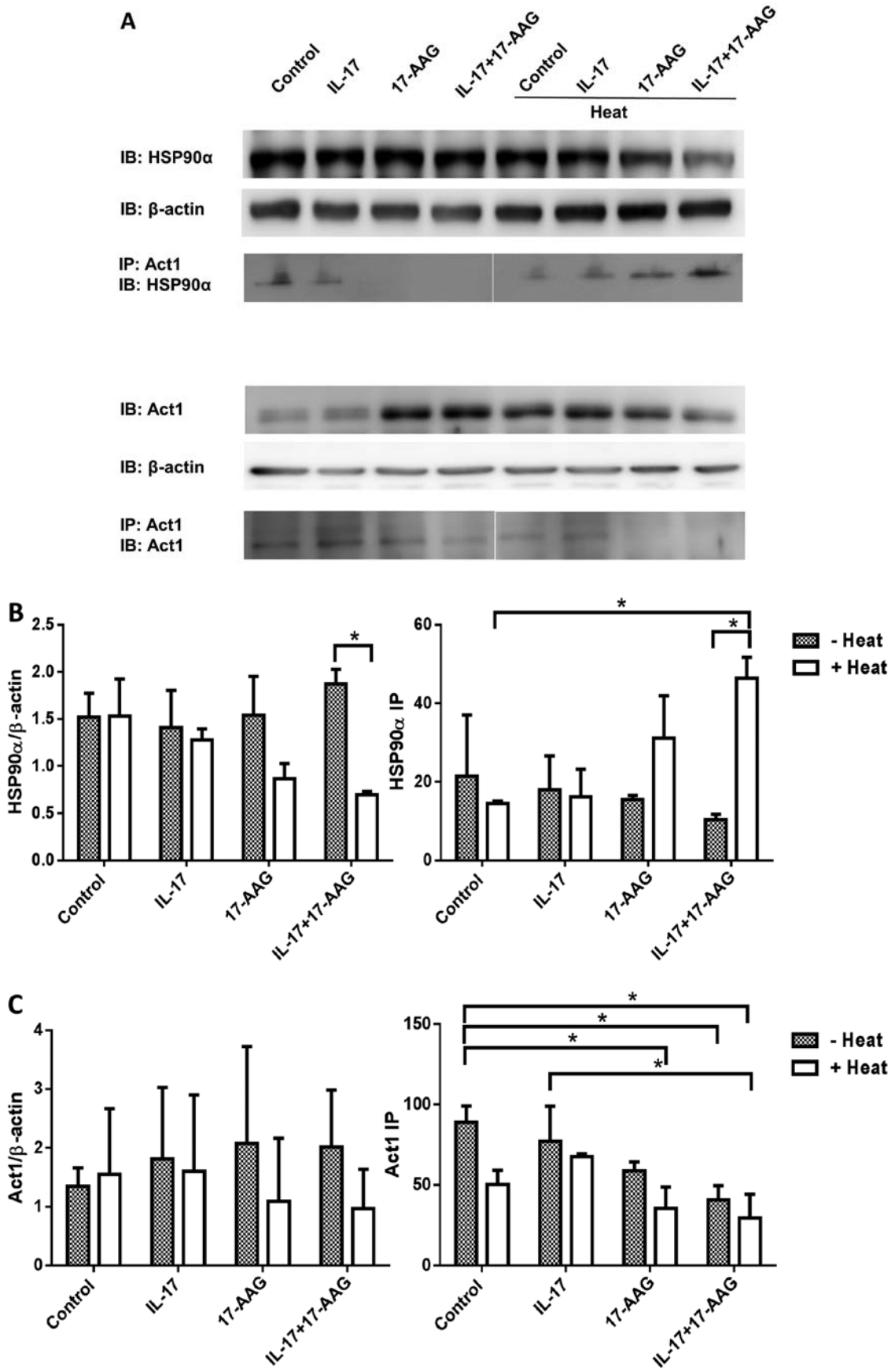

Figure 1. Heat stimulation increases Act1 binding to heat shock protein 90 (HSP90α) in HaCaT cells. The cells were incubated with interleukin (IL)-17 overnight, in the presence or absence of 17-N-allylamino-17-demethoxygeldanamycin (17-AAG) for 1 h, followed by cell lysis. The cleared cell lysates were incubated with antibodies (2 μg) and protein G sepharose beads (10 μl of 50% slurry in lysis buffer). (A) Representative blots from three independent experiments are shown. (B) Act1 binding to HSP90α are pixel densities of immunoprecipitated (IP) HSP90α. The band pixel densities were divided by the pixel densities of the corresponding β-actin band for each of three independent datasets. (C) Act1 expression and IP Act1 levels are depicted as pixel densities. Data are expressed as the means ± SEM of triplicate samples (*P<0.05). IB, immunoblot analysis (also known as western blot analysis).

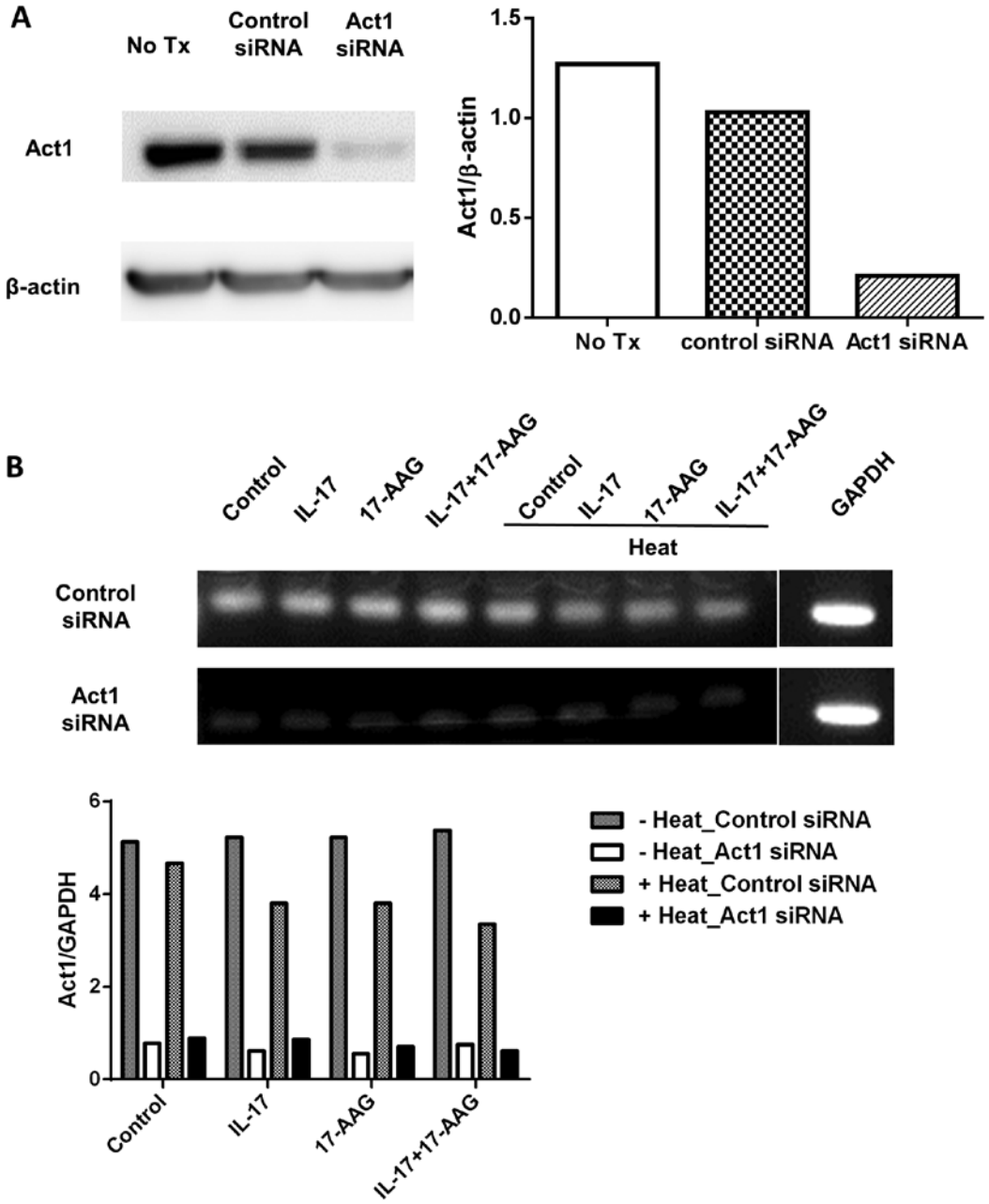

Figure 2. Effect of Act1 knockdown by siRNA transfection on HaCaT cells following heat treatment. (A) To knockdown Act1 expression, HaCaT cells were grown until 70-80% confluent and then transfected with control or Act1 siRNAs. Act1 knockdown was confirmed by western blot analysis with the anti-Act1 antibody. (B) Act1 knockdown in each of the treatment groups was confirmed by RT-qPCR. Control or Act1 siRNA-transfected HaCaT cells were treated with 100 ng/ml interleukin (IL)-17 for 24 h, followed by incubation with 1 μM 17-N-allylamino-17-demethoxygeldanamycin (17-AAG) for 1 h. For heat stimulation, cells were incubated at 42˚C for an additional hour after the addition of 17-AAG. Pixel densities are shown for the representative blot or gel.

however, there were no differences between the control and the IL-17-treated groups (Fig. 1B). Although the expression of Act1 did not significantly differ, the immunoprecipitated amount of Act1 following IL-17 stimulation and 17-AAG treatment decreased (Fig. 1C). Thus, under 37˚C culture conditions, IL-17 or the HSP90α inhibitor 17-AAG did not affect Act1 or HSP90α expression in HaCaT cells; however, following heat treatment, Act1-bound HSP90α significantly increased in the presence of IL-17 and 17-AAG.

Effect of Act1 knockdown on HSP90 expression in HaCaT cells following heat treatment. In order to compare the levels of HSP90 following the knockdown of Act1 in the HaCaT cells, we transfected HaCaT cells with Act1 siRNA, heated the cells, and confirmed the decreased expression of Act1 using western blot analysis and RT-qPCR (Fig. 2). We then transfected HaCaT cells with Act1 siRNA which was followed by heat treatment and the addition of 17-AAG. We compared the levels of HSP90 and Act1 in these cells. We found that after thermal stimulation, HSP90α expression was decreased in the control siRNA-transfected HaCaT cells in the presence of IL-17 and 17-AAG, which is nearly identical to the result shown in Fig. 1B. However, in the Act1 knockdown HaCaT cells following heat treatment, HSP90 expression did not

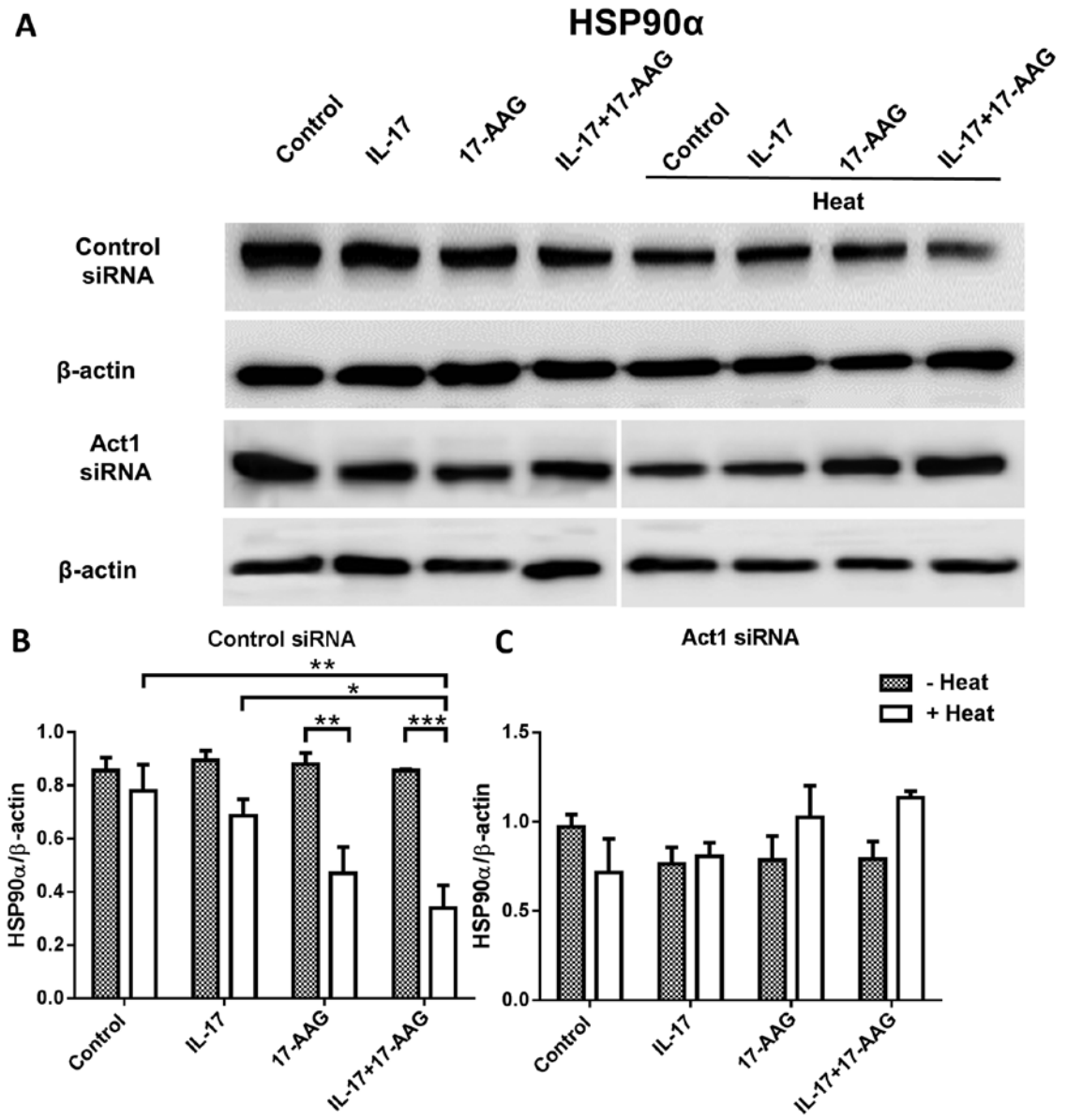

Figure 3. Heat treatment and Act1 knockdown affect heat shock protein 90 (HSP90) expression in HaCaT cells. (A) Control siRNA- or Act1 siRNA-transfected HaCaT cells were treated with interleukin (IL)-17, heat, or 17-N-allylamino-17-demethoxygeldanamycin (17-AAG) and lysed for western blot analysis of HSP90α expression. (B and C) Band pixel densities were divided by the pixel densities of the corresponding β-actin band for each of three independent datasets. Data are expressed as the means ± SEM of triplicate samples (*P<0.05 and **P<0.001).

significantly differ among the groups (Fig. 3A-C). Finally, we compared Act1 expression in the HaCaT cells following heat treatment, in the presence or absence of the HSP90 inhibitor, following Act1 siRNA transfection. Following thermal stimulation, we observed increased Act1 levels in the control cells and those treated with IL-17 (Fig. 3D-F).

Effect of 17-AAG on antimicrobial peptide and cytokine expression in HaCaT cells following Act1 knockdown and thermal stimulation. To examine the effect of IL-17 receptor-mediated expression of antimicrobial peptides or inflammatory chemokines in HaCaT cells, Act1 siRNA-transfected HaCaT cells were stimulated with heat and 17-AAG was added. RNA was extracted to compare the levels of BD1, LL-37, S100A8, S100A9, CXCL1, CXCL5 and CXCL8 (Fig. 4). At 37˚C, Act1 knockdown with IL-17 stimulation tended to decrease LL-37, S100A8, S100A9, CXCL1 and CXCL5 expression; however, the expression of these antimicrobial peptides and chemokine increased after incubation at 42˚C. This thermal-mediated effect was suppressed upon treatment with 17-AAG.

We also examined IL-1β expression after Act1 knockdown in thermal-stimulated HaCaT cells treated with IL-17 and 17-AAG. We found that IL-1β expression decreased, and 17-AAG synergistically affected the control siRNA cells after heat stimulation. Act1 siRNA-treated cells showed a significant decrease in IL-1β expression after heat treatment (Fig. 5).

Discussion

In the present study, we evaluated the effect of heat on keratinocytes following IL-17 stimulation. We found that under heat-treated conditions, Act1-bound HSP90α signifi-

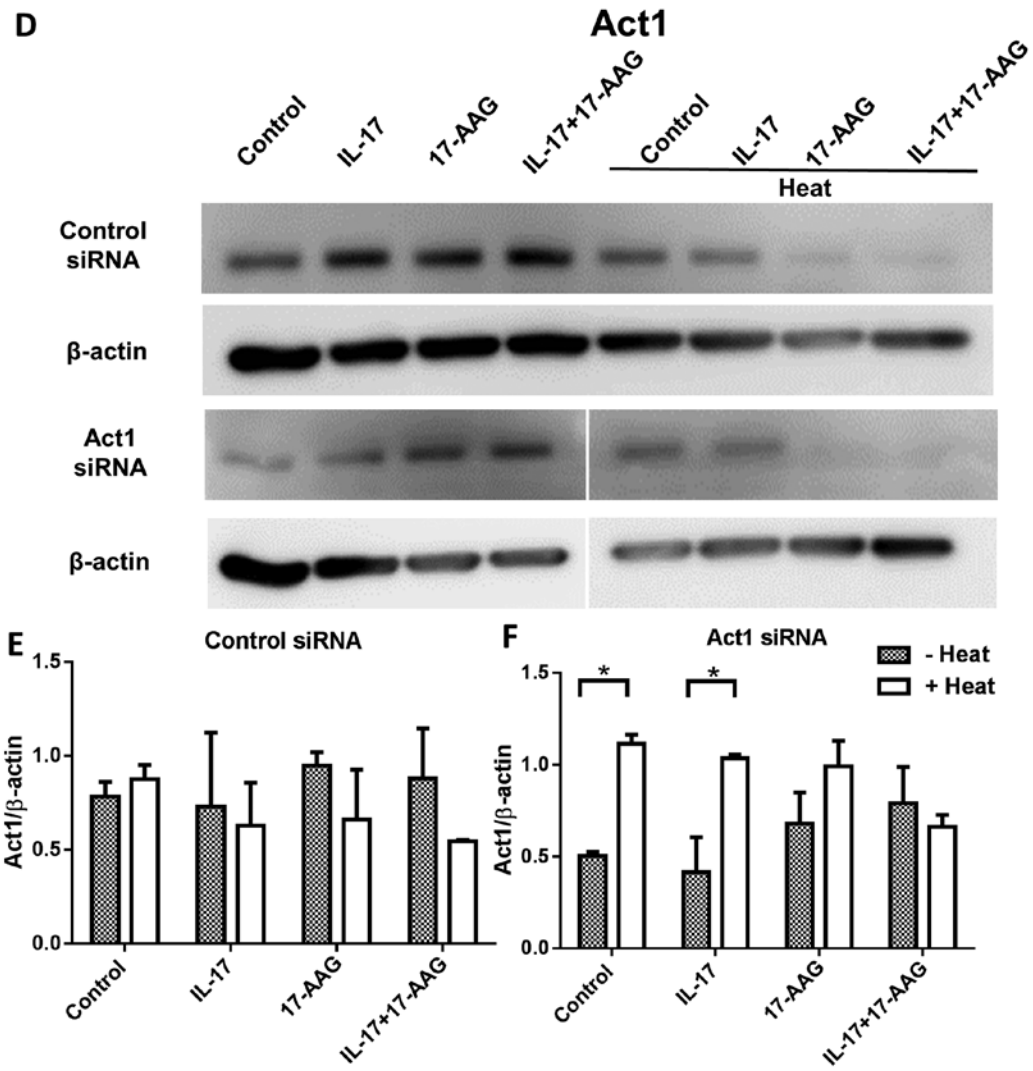

Figure 3. Continued. (D) Control siRNA- or Act1 siRNA-transfected HaCaT cells were treated with IL-17, heat, or 17-AAG, and lysed for western blot analysis of Act1 expression. (E and F) Act1 band pixel densities were divided by the pixel densities of the corresponding β-actin band for each of three independent datasets. Data are expressed as the means ± SEM of triplicate samples.

cantly increased in the presence of IL-17 (100 ng/ml) and 17-AAG (1 μM). Antimicrobial peptide and chemokine expression generally increased after heat treatment; however, Act1 knockdown and 17-AAG treatment inhibited the production of antimicrobial peptides and chemokines.

A previous study of hyperthermia (41±0.5˚C for 1 h), applied to normal human skin has indicated that the HSPs 27, 60, 72i and 90 were upregulated, with maximal increases noted 24 h following hyperthermia (4). However, increased HSP expression poorly correlated with thermotolerance, and did not improve cell survival after heat shock. In addition, it has been shown that the upregulation of HSP90, HSP70, IL-33, TNF-α and CXCL8 (also known as IL-8) mRNA after tape stripping induced the production of alarmins from keratinocytes (5). Although the possible roles of several HSPs under various stresses in skin diseases remain unclear, their importance in cutaneous aging, skin cancer and wound healing is increasingly recognized (10).

Psoriasis is a chronic inflammatory skin disease characterized by keratinocyte hyperplasia, dermal leukocyte infiltration and vascular enhancement. The cytokine milieu, through activation of Th1 and Th17 cells, contributes to the establishment of skin inflammation. Keratinocytes exposed to IL-17 or IL-22 are further activated, which has been demonstrated to result in the abnormal expression of antimicrobial peptides and defensins (11). It has been previously reported that Act1 is a client protein of the molecular chaperone HSP90, and that HSP90 activity is required for IL-17 signaling (2). In addition, it has been demonstrated that there is increased expression of HSP90 in keratinocytes isolated from patients with psoriasis. The HSP90 levels were decreased following therapy with ustekinumab (blocking antibody to p40 of the IL-12 and IL-23 receptor) (6). The HSP90 inhibitor, 17-AAG, has been found to repress the differentiation of HaCaT keratinocytes (12). It has been suggested that HSP90 inhibitors may offer a novel therapeutic approach for treating inflammatory skin diseases.

HSP90 is a molecular chaperone that is critical for the function and stability of proteins necessary for cell survival. Many molecules involved in signal transduction pathways are client proteins of HSP90, including tyrosine-kinase receptors, adapter proteins, transcription factors, cell cycle proteins and anti-apoptotic proteins (13). HSP90 inhibitors have been

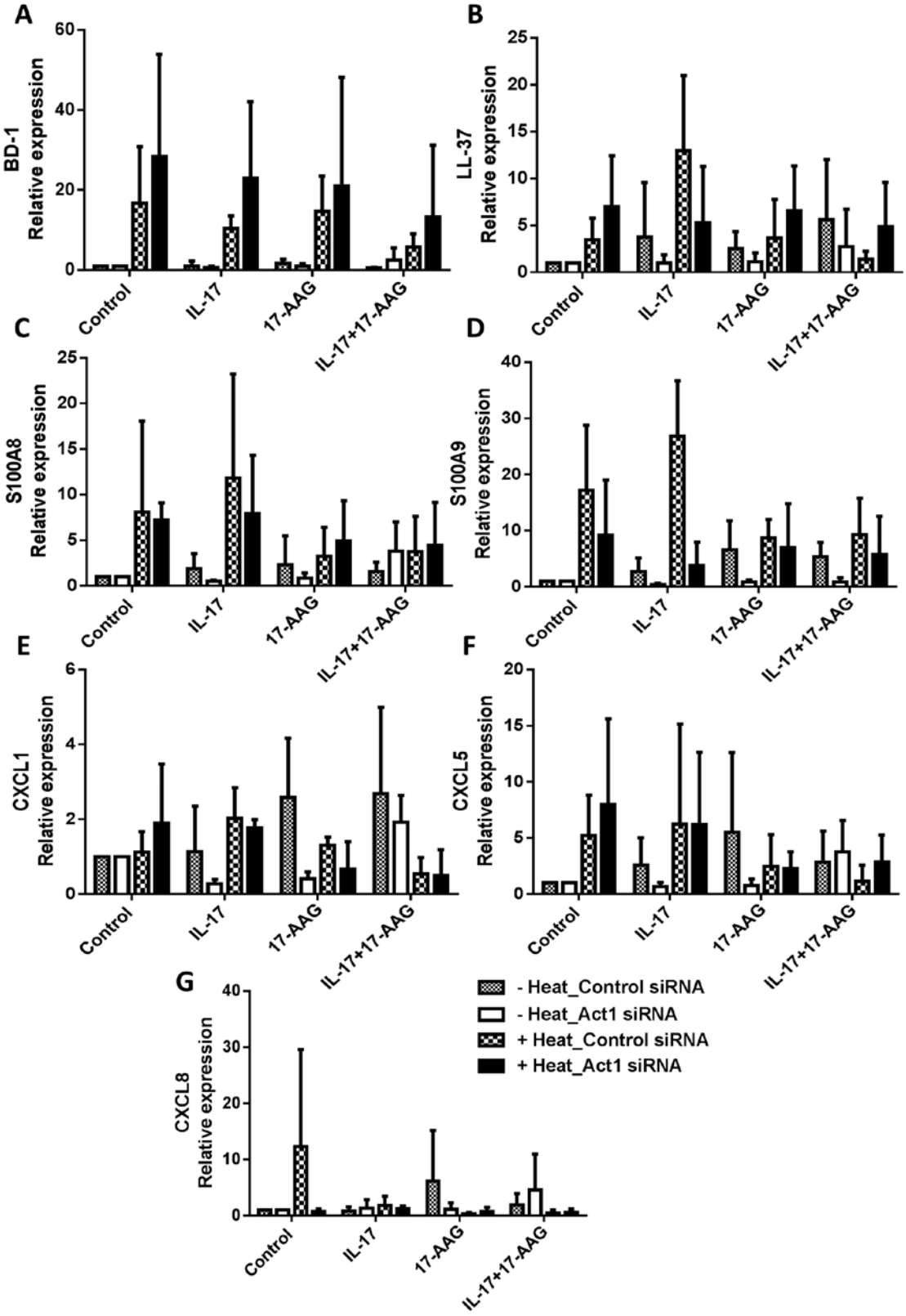

Figure 4. Antimicrobial peptide and chemokine expression in the HaCaT cells following treatment with interleukin (IL)-17 and 17-N-allylamino-17-demethoxygeldanamycin (17-AAG), with or without thermal stimulation. Control siRNA- or Act1 siRNA-transfected HaCaT cells were treated with IL-17, 17-AAG, and heat, and RNA was extracted for RT-qPCR. The results of (A) β-defensin 1 (BD1), (B) cathelicidin LL-37, (C) S100A8, (D) S100A9, (E) chemokine (C-X-C motif) ligand (CXCL)1, (F) CXCL5 and (G) CXCL8 are shown. Data are expressed as the means ± SEM of the three independent experiments and compared with the results from the 'no heat' and 'heat treatment' groups ($^{*}P<0.05$, and $^{**}P<0.001$).

used to target the function of HSP90 in cell proliferation and survival signaling pathways (14-16). Currently, HSP90 inhibitors include derivatives of geldanamycin and resorcinol as well as purine analogues and other synthetic inhibitors. The first class of HSP90 inhibitors, the benzoquinone ansamycin antibiotics, includes 17-AAG. The HSP90 inhibitor binds to

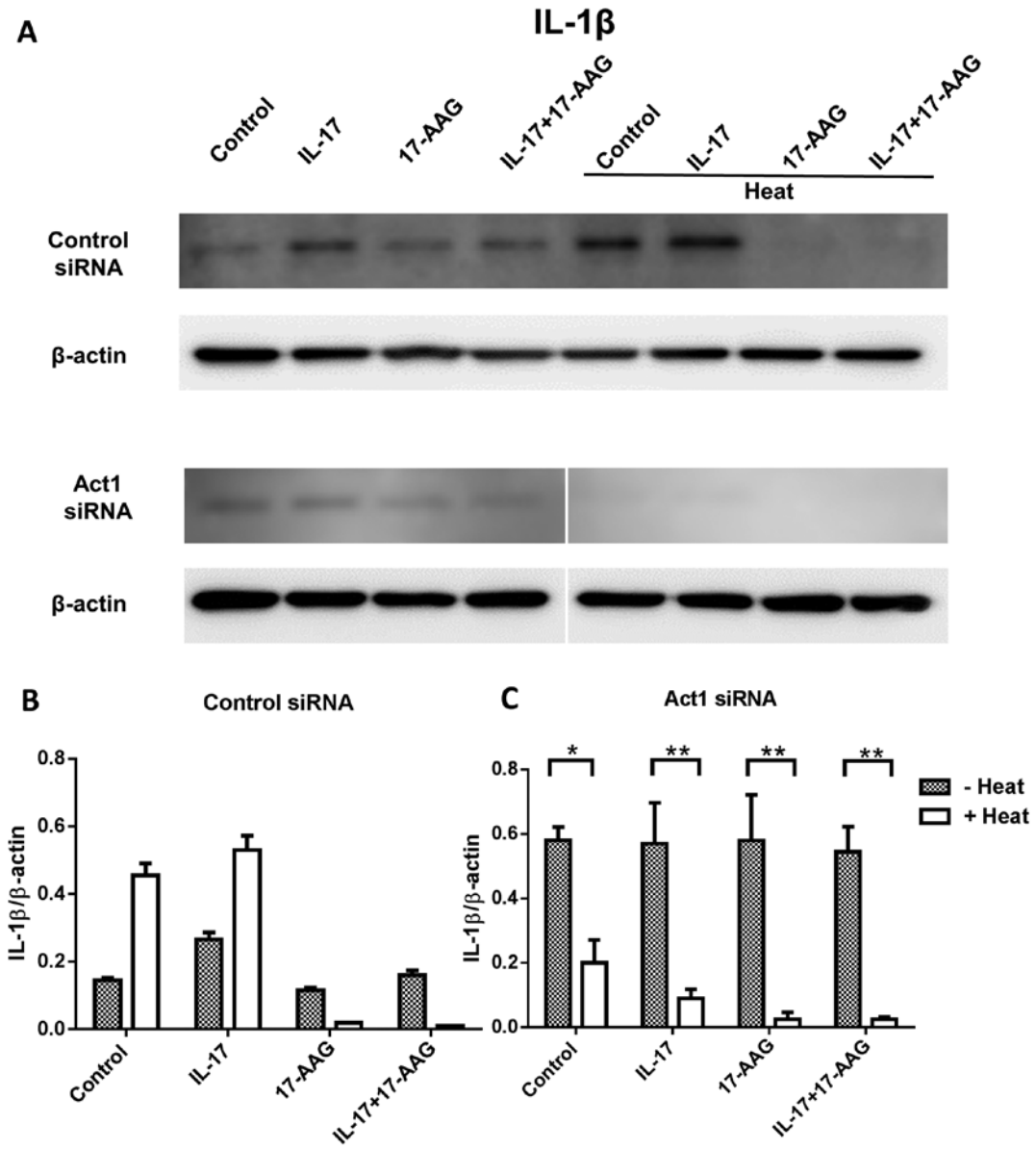

Figure 5. Heat treatment and Act1 knockdown affect interleukin (IL)-1β expression in HaCaT cells. (A) Control siRNA- or Act1 siRNA-transfected HaCaT cells were treated with IL-17, 17-N-allylamino-17-demethoxygeldanamycin (17-AAG), and heat. The cells were lysed and the lysates were evaluated for IL-1β expression using western blot analysis. (B and C) Band pixel densities were divided by the pixel densities of the corresponding β-actin band for each of the three independent datasets. Data are expressed as the means ± SEM of triplicate samples ($^{*}P<0.05$ and $^{**}P<0.001$).

HSP90 and leads to proteasomal degradation of the HSP90 client protein, thereby disrupting the signaling pathway. Thus, HSP90 inhibitors are promising novel treatments targeting cancer (13) and immune diseases. Clinically, they have been used to target the leukemic blast phase of cells to induce apoptosis and differentiation (17). Elevated HSP90 expression has been reported in systemic lupus erythematosus (SLE) patients, and HSP90 inhibition has been shown to lessen disease in the MRL/lpr mouse model of SLE (18). HSP90 inhibitors have been demonstrated to be effective in murine models of sepsis (19), arthritis (20), uveitis (21), multiple sclerosis (22), and inflammatory bowel disease (23).

A previous study has found that cathelicidin LL-37 posseses antimicrobial and immunomodulatory activity, and the expression of this type of antimicrobial peptide may ameliorate skin inflammation (24). S100A8 and S100A9 are known mediators of human keratinocyte growth stimulation, and these peptides have been implicated in the onset and progression of hyperproliferative skin diseases, such as psoriasis (25,26). Although the precise role of antimicrobial peptides in inflammatory skin diseases is not fully known and often controversial, we found that antimicrobial peptides (BD1, LL-37, S100A8 and S100A9), chemokines (CXCL1, CXCL5 and CXCL8), and IL-1β were elevated upon IL-17 addition or thermal stimulation, and inhibited by 17-AAG treatment or Act1 knockdown (Figs. 4 and 5).

In conclusion, our data suggests that HSP90 is involved in IL-17-mediated keratinocyte activation through Act1 following thermal stimulation. Although HSP90 enhanced the expression of antimicrobial peptides or chemokines in keratinocytes after heat treatment, HSP90 inhibitors reversed these effects. Thus, the administration of HSP90 inhibitors following heat

stimulation (thermal baths) may be a beneficial therapeutic approach for IL-17-mediated inflammatory skin diseases.

Acknowledgements

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