INTRODUCTION

Genomic DNA is highly folded and compacted by histones in the nucleus, in which 147 base pairs of DNA are wrapped around a histone octamer with two each of histone H2A, H2B, H3 and H4: a tripartite structure with an H3-H4 tetramer and two H2A-H2B dimers (Luger et al., 1997). An interesting feature of histones is that histone tails protrude from the nucleosome and are subject to a wide array of post-translational modifications (PTMs), such as phosphorylation, ubiquitination, methylation, acetylation, SUMOylation, ADP-ribosylation, deimination and proline isomerization (Strahl and Allis, 2000). Because a large number of cellular functions can be mediated by histone PTMs, significant efforts have been devoted to identify the enzymes that can add or remove the individual histone PTMs (Allis et al., 2007). At present, two hypothetic models, e.g. the direct model and the effector-mediated model, have been proposed to explain how individual histone PTMs lead to the suppression of gene expression. On the other hand, the more prevailing ‘effector-mediated’ model was proposed. This model views histones as active mediators of biological responses, in which cues from the intracellular signaling cascades affect ‘writer’ proteins to modulate histone PTMs that, in turn, serve as the binding platform for ‘reader and effector’ proteins to recruit or exclude the binding of transcription factors or other chromatin remodeling proteins, resulting in the initiation of appropriate biological responses.

Since the discovery of leukocytes in neoplastic tissues by Rudolf Virchow in 1863, the connection between chronic inflammation and cancer was first noted (Cardesa et al., 2011). It is now well accepted that chronic inflammation contributes to tumor promotion by creating pro-inflammatory and oxidative microenvironments. The activator protein-1 (AP-1) is a redox-sensitive transcription factor and serves as a critical component that bridges inflammation and cancer. The AP-1 is a cytosolic protein and exists as different dimeric combinations of basic leucine zipper proteins from the Jun (c-Jun, JunB and JunD) and Fos (c-Fos, FosB, Fra-1 and Fra-2) family (Wisdom, 1999). The activation of AP-1 can be mediated by sulfhydryl modification of critical cysteine residues found on...
this protein and/or other upstream redox-sensitive molecular targets in response to pro-inflammatory cytokines or oxidative stimuli (Angel and Karin, 1991). In addition, the cellular expression of AP-1 components is subject to the activity of various intracellular signaling kinase cascades as well (Karin, 1995). Therefore, the targeted inhibition of AP-1 via modulating the intracellular kinase activities has been achieved as a prime molecular basis for chemoprevention by naturally-occurring phytochemicals (Surh et al., 2005). When activated, cytosolic AP-1 translocates into the nucleus, recognizes either 12-O-tetradecanoylphorbol-13-acetate (TPA) response elements (TRE, 5′-TGAG/CTCA-3′) or cAMP response elements (CRE, 5′-TGACGCTCA-3′) existing in the genome and induces a variety of pro-inflammatory gene expression (Chinenov and Kerppola, 2001). Therefore, investigating the molecular mechanisms that govern transcriptional regulation of AP-1 has attracted significant interests in the scientific community during the last decade. However, another unequivocally important issue still remains unresolved regarding to the AP-1 regulation: does there exist any histone PTMs that are responsible for transcriptional regulation of AP-1? Our study was initiated to address this issue.

**MATERIALS AND METHODS**

**Cell culture, chemicals, plasmids, and antibodies**

Dulbecco’s modified Eagle’s medium (DMEM) and fetal bovine serum (FBS) were purchased from Welgene Corporation (Daegu, Republic of Korea). HaCaT cells were grown in DMEM, supplemented with 10% heat-inactivated FBS, penicillin (100 U/ml) and streptomycin (100 U/ml). HaCaT cells were incubated at 37°C in a humidified atmosphere of 95% air and 5% CO₂. 12-O-tetradecanoylphorbol-13-acetate (TPA) and FLAG-agarose bead were purchased from Sigma (St. Louis, MO, USA). Polybrene, recombinant Akt1 and a polyclonal antibody that detects H3K9me3/p-H3S10 were purchased from Millipore (Billerica, MA, USA). Lentiviral helper plasmids (pMD.2G and pSAX.2) were acquired from Addgene (Cambridge, MA, USA), pGL3-AP-1-luciferase vector was generated by cloning 3x AP-1 consensus sequence DNA and Renilla luciferase reporter plasmid (pGL4.74) was acquired from Promega (Madison, WI, USA). Human H3.3, HP1γ and 14-3-3ε cDNAs were amplified from human cDNA library by PCR and subcloned into pcDNA3 plasmid. LY294002, rapamycin, rabbit polyclonal antibodies against c-Jun, c-Fos, HP1γ, Akt1, phospho-Akt1, S6K, phospho-S6K1, HA, DYKDDDDK (FLAG) tag were purchased from Cell Signaling Technology (Beverly, MA, USA). Total actin antibody was acquired from Developmental Studies Hydridoma Bank (Iowa City, IA, USA).

**Isolation of histones, Western blotting and immunoprecipitation**

The isolation of histones is as follows. Cultured cells were collected and washed twice with ice-cold 1x phosphate-buffered saline (PBS). After centrifugation at 12,000 rpm for 5 min, cells were resuspended with 200 μl 1% SDS histone lysis buffer (1% SDS in Tris-EDTA buffer, pH 8.0) and kept on ice for 30 min. After lysesates were collected in 1% SDS lysis buffer, they were heavily sonicated on ice to disrupt genomic DNA and used for Western blot. For general Western blot analysis, cultured cells were collected and washed twice with ice-cold 1x phosphate-buffered saline (PBS). After centrifugation at 12,000 rpm for 5 min, cells were resuspended with 200 μl RIPA buffer [50 mM Tris-HCl at pH 8.0, 150 mM NaCl, 1% NP-40, 0.5% deoxycholic acid, 0.1% sodium dodecyl sulfate (SDS), 1 mM NaVO₃, 1 mM diethiothreitol (DTT), 1 mM phenylmethylsulfonyl fluoride (PMSF)] and kept on ice for 30 min. After centrifugation at 12,000 rpm for 10 min, protein concentration was measured using a BCA Protein Assay Kit (Thermo Fisher Scientific, Waltham, MA, USA). Cell lysates were then resolved by SDS-PAGE and transferred to PVDF membranes (BioRad, Hercules, CA, USA). The membranes were incubated in blocking buffer (5% skim milk in 1x PBS-0.1% Tween-20, PBST) for 1 h and hybridized with the appropriate primary antibodies in 1x PBS containing 3% bovine serum albumin (BSA) or 3% skim milk overnight at 4°C. After washing three times with 1x PBST for 30 min, the membrane was hybridized with horseradish peroxidase (HRP)-conjugated secondary antibody (Santa Cruz Biotechnology, Santa Cruz, CA, USA) for 1 h at room temperature and washed three times with 1x PBST solution for 30 min. The membrane was visualized by using an enhanced chemiluminescence (ECL) detection system. Actin was used as the control for an equal loading of samples in Western blots. The interaction between FLAG-H3.3 and HA-14-3-3ε was examined by immunoprecipitation, followed by Western blot analysis. In brief, HaCaT cells transiently transfected with pcDNA3-FLAG-H3.3 and pcDNA3-HA-14-3-3ε. After 48 h, cells were lysed with 200 μl NP-40 buffer [50 mM Tris-HCl at pH 7.5, 150 mM NaCl, 0.5% NP-40, 50 mM NaF, protease inhibitors cocktail (Roche, Indianapolis, IN, USA)] for 30 min on ice and cell lysates were immunoprecipitated with FLAG-agarose beads overnight at 4°C. The immunoprecipitated beads were washed with 1x PBS three times, denatured in 1x sample buffer and used for Western blot against HA antibody.

**Generation of stable cells by lentiviral transduction**

Stable gene knockdown cell lines were established by lentiviral transduction. In brief, 293T packaging cells were co-transfected with 3 μg lentiviral HP1γ shRNA constructs together with an equal amount of lentiviral helper vectors (pMD.2G and pCMV-VSVG). Media for 293T cells was replaced after 24 h with MEM/0.5% FBS and incubated for another 24-48 h. The viral supernatant fraction was collected and filtered using a 0.45 μm syringe filter. HaCaT cells were infected with 10 μl of the viral supernatant fraction, supplemented with 5% FBS and 10 μg/mL polybrene for 12 h at 37°C, and further selected with 4 μg/ml puromycin (Calbiochem, La Jolla, CA, USA) for 2 days. Multiple sets of pLKO.1 vector-based shRNA constructs were acquired from Sigma (St. Louis, MO, USA) and the gene knockdown efficiency of individual viral constructs was evaluated by Western blotting.

**Preparation of recombinant GST-fused proteins and in vitro kinase assay**

GST-fused recombinant 14-3-3ε and HP1 isoform proteins were purified on glutathione-Sepharose beads (GE Healthcare, Piscataway, NJ, USA) and dialyzed. Recombinant Akt1 protein (Millipore, Billerica, MA, USA) was mixed with GST or GST-HP1 isoform proteins and the phosphorylation level of GST-fusion proteins was measured by Western blotting against Akt1 phospho-motif antibody (Cell Signaling Technology, Beverly, MA, USA).
**Dual luciferase assays**

HaCaT cells were seeded on 70% confluence in six-well plate and transfected with 3 μg pGL3-AP-1-firefly luciferase plasmid and 3 μg Renilla luciferase reporter plasmid. After 48h, cells were lysed with luciferase lysis buffer [0.1 M potassium phosphate buffer at pH 7.8, 1% Triton X-100, 1 mM DTT, 2 mM EDTA] and the dual luciferase activity was measured by GLOMAX Multi-system (Promega, Madison, WI, USA). The data is depicted as a ratio of the firefly luciferase activity, compared with Renilla luciferase activity. Statistical analysis was conducted by Student t-test with n=6.

**RESULTS**

**HP1γ suppresses TPA-mediated induction of c-Jun and c-Fos via histone H3 lysine tri-methylation**

It is known that histone modifications contribute to the changes in gene expression by altering chromatin structure (Jenuwein and Allis, 2001). Histone H3 proteins consist of three isoforms (H3.1, H3.2 and H3.3) and their protein sequence homology in the N-terminus is highly conserved between each other (Fig. 1A). A growing evidence indicates that histone H3 phosphorylation at Ser10 (p-H3S10) and Ser28 (p-H3S28) is important for stress-induced responses and closely related to the transcriptional activation of immediate-early (IE) genes, such as c-jun and c-fos (Nowak and Corces, 2004). However, the underlying molecular mechanisms by which histone H3 phosphorylation at Ser10 and Ser28 contributes to the IE gene activation are largely unclear. It is particularly interesting to note that Ser10 and Ser28 residues in histone H3 located next to tri-methylated histone H3 at Lys27. Together this result suggests a possibility that TPA-mediated induction of H3K9me3/p-H3S10 double mark by TPA is inducible and might be involved in the IE gene activation.

Histone H3K9 methylation is an epigenetic marker that signifies the heterochromatin region and histone H3K9 methylation-mediated suppression of gene expression is possible by the recruitment of heterochromatin protein 1 (HP1) (Shilatifard, 2006). HP1 contains three isoforms (HP1α, HP1β, HP1γ) and all of them recognize H3K9me3 mark, using a conserved inherent chromodomain domain (Kwon and Workman, 2011). While HP1α and HP1β are exclusively localized in heterochromatin, it is known that HP1γ has the ability to regulate both heterochromatin and euchromatin structure. Therefore, we have decided to examine if HP1γ has a suppressive role in the IE gene activation by TPA. To this end, we have silenced the

![Fig. 1](http://dx.doi.org/10.4062/biomolther.2014.057)

**SUPPORTING INFORMATION**

- **Fig. 1**. HP1γ exerts inhibitory effects on TPA-induced c-Jun and c-Fos Expression. (A) Sequence homology between HP1 isoforms in the N-terminus. (B) TPA induces histone H3 phosphorylation at Ser10 (p-H3S10) and Ser28 (p-H3S28), together with a tri-methyl/phospho double mark in histone H3 at Lys9 and Ser10 (H3K9me3/p-H3S10). (C) Lentivirally-transduced HaCaT-mock and HaCaT-shHP1γ cells were exposed to TPA (10 nM) at different times and Western blot analysis was conducted against c-Jun and c-Fos polyclonal antibodies.
The Heterochromatin-1 Phosphorylation Contributes to TPA-Induced AP-1 Expression

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HP1γ expression in HaCaT cells, using the lentiviral transduction and examined the induction pattern of c-Jun and c-Fos following TPA treatment. As a result, we observed that silencing HP1γ accelerated TPA-mediated induction of c-Jun protein and potentiated TPA-mediated induction of c-Fos proteins in HaCaT cells (Fig. 1C). This result suggests that HP1γ exerts a suppressive role in TPA induction of c-Jun and c-Fos via histone H3 tri-methylation at Lys9 and, presumably, at Lys27.

TPA-induced activation of the PI3K pathway contributes to HP1γ phosphorylation

The intracellular signaling kinase pathways that are involved in TPA-induced AP-1 activation are fairly elucidated, in which TPA causes a generation of intracellular reactive oxygen species (ROS) and activates two major intracellular signaling cascades, e.g. the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3'-kinase (PI3K) pathways (Kundu and Surh, 2004). The activation of MAPK pathways can either result in a direct transcriptional activation of c-jun and c-fos genes or induce histone H3 phosphorylation at Ser10 and Ser28 via MSK1 activation, leading to the induction of c-Jun and c-Fos (Clayton and Mahadevan, 2003). However, whether and, if so, how TPA-mediated activation of the PI3K and its downstream pathways, e.g. Akt1/mTOR/S6K1, affects the epigenetic proteins to elicit the AP-1-dependent gene expression is largely elusive. To address this question, we have cotransfected HaCaT cells with the pGL3-AP-1 luciferase and renilla-luciferase plasmids, and exposed them to LY294002, a chemical inhibitor of PI3K or rapamycin, a chemical inhibitor of mTOR. The resulting luciferase activity was then measured at 24 h or 48 h post-treatments. Our result shows that suppression of PI3K or mTOR activity significantly suppressed TPA-induced AP-1 luciferase activation (Fig. 2A), implying that the PI3K/Akt1/mTOR pathway is implicated in TPA-induced AP-1 transcriptional activation.

The protein sequence analysis of HP1γ has revealed that HP1γ possesses a highly conserved phosphorylation motif (Fig. 2C). Lomberk et al. have previously demonstrated that a direct phosphorylation of HP1γ at Ser93 exhibits a suppressive effect on the binding capacity of HP1γ to histone H3

Fig. 2. The PI3K/Akt1 pathway contributes to HP1γ phosphorylation. (A) Exposure of LY294002 and rapamycin suppresses TPA-induced AP-1 luciferase activity. * signifies a statistically significance with <0.05. (B) Western blot analysis indicates that TPA can induce Akt1 and S6k1 phosphorylation in HaCaT cells. (C) Sequence homology of HP1γ proteins between different species illustrates that potential phosphorylation residues in HP1γ are highly conserved (Upper Panel). A phosphorylation motif for Akt1 (Middle Panel) and the induction of HP1γ phosphorylation at Ser93 by TPA (Lower Panel) are illustrated. (D) The in vitro kinase assay illustrates that Akt1 can induce phosphorylation of HP1α and HP1γ, but not HP1β. Purified GST (1 μg) or GST isoform proteins (1 μg) were incubated with a recombinant Akt1 at 20°C for 1h. Western blot analysis was then conducted to examine the in vitro phosphorylation of purified HP-1 isoforms, using Akt1 phospho-motif antibody. Coomassie blue staining indicates an equal loading of samples.
we demonstrate that TPA-induced Akt1 activation can induce between extracted histone H3 and 14-3-3 ε isoforms are known to recognize histone H3 phosphorylation at Ser10 and Ser28 (Macdonald et al., 2006). Using PhosphoMotif Finder program (http://www.hprd.org/PhosphoMotif_finder), we have observed that HP1γ at Ser93 can serve as a potential phosphorylation site for several kinases, such as PKA, PKC and PAK2. Consistent with this idea, we found that HP1γ phosphorylation at Ser93 was inducible by the treatment of TPA, known as a strong PKC activator (Fig. 2C). In addition, we noted that an additional putative phosphorylation site for Akt1, e.g. HP1γ at Ser95, resides in HP1γ (Fig. 2C) and that this Akt1 phosphorylation consensus site was also found in HP1α (82REKSES), but not in HP1γ. Based on this prediction, we have attempted to examine whether HP1 isoforms can be directly phosphorylated by Akt1. To this end, recombinant full-length GST or GST-fused HP1 isoform proteins were prepared by IPTG induction and an affinity chromatography with GSH-sepharose beads in E. Coli. Purified GST or GST-fused proteins were then incubated with a recombinant Akt1 in vitro and phosphorylation of HP1 isoforms was examined by Western blot, using phospho-Akt substrate motif antibody. Consistent with our speculation, we observed that Akt1 can directly phosphorylate HP1α and HP1γ, but not HP1β (Fig. 2D). Together, we demonstrate that TPA-induced Akt1 activation can induce HP1γ phosphorylation.

**TAA treatment increases the protein-protein interaction between H3.3 and 14-3-3ε:**

14-3-3 proteins control diverse cellular processes, such as cell cycle checkpoint, MAPK activation, apoptosis and transcriptional activation (Yaffe, 2002). By far, seven 14-3-3 isoforms have been identified in mammals and selected 14-3-3 isoforms are known to recognize histone H3 phosphorylation at Ser10 and Ser28 (Macdonald et al., 2005). At present, it is believed that TPA-induced MAPK activation and histone H3 phosphorylation at Ser10 and Ser28 promote transcriptional activation of c-jun and c-fos genes via the recruitment of 14-3-3 proteins to phosphorylated histone H3 at Ser10 and Ser28 (Winter et al., 2008). Because TPA-induced PI3K/Akt1 activation contributed to HP1γ phosphorylation and its inactivation (Fig. 2C, D), we assumed that HP1γ phosphorylation would promote the recruitment of 14-3-3 isoforms to phosphorylated histone H3 at Ser10. To examine this possibility, HaCaT cells were or were not exposed to TPA for 1 h and cell lysates were collected. Total histone proteins were then isolated by acid extraction followed by trichloroacetic acid precipitation. After the extracted histone proteins were subject to a pull-down assay with recombinant GST or GST-14-3-3ε proteins, Western blot analysis was conducted. Our results reveal that GST-14-3-3ε precipitation of phosphorylated H3S10 mark was significantly increased when HaCaT cells were exposed to TPA (Fig. 3A). To examine whether a stronger interaction between 14-3-3ε and histone H3 occurs in cells after TPA treatment, HaCaT cells were cotransfected with pcDNA3-FLAG-H3.3 and pcDNA3-HA-14-3-3ε and exposed to TPA at various times. Collected cell lysates were then immunoprecipitated with FLAG-agarose beads and Western blot analysis was conducted. As a result, we observed that the molecular interaction between FLAG-H3.3 and HA-14-3-3ε was evident after TPA treatment (Fig. 3B). Together our results indicate that TPA increases the recruitment of 14-3-3ε to phosphorylated histone H3.

**DISCUSSION**

The intracellular mechanisms underlying how TPA activation of MAPK and PI3K pathway contributes to the induction of c-Jun and c-Fos have been fairly elucidated. The most common mechanism, by which TPA transcriptionally activates c-jun and c-fos genes includes phosphorylation of transcription factors and other coactivators in the genome (Kong et al., 2001). In addition, TPA induction of c-Jun and c-Fos can be regulated at post-transcription and post-translational levels as well (Calixto et al., 2004). However, the issues whether TPA activation of MAPK and PI3K pathways contribute to the changes in TPA-mediated global or local histone PTMs and, if so, how does it contribute to the induction of c-Jun or c-Fos are largely unclear. A recent study has illustrated that UVB-induced MAPK activation, e.g. p38MAPK and its downstream kinase, MSK1, leads to a direct phosphorylation of histone H3 at Ser10 and Ser28, and this event causes the recruitment of 14-3-3ε and Cdk9 to the chromatin, thereby facilitating RNA polymerase II elongation (Keum et al., 2013). Here, we provide additional epigenetic mechanism, by which TPA activation of PI3K/Akt1 pathway contributes to TPA-induced c-Jun and c-Fos: TPA directly phosphorylates HP1γ and abrogates its suppressive function, thereby permitting the binding of 14-3-3 to phosphorylated histone H3. Based on these results, it is possible for us to propose the mechanism underlying how MAPK and PI3K pathways cooperate each other to activate...
the AP-1 dependent gene expression. TPA activation of MAPK pathway, particularly p38 MAPK and MSK1, contributes to direct phosphorylations of histone H3 at Ser10 and Ser28. On the other hand, it seems that TPA-induced PI3K/Akt1 activation is not directly implicated in histone H3 phosphorylation. Instead, TPA-mediated PI3K/Akt1 activation is likely to contribute to phosphorylation of the chromatin regulatory proteins, including HP1γ. If this speculation holds, we propose that TPA activation of PI3K/Akt1 pathway would play a permissive role in creating favorable chromatin conditions for the transcriptional activation of the IE genes, possibly by excluding chromatin factors that are responsible for heterochromatin silencing.

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