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ORIGINAL ARTICLE

15-Deoxy-$\Delta^{12,14}$-prostaglandin J_2 Upregulates the Expression of 15-Hydroxyprostaglandin Dehydrogenase by Inducing AP-1 Activation and Heme Oxygenase-1 Expression in Human Colon Cancer Cells

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Background: Abnormal upregulation of prostaglandin E_2 (PGE_2) is considered to be a key oncogenic event in the development and progression of inflammation-associated human colon cancer. It has been reported that 15-hydroxyprostaglandin dehydrogenase (15-PGDH), an enzyme catabolizing PGE_2, is ubiquitously downregulated in human colon cancer. 15-Deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ_2), a peroxisome proliferator-activated receptor γ ligand, has been shown to have anticarcinogenic activities. In this study, we investigate the effect of 15d-PGJ_2 on expression of 15-PGDH in human colon cancer HCT116 cells.
Methods: HCT116 cells were treated with 15d-PGJ_2 analysis. The expression of 15-PGDH in the treated cells was measured by Western blot analysis and RT-PCR. In addition, the cells were subjected to a 15-PGDH activity assay. To determine which transcription factor(s) and signaling pathway(s) are involved in 15d-PGJ_2-induced 15-PGDH expression, we performed a cDNA microarray analysis of 15d-PGJ_2-treated cells. The DNA binding activity of AP-1 was measured by an electrophoretic mobility shift assay. To determine whether the AP-1 plays an important role in the 15d-PGJ_2-induced 15-PGDH expression, the cells were transfected with siRNA of c-Jun, a major subunit of AP-1. To elucidate the upstream signaling pathways involved in AP-1 activation by 15d-PGJ_2, we examined its effect on phosphorylation of Akt by Western blot analysis in the presence or absence of kinase inhibitor.
Results: 15d-PGJ_2 (10 μM) significantly upregulated 15-PGDH expression at the mRNA and protein levels in HCT-116 cells. 15-PGDH activity was also elevated by 15d-PGJ_2. We observed that genes encoding C/EBP delta, FOS-like antigen 1, c-Jun, and heme oxygenase-1 (HO-1) were most highly induced in the HCT116 cells following 15d-PGJ_2 treatment. 15d-PGJ_2 increased the DNA binding activity of AP-1. Moreover, transfection with specific siRNA against c-Jun significantly reduced 15-PGDH expression induced by 15d-PGJ_2. 15d-PGJ_2 activates Akt and a pharmacological inhibitor of Akt, LY294002, abrogated 15d-PGJ_2-induced 15-PGDH expression. We also observed that an inhibitor of HO-1, zinc protoporphyrin IX, also abrogated upregulation of 15-PGDH and down-regulation of cyclooxygenase-2 expression induced by 15d-PGJ_2.
Conclusions: These finding suggest that 15d-PGJ_2 upregulates the expression of 15-PGDH through AP-1 activation in colon cancer HCT116 cells.
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Key Words: 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2, 15-PGDH, AP-1, HO-1, Colon cancer

INTRODUCTION

Prostaglandin E_2 (PGE_2), one of the major metabolites of cyclooxygenase-2 (COX-2), plays a role in the proliferation, invasion, angiogenesis, and apoptosis resistance of malignant and cancerous cells [1]. It is widely accepted that aberrant overexpression of COX-2 and the abundance of its product PGE_2 contribute to the development of colorectal cancer [2]. Therefore,

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deregulation of the COX-2/PGE_2 pathway appears to impact colorectal tumorigenesis via a number of distinct mechanisms, including the promotion of tumor maintenance, progression, metastatic spread, and perhaps even tumor initiation [2]. Notably, PGE_2 levels are elevated in colon cancer due to aberrant expression of COX-2 [1]. The levels of PGE_2 are regulated not only by its synthesis via the COX-2-catalized arachidonic acid cascade but also by its metabolism [3]. 15-Hydroxyprostaglandin dehydrogenase (15-PGDH) is a representative enzyme that oxidizes PGE_2 to 15-keto PGE_2 [3].

Recent studies showed that 15-PGDH has tumor suppressor function in colon cancer [4]. 15-PGDH was shown to be upregulated in normal colon epithelium but downregulated in colon cancer and was involved in the cancer progression of initiated colon epithelial cells [5]. In this study, 15-PGDH wild type mice are highly resistance to azoxymethane-induced colon carcinogenesis, whereas loss of 15-PGDH conferred increased susceptibility to colon tumor induction [5]. Moreover, 15-PGDH also reduced the metastatic potential of cancer by inactivating matrix metalloproteinase-2 (MMP-2) [6]. Thus, upregulation of 15-PGDH levels in cancer cells resulted in decreased clonal growth, leading to reduced tumorigenesis [5]. In addition, 15-PGDH also functions as inhibitor of COX-2 signaling [3]. Thus, 15-PGDH functions, along with COX-2, to regulate metabolism of prostaglandins, and their reciprocal regulation appears to determine cell fate [3].

15-Deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ_2), one of the terminal products of COX-2-mediated catabolism, has been shown to inhibit growth of several different types of cancer cells and to induce their apoptosis [7]. We have previously shown that 15d-PGJ_2 increases 15-PGDH expression through reactive oxygen species (ROS)-mediated activation of ERK1/2 and Elk-1 in human breast cancer cells [8] and through suppression of DNA methyltransferase 1 (DNMT1)-mediated hypermethylation of the 15-PGDH promoter via its direct interaction with DNMT1 in MDA-MB-231 cells [9]. However, the molecular mechanisms underlying the regulation of 15-PGDH remain unclarified. Here, we examined the effects of 15d-PGJ_2 on 15-PGDH expression in human colon cancer cells (HCT116).

MATERIALS AND METHODS

1. Reagents

All chemical reagents were obtained from Sigma (St. Louis, MO). 15d-PGJ_2 was purchased from Cayman Chemical Co. (Ann Arbor, MI). MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] was purchased from Sigma Chemical Co. (St. Louis, MO). Fetal Bovine Serum, penicillin/streptomycin, McCoy's 5A medium were obtained from Gibco BRL (Grand Island, NY). Reagents for Western blotting analysis were obtained from Amersham Biotechnology (Bucks, UK). LY294002 and zinc protoporphyrin IX (ZnPP) were purchased from Calbiochem (San Diago, CA). Primers for RT-PCR were synthesized by Bioneer (Daejeon, Korea). Reverse transcriptase was purchased from Promega (Madison, WI). Antibodies for 15-PGDH, p-Akt, and Akt were obtained from Cell signaling Technology, Inc. (Beverly, MA), COX-2 was from Lab Vision Co. (Fremont, CA, USA), β-Actin was from Santa Cruz Biotechnology (Santa Cruz, CA). Oligonucleotide probes containing AP-1 consensus sequences located in the human 15-PGDH promoter region was obtained from Promega (Madison, WI, USA). The enhanced chemiluminescence (ECL) and [γ-^{32}P]ATP were supplied from Amersham Pharmacia Biotech (Buckinghamxhire, UK).

2. Cell culture and cytotoxicity

HCT116 cells were grown in McCoy's 5A medium (Gibco, CA) supplemented with 100 ng/mL penicillin and 10% fetal bovine serum in a 5% CO_2 incubator at 37°C. To evaluate cytotoxicity, cells were treated with MTT solution (Roche Molecular Biochemicals, Germany), as described in the supplier's protocol.

3. Western blot analysis

Protein in lysates were generated with cell lysis buffer (Cell Signaling Technology, MA), following the manufacturer's instructions. Proteins were separated by SDS-PAGE and transferred to Hybond-ECL (Amersham Biosciences, UK) membranes. Blots were incubated with primary antibodies and peroxidase-conjugated secondary antibodies. Blots were visualized using ECL.

4. Reverse transcriptase-polymerase chain reaction (RT-PCR)

Total RNA from HCT116 cells was isolated using Trizol® (GibcoBRL, NY). The following primers were used for amplification: 15-PGDH, 5'-GTAAAGCTGCCCTGGATGAG-3' and 5'-AACAAAGCCTGGACAAATGG-3'; HO-1, 5'-GAGCGGCTTCAAG CTGGTGA-3' and 5'-TAGGGGATGACCTCCTGCCA-3'; GAPDH, 5'-CCATGGAGAAGGCTGGGG-3' and 5'-CAAAGTTGTCATGGATG ACC-3'. PCR were performed over 32 cycle (95°C for 30 s, 62°C for 30 s, and 70°C for 45 s for 15-PGDH and GAPDH; 94°C for 30 s, 64°C for 30 s, and 72°C for 60 s for HO-1), using 2X PCR Mastermix (Bioneer, Korea). Each PCR products was resolved on 1% agarose

gels, and visualized by Redsafe staining (iNtRON Biotechnology, Korea).

5. 15-PGDH activity assay

15-PGDH activity was assessed by the tritium release assay with cellular lysates as described previously [8]. Briefly, the transfer of tritium from 15(S)-[15-^{3}H]PGE$_2$ to glutamate by 15-PGDH was assayed.

6. Electrophoretic mobility gel shift assay (EMSA)

Nuclear extracts were obtained using NE-PER Nuclear and Cytoplasmic Extraction Reagents (Pierce, IL). The oligonucleotide containing to the AP-1 sequence was end-labeled with [γ-^{32}P]ATP using T4 polynucleotide kinase and 10 μg of nuclear extracts were incubated with [γ-^{32}P]ATP labeled DNA probe in gel shift binding buffer (10 mM Tris-HCl (pH 7.5), 1 mM EDTA, 1 mM dithiothreitol, 1 μg/μL poly (dI-dC), 4% glycerol and 100 mM NaCl). The DNA-protein complexes were resolved by a 6% non-denaturating polyacrylamide gel electrophoresis and analyzed by autoradiography.

7. Transient transfection

siRNA against c-Jun was obtained from Santa Cruz Biotechnology (Santa Cruz, CA). HCT116 cells were transiently transfected with siRNA against c-Jun using the RNAiMax transfection reagent (Invitrogen, CA) and were incubated overnight, according to the manufacturer's instructions. After the 24 h transfection, the cells were treated with 15d-PGJ$_2$.

8. Statistical analysis

All data were expressed as the means ± SD. Statistical significance was determined by Student's *t*-test. Differences between two groups or between more than three groups were considered to be significant for values of $P < 0.01$.

9. Supplementary information

Detailed Materials and Methods for RNA preparation, Labeling, and purification, Hybridization and data export, and Raw data preparation can find in *Supplementary information.*

RESULTS

1. 15d-PGJ$_2$ induces the expression of 15-PGDH in human colon cancer cells

To determine the optimal dose of 15d-PGJ$_2$, HCT116 cells were treated with various concentrations of 15d-PGJ$_2$ and cell viability was determined by the MTT assay (Fig. 1). Then, a non-cytotoxic concentration of 15d-PGJ$_2$ (10 μM) was used for all subsequent experiments. Treatment of HCT116 cells with 15d-PGJ$_2$ at 0, 5, 10, and 15 μM for 24 h induced 15-PGDH expression (Fig. 2A). A kinetic study showed that 15-PGDH protein was induced by 15d-PGJ$_2$ in a time-dependent manner (Fig. 2B). Upregulation of 15-PGDH was observed beginning at 12 h, and it continued to increase until 24 h in the presence of 15d-PGJ$_2$ (Fig. 2B). RT-PCR analysis showed that 15-PGDH mRNA accumulation was transient and was only observed between 1 and 6 h (Fig. 2C). 15-PGDH activity, as determined by the production of α-keto-glutamate, was markedly increased in cells treated with 15d-PGJ$_2$ for 24 h (Fig. 2D). Thus, 15d-PGJ$_2$ upregulates expression of 15-PGDH and increases its cataltytic activity as well.

2. 15d-PGJ$_2$ upregulates the expression of 15-PGDH through activation of AP-1

15-PGDH synthesis is controlled mainly at transcription level. Within the 15-PGDH promoter region, there are binding cites for several transcription factors, such as activating protein-1 (AP-1), Ets, and cAMP-responsive element-binding protein (CREB) [10,11]. 15d-PGJ$_2$ is known to enhance AP-1 activation [12]. Moreover, microarray analysis data revealed that C-Jun, a subunit of AP-1, was most highly induced in the HCT116 cells following 15d-PGJ$_2$ treatment (Supplementary Table 1). Therefore, we examined the DNA binding activity of AP-1 in cells treated with 15d-PGJ$_2$. When HCT116 cells were treated with 15d-PGJ$_2$,

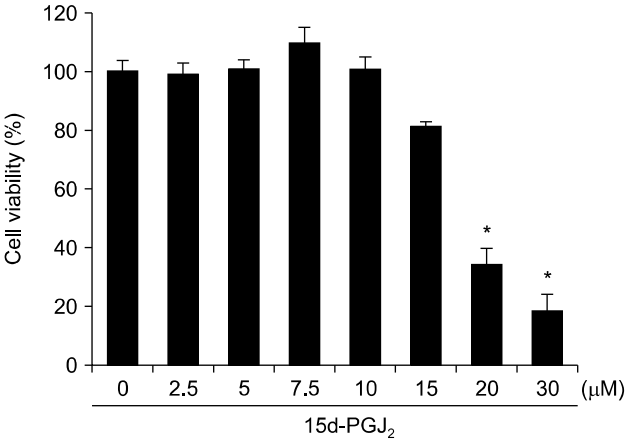

Figure 1. Effect of 15d-PGJ$_2$ on viability of human colon cancer cell line. HCT116 cells were treated with indicated concentrations of 15d-PGJ$_2$ for 24 h, and their viability was determined by the MTT assay. The data represent mean ± SD (n = 3). Significant differences between the compared groups are indicated (*$P < 0.05$).

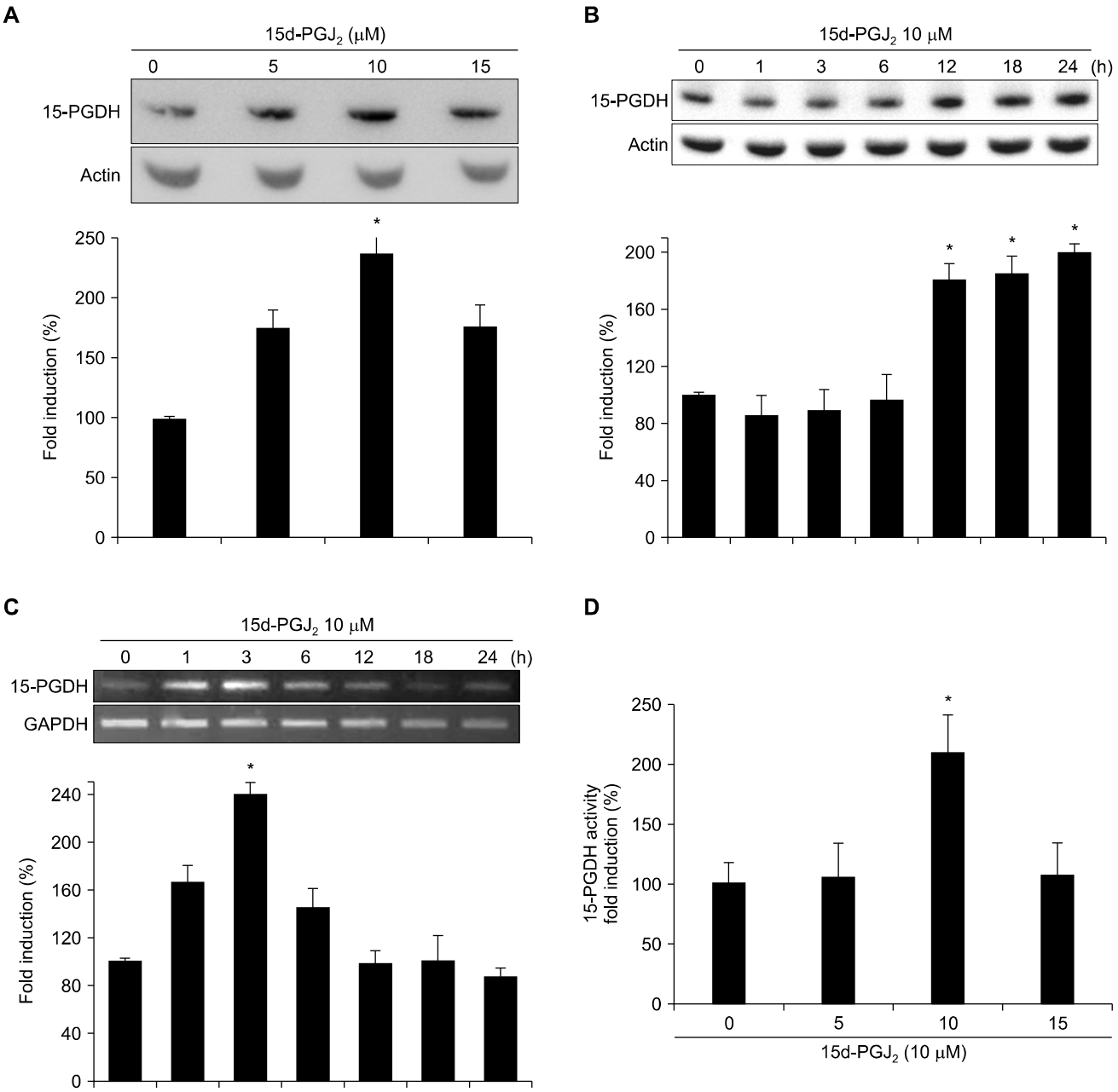

Figure 2. 15d-PGJ_2-induced expression and catalytic activity of 15-PGDH in HCT116 cells. HCT116 cells were treated with 5, 10 or 15 μM of 15d-PGJ_2 for 24 h (A) and with 10 μM 15d-PGJ_2 for 1, 3, 6, 12, 18, and 24 h (B). Total protein isolated from cell lysates was subjected to immunoblot analysis for the measurement of 15-PGDH. (C) The mRNA level of 15-PGDH was determined by quantitative RT-PCR. The mRNA level of GAPDH was used as an internal control. (D) HCT116 cells were treated with 15d-PGJ_2 (0, 5, 10 or 15 μM) for 24 h. By measuring the transfer of tritium from titiated PGE_2 to glutamate, the activity of 15-PGDH was determined. The data are expressed as the mean ± SD (n = 3). Significant differences between the compared groups are indicated (*$P < 0.05$).

increased DNA binding of AP-1 was only transiently observed, between 1 and 6 h (Fig. 3A). The specificity of the 15d-PGJ_2-induced AP-1 DNA binding was verified by a competition experiment in which the addition of an 100-fold molar excess of unlabeled human AP-1 oligonucleotides completely blocked formation of the radiolabeled DNA-AP-1 protein complex (Fig. 3A, cold probe). AP-1 proteins are homo- or heterodimers composed of basic region-leucine zipper proteins, including Jun and Fos [13]. Therefore, to further confirm that 15d-PGJ_2-induced 15-PGDH expression was specifically due to AP-1-mediated transcriptional regulation, we conducted additional experiments using HCT116 cells transfected with c-Jun siRNA. The results

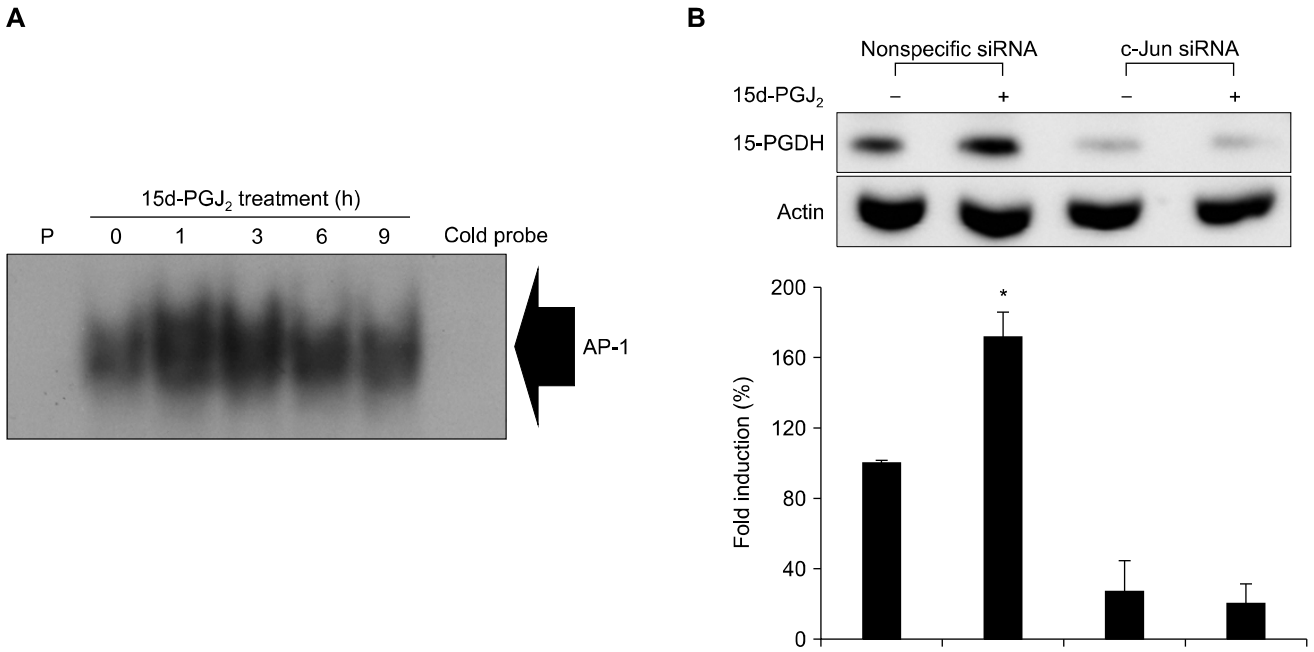

Figure 3. Involvement of AP-1 in the induction of 15-PGDH by 15d-PGJ$_2$ in HCT116 cells. (A) HCT116 cells were treated with 15d-PGJ$_2$ (10 μM) for indicated time periods. The DNA-binding activity of AP-1 in HCT116 cells treated with 15d-PGJ$_2$ was measured by EMSA as described in Materials and Methods. (B) HCT116 cells were transfected with nonspecific or c-Jun siRNA using lifopectamineTM RNAiMAX transfection reagent. After 24 h transfection, cells were treated with 10 μM 15d-PGJ$_2$ for an additional 24 h. Protein extracts from cell lysates were analyzed by Western blot with 15-PGDH and Actin antibodies.

showed that 15d-PGJ$_2$-induced upregulation of 15-PGDH in HCT116 cells was abolished by the silencing of c-Jun gene expression with specific siRNA (Fig. 3B). These results indicate that 15d-PGJ$_2$-induced upregulation of 15-PGDH is mediated, at least in part, by activation of AP-1 signaling.

3. The expression of 15-PGDH is regulated by Akt activation

To elucidate the upstream signaling events that lead to the activation of AP-1 and the induction of 15-PGDH expression, we examined the 15d-PGJ$_2$-induced phosphorylation levels of representative signal-transducing kinases. We noted that Akt phosphorylation was transiently increased between 1 and 6 h after treatment with 15d-PGJ$_2$ (Fig. 4A). To verify the involvement of the Akt pathway in AP-1-mediated induction of 15-PGDH expression, cells were pre-incubated with the Akt inhibitor (LY294002) and then treated with 15d-PGJ$_2$ for 24 h. Pharmacologic inhibition of Akt with LY294002 abrogated 15d-PGJ$_2$-induced 15-PGDH expression (Fig. 4B). These findings indicate that the Akt pathway is involved in 15d-PGJ$_2$-induced upregulation of 15-PGDH in HCT116 cells.

4. The expression of 15-PGDH is regulated by HO-1 expression

To elucidate the target genes regulated by 15d-PGJ$_2$ in HCT116 cells, we performed a microarray analysis (Supplementary Table 1). Notably, heme oxygenase 1 (HO-1), a representative antioxidant enzyme regulated by Nrf2, was most highly elevated by 15d-PGJ$_2$. Treatment with 15d-PGJ$_2$ for 24 h resulted in the induction of HO-1 expression in a concentration-dependent manner (Fig. 5A). The RT-PCR analysis showed that accumulation of HO-1 mRNA occurred between 1 and 24 h (Fig. 5B). To further verify the involvement of HO-1 expression in the induction of 15-PGDH expression, cells were pre-incubated with the HO-1 inhibitor ZnPP for 12 h and then treated with 15d-PGJ$_2$ for additional 24 h. Pharmacologic inhibition of HO-1 with ZnPP abrogated 15d-PGJ$_2$-induced 15-PGDH expression (Fig. 5C) and basal level of 15-PGDH expression in HCT116 cells (Fig. 5D). However, ZnPP induced expression of COX-2 in a concentration-dependent manner while 15-PGDH expression was down-regulated (Fig. 5C and 5D). These findings indicates that 15d-PGJ$_2$-induced upregulation of 15-PGDH expression is mediated, at least in part, by HO-1 induction.

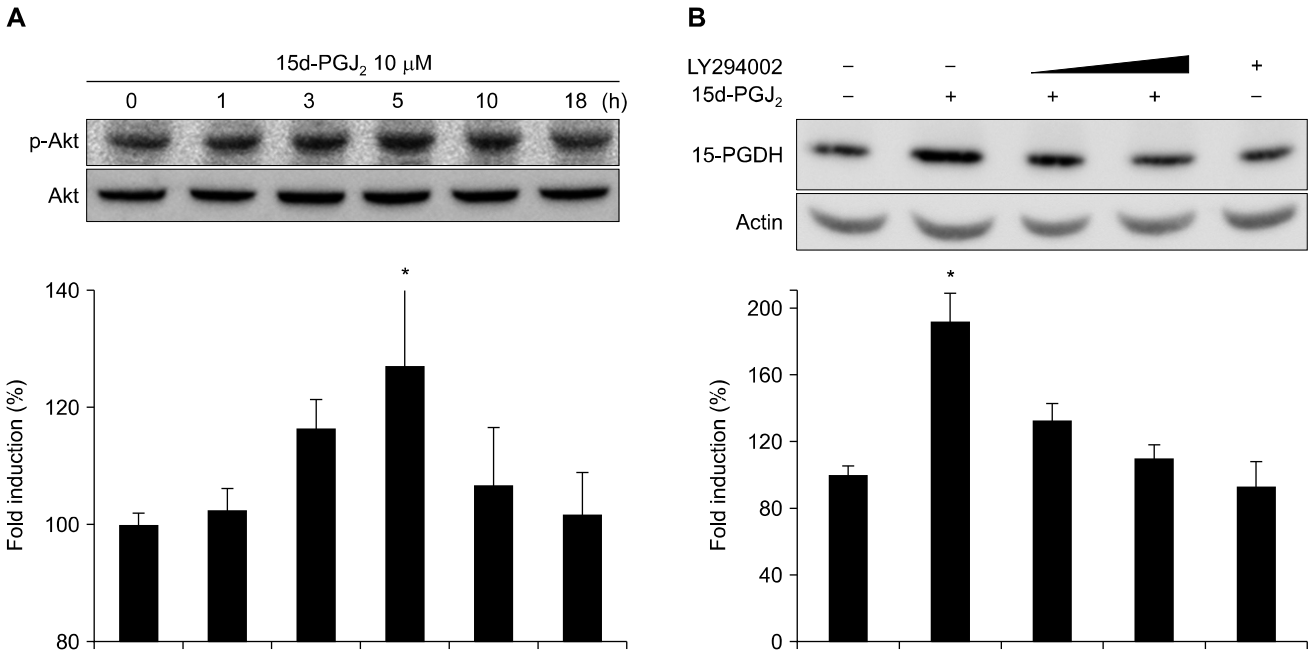

Figure 4. 15d-PGJ_2-induced expression of 15-PGDH through activation of Akt signaling. (A) The time-related activation of Akt was assessed by measuring the phosphorylated form of Akt. HCT116 cells were treated with 10 μM 15d-PGJ_2 for the indicated time periods followed by immunoblot analysis with specific antibodies. (B) The effect of the Akt inhibitor on the induction of 15-PGDH was assessed by Western blot analysis in HCT116 cells. HCT116 cells were exposed to 10 μM 15d-PGJ_2 for 24 h in the presence of 0, 5 or 20 μM LY294002. Whole-cell lysates were subjected to Western blot analysis with the indicated antibodies.

DISCUSSION

Colorectal cancer (CRC) is the fourth leading cause of cancer death and the third most common cancer worldwide [14]. Colitis-associated cancer develops from chronically inflamed mucosa and progresses through dysplasia to adenocarcinoma in the so-called inflammation-dysplasia-carcinoma sequence [15]. Therefore, persons with chronic inflammatory bowel disease (IBD) show elevated risk of CRC [16]. In addition to IBD, *Helicobacter pylori*-induced gastritis, viral-, toxin-, and alcohol-induced hepatitis, and Barrett's esophagus are other well-known inflammatory diseases that predispose to the development of gastroenterological cancers [17].

Although chronic inflammation can initiate and promote gastrointestinal cancer, the molecular mechanisms are still not well understood [18]. Several studies have suggested that colon cancer has increased levels of prostaglandin, especially, PGE_2. The increase in PGE_2 levels induced by COX-2 upregulation can promote apoptosis resistance in transformed cells and accelerate metastasis in colon cancer [19]. A positive feedback has been proposed between PGE_2 and COX-2 in colon cancer, in which PGE_2 induces the expression of COX-2, and upregulation of COX-2 increases the generation of PGE_2 [1]. Therefore, inactivation of PGE_2 could inhibit the development and progression of colon cancer.

Excess PGE_2 is inactivated by overexpression of 15-PGDH, a key enzyme that catalyzes the conversion of oncogenic PGE_2 to a biologically inactive keto metabolite [19]. Chemopreventive/chemoprotective agents, such as NSAIDs, histone deacetylase (HDAC) inhibitors, calcitriol, PPARγ ligands, and glucocorticoids have been known to exert their chemopreventive and chemotherapeutic activities by inducting expression of 15-PGDH while suppressing COX-2 expression [20]. Tai et al. reported that NSAIDs induced 15-PGDH expression by up-regulation of its transcription and suppression of its degradation [21]. 15d-PGJ_2 is a ligand of peroxisome proliferator-activated receptor gamma (PPARγ). It is produced in inflamed cells and tissues as a consequence of COX-2 upregulation [22]. 15d-PGJ_2 has been shown to have significant anti-cancer effects such as anti-inflammatory, pro-apoptotic, anti-metastatic, and anti-angiogenic activities [7]. Here, we report that 15d-PGJ_2 upregulates the expression of 15-PGDH in the HCT116 human colon cancer cell line. In our previous study, down-regulation of 15-PGDH promoted the migration of breast cancer cells [8]. In a recent study, Mehdawi et al. reported that recombinant WNT5A (rWNT5A) and a WNT5A-mimicking peptide (Foxy-5) induced

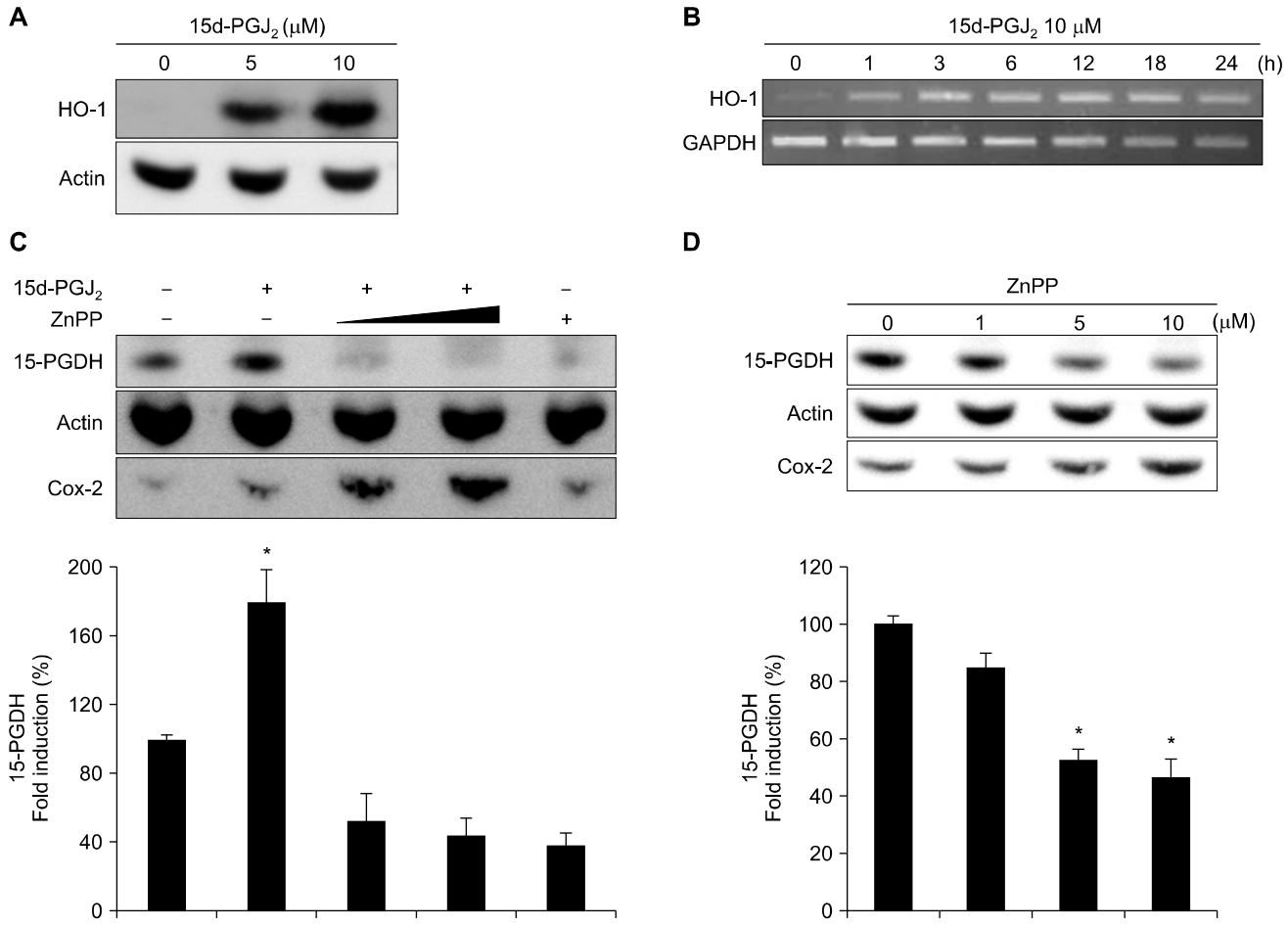

Figure 5. Effect of HO-1 on 15d-PGJ$_2$-induced 15-PGDH expression. (A) HCT116 cells were treated with indicated concentrations of 15d-PGJ$_2$ for 24 h. Total protein isolated from cell lysates was subjected to immunoblot analysis for the measurement of HO-1. (B) The mRNA level of HO-1 was determined by quantitative RT-PCR. The mRNA level of GAPDH was used as an internal control. (C) The effect of the HO-1 inhibitor ZnPP on the induction of 15-PGDH was assessed by Western blot analysis. HCT116 cells were pretreated with ZnPP (0, 5 10 μM) for 12 h. After changing the medium with a fresh one, cells were exposed to 15d-PGJ$_2$ (10 μM) for additional 24 h. (D) HCT116 cells were treated with ZnPP (0, 1, 5 or 10 μM) for 24 h. Expression levels of 15-PGDH and COX-2 protein were determined by Western blot analysis. The data are expressed as the mean ± SD (n =3). Significant differences between the compared groups are indicated (*$p < 0.05$).

15-PGDH expression through down-regulated β-catenin and induced AP-1 in colon and breast cancer cells [23]. They also demonstrated that LTC4, a cysteinyl leukotriene 2 ligand, upregulated 15-PGDH expression by inducing 15-PGDH promoter activity through JNK/AP-1 signaling [24]. Similarly, our study proved that 15d-PGJ$_2$ induced 15-PGDH expression by stimulating binding of AP-1 to the *15-PGDH* gene promoter. We then confirmed that treatment of 15d-PGJ$_2$-stimulated HCT-116 cells with c-Jun siRNA abrogated 15-PGDH expression. Therefore, activation of AP-1 signaling by 15d-PGJ$_2$ is considered to contribute to the induced 15-PGDH expression.

Besides AP-1, the 15-PGDH promoter regions also have several E-boxes, which are bound by the transcriptional repressors Snail, Slug, and ZEB1 [25]. These transcriptional repressors bind to the conserved E-box elements of 15-PGDH promotor and reduce its transcription. Elevated Snail expression is correlated with the down-regulation of 15-PGDH expression in colon cancer [25]. Mann et al. reported that epidermal growth factor inhibits 15-PGDH activity in colon cancer cells by inducing of Snail [25]. Yang et al. have shown that inhibition of epidermal growth factor receptor (EGFR) signaling elevates 15-PGDH in non-small-cell lung cancer [26]. The EGFR tyrosine kinase inhibitor increased 15-PGDH expression by reducing Slug levels.

15d-PGJ$_2$ has therapeutic potential for the prevention of inflammatory diseases [22]. 15d-PGJ$_2$ exerts potent anti-inflammatory effects by activating of Nrf2, leading to the resolution of inflammatory responses [22,27]. Many studies have suggested that 15d-PGJ$_2$ induces HO-1 expression in various cells

by activating Nrf2. Because 15d-PGJ_2 has an α,β-unsaturated ketone moiety, it functions as an electrophile. Therefore, 15d-PGJ_2 can easily interact with cysteine residues of proteins via the Michael addition reaction [28]. In this study, cDNA microarray analysis showed that HO-1 was the most highly elevated gene induced by 15d-PGJ_2 treatment. Interestingly, a HO-1 inhibitor significantly abrogated 15d-PGJ_2-induced 15-PGDH expression and induced COX-2 expression, and this is the first study to report the effect of HO-1 on the expression of 15-PGDH. 15d-PGJ_2 may also upregulate 15-PGDH by inducing protein translation and reducing protein degradation by HO-1. However, the precise mechanism underlying the association between 15-PGDH and HO-1 in 15d-PGJ_2-induced signaling cascades requires further research.

Expression of 15-PGDH and COX-2 has been known to be reciprocally regulated [29]. In this study, treatment with an HO-1 inhibitor significantly decreased 15-PGDH expression but increased COX-2 expression. Many studies have suggested that several chemopreventive agents show anti-inflammatory activity by up-regulation of HO-1 [30,31]. Kim et al. reported that 15d-PGJ_2 facilitated the resolution of inflammation by promoting Nrf2-induced expression of CD36 and HO-1 in macrophages [27]. Therefore, pretreatment with an HO-1 inhibitor reduced their anti-inflammatory activity. Taken together, 15d-PGJ_2, acting as a potent HO-1 inducer, may have health-promoting effects by preventing inflammation through induction of HO-1.

In conclusion, our present study showed that 15d-PGJ_2 significantly induced 15-PGDH expression in HCT116 human colon cancer cells via AP-1 activation, Akt phosphorylation, and HO-1 induction. These findings provide a novel mechanism by which 15d-PGJ_2 exhibits a remarkable capability of inducing 15-PGDH expression.

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CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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