Research Article

UV Radiation Inhibits 15-Hydroxyprostaglandin Dehydrogenase Levels in Human Skin: Evidence of Transcriptional Suppression

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Abstract

Elevated levels of prostaglandins (PG) have been detected in the skin following UV radiation (UVR). PGs play an important role in mediating both the acute and the chronic consequences of UVR exposure. UVR-mediated induction of cyclooxygenase-2 (COX-2) contributes to increased PG synthesis. In theory, reduced catabolism might also contribute to increased PG levels. 15-Hydroxyprostaglandin deyhdrogenase (*15-PGDH*), a tumor suppressor gene, plays a major role in PG catabolism. In this study, we investigated whether UVR exposure suppressed 15-PGDH while inducing COX-2 in keratinocytes and in human skin. UVR exposure caused dose-dependent induction of COX-2, suppression of 15-PGDH, and increased prostaglandin E_2 (PGE_2) production in HaCaT cells. Exposure to UVR suppressed the transcription of *15-PGDH*, resulting in reduced 15-PGDH mRNA, protein, and enzyme activities. UVR exposure induced Slug, a repressive transcription factor that bound to the *15-PGDH* promoter. Silencing Slug blocked UVR-mediated downregulation of 15-PGDH. The effects of UVR were also evaluated in the Epi-Derm skin model, a three-dimensional model of human epidermis. Here too, COX-2 levels were induced and 15-PGDH levels suppressed following UVR exposure. Next, the effects of UVR were evaluated in human subjects. UVR treatment induced COX-2 while suppressing 15-PGDH mRNA in the skin of 9 of 10 subjects. Collectively, these data suggest that reduced expression of 15-PGDH contributes to the elevated levels of PGs found in the skin following UVR exposure. Possibly, agents that prevent UVR-mediated downregulation of 15-PGDH will affect the acute or the long-term consequences of UVR exposure, including nonmelanoma skin cancer. *Cancer Prev Res; 3(9); 1104–11. ©2010 AACR.*

Introduction

The synthesis of prostaglandins (PG) from arachidonic acid requires two sequential enzymatic steps. Cyclooxygenase (COX) catalyzes the synthesis of PGH_2 from arachidonic acid. There are two isoforms of COX. *COX-1* is a housekeeping gene that is expressed constitutively in most tissues (1). *COX-2* is an immediate-early response gene that is undetectable in most normal tissues including the skin but is rapidly induced by oncogenes, growth factors, cytokines, UV radiation (UVR), and tumor promoters (2–4). Specific synthases then convert

PGH_2 to a variety of PGs including prostaglandin E_2 (PGE_2) and PGF2α (3, 5).

Multiple lines of evidence suggest an important role for the COX-PG axis in the development of nonmelanoma skin cancers (5–8). Exposure to UVR induces COX-2 and PG levels in the skin (4, 9, 10). PGE_2 stimulates cell proliferation, angiogenesis, and vascular permeability while inhibiting apoptosis and immune function (3, 7, 11, 12). Both genetic and pharmacologic studies indicate a role for the COX-PG pathway in skin carcinogenesis. In UV studies, skin tumor latency was decreased and multiplicity increased in COX-2 transgenic mice compared with wild-type mice (13). Knocking out COX-2 or treatment with celecoxib, a selective COX-2 inhibitor, protected against skin carcinogenesis (14–16). In a clinical trial, celecoxib was suggested to have protective effects against basal cell carcinoma (17). Recent studies have attempted to elucidate the downstream effectors of PGE_2. PGE_2 exerts its effects by binding to and activating four G-protein–coupled receptors known as EP_1 to EP_4. EP_2-knockout mice developed fewer skin tumors (18–20). Others have suggested that EP_1 may be important in skin carcinogenesis (21). Collectively, these EP receptor studies

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provide additional evidence of the importance of PGE_2 in skin carcinogenesis.

Although there is excellent evidence that UVR-mediated induction of COX-2 leads to increased PG synthesis, other mechanisms may also contribute to increased PG levels in the skin. Reduced catabolism of PGs may lead to elevated PG levels (22). The key enzyme responsible for the degradation of PGs is NAD^+-dependent 15-hydroxyprostaglandin dehydrogenase (15-PDGH; ref. 23). 15-PGDH, a 29-kDa enzyme, catalyzes the formation of 15-keto-PGs, which possess greatly reduced biological activities compared with PGs (23, 24). Mice engineered to be 15-PGDH deficient have increased PG levels in tissues (22, 25). Skin constitutively expresses 15-PGDH and is capable of enzymatically degrading PGE_2 into 15-keto metabolites (26). Therefore, it is possible that UVR-mediated increases in PG levels in the skin reflect downregulation of 15-PGDH in addition to upregulation of COX-2.

In the present study, we first determined that UVR exposure downregulated *15-PGDH* while inducing COX-2 and PGE_2 levels in HaCaT cells. After showing that UVR had similar effects in a three-dimensional skin model, we carried out a clinical trial. Consistent with the preclinical findings, exposure to UVR led to upregulation of COX-2 and downregulation of 15-PGDH in the skin. These results provide new insights into the mechanism by which UVR alters PG levels, which is likely to be important for understanding both the acute and the chronic effects of UVR.

Materials and Methods

Materials

DMEM was obtained from Invitrogen. Antiserum to β-actin, L-glutamic dehydrogenase, α-ketoglutaric acid, NAD^+ and Lowry protein assay kits were obtained from Sigma-Aldrich Corp. Antibodies to COX-2 and Slug were obtained from Santa Cruz Biotechnology. Antihuman polyclonal antiserum to 15-PGDH was from Novus Biologicals, Inc. Western blot analysis detection reagents (enhanced chemiluminescence) were from Perkin-Elmer Life and Analytical Sciences, Inc. Nitrocellulose membranes were from Schleicher & Schuell. Enzyme immunoassay kits for PGE_2 assays were from Cayman Chemical Co. Charcoal-activated powder was from EM Science. The RNeasy Mini kit was from QIAGEN, Inc. Murine leukemia virus reverse transcriptase, RNase inhibitor, oligo $d(T)_{16}$, and SYBR Green PCR Master mix were from Applied Biosystems. Real-time PCR primers were synthesized by Sigma-Genosys. DharmaFECT 4 was obtained from Thermo Fisher Scientific Co. Chromatin immunoprecipitation (ChIP) assay kits were purchased from SA Bioscience Corp.

Tissue culture

HaCaT cells were a generous gift of Dr. Sam W. Lee (Harvard University, Boston, MA). These cells are spontaneously immortalized human epithelial keratinocytes (27). Cells were routinely maintained in DMEM supplemented with 10% fetal bovine serum, 100 IU/mL penicillin, and 100 μg/mL streptomycin; grown to 70% confluence; and trypsinized with 0.125% trypsin-2 mmol/L EDTA solution. Cells were grown in basal medium (DMEM without serum) for 24 hours before treatment.

UV radiation

UV irradiation was done in 10-cm cell culture dishes containing growth factor–free, phenol red–free DMEM. For UV irradiation, a bank of six FS-40 sunlamps (Philips) in parallel connection was used. These lamps emit a continuous spectrum from 270 to 390 nm with a peak emission at 313 nm; approximately 65% of the radiation emitted by these lamps is within the UVB range (280-320 nm; ref. 28). These bulbs also emit approximately 0.5% of their energy in the UVC region (200-280 nm; ref. 29). Measured by an IL-1700 UVR meter (International Light), this bank of bulbs deliver an average flux of 0.9 mW/cm^2 at the level of exposure of the cells. Control cells were treated identically except that the UVR lamps were not turned on.

Western blot analysis

Cell lysates were prepared by treatment with lysis buffer as described previously (30). Lysates were sonicated for 8 minutes on ice and centrifuged at 14,000 × *g* for 10 minutes at 4°C to sediment the particulate material. The protein concentration of the supernatant was measured by the method of Lowry et al. (31). SDS-PAGE was done under reducing conditions on 10% polyacrylamide gels. The resolved proteins were transferred onto nitrocellulose sheets and then incubated with antisera to COX-2, 15-PGDH, Slug, and β-actin. Secondary antibody to IgG conjugated to horseradish peroxidase was used. The blots were probed with the enhanced chemiluminescence Western blot detection system. All experiments were repeated and representative results are shown.

15-PGDH activity assay

15-PGDH enzyme activity in cellular lysates was assayed by measuring the transfer of tritium from $15(S)$-[15-^{3}H] PGE_2 to glutamate by coupling 15-PGDH with glutamate dehydrogenase as described previously (32).

Real-time PCR

Total RNA was isolated using RNeasy Mini Kit. One microgram of RNA was reverse transcribed using murine leukemia virus reverse transcriptase (Roche Applied Science) and oligo $d(T)_{16}$ primer. The resulting cDNA was then used for amplification. Each PCR was 20 μL and contained 5 μL of cDNA, 2× SYBR Green PCR master mix, and primers. Primer pairs were as follows: COX-2, 5′-CCCTTGGGTGTCAAAGGTAA-3′ (forward) and 5′-GCCCTCGCTTATGATCTGTC-3′ (reverse); 15-PGDH, 5′-TCTGTTCATCCAGTGCGATGT-3′ (forward) and 5′-ATAATGATGCCGCCTTCACCT-3′ (reverse). β-Actin

(forward, 5′-AGAAAATCTGGCACCACACC-3′, and reverse, 5′-AGAGGCGTACAGGGATAGCA-3′) served as an endogenous normalization control. Experiments were done using a 7500 real-time PCR system (Applied Biosystems). Relative fold induction was determined by $\Delta\Delta C_T$ (relative quantification) analysis.

Transient transfections

Slug siRNA was obtained from Dharmacon, Inc. HaCaT cells were transfected with 100 pmol of Slug siRNA or nonspecific siRNA using DharmaFECT 4 transfection reagent according to the manufacturer's instructions. The medium was changed after 24 hours and cells were allowed to grow in basal medium for another 12 hours before UVR or sham treatment.

Chromatin immunoprecipitation assay

ChIP assay was done with a kit according to the manufacturer's instructions. Briefly, 4×10^6 cells were cross-linked in a 1% formaldehyde solution at 37°C for 10 minutes. Cells were then lysed and sonicated to generate 200- to 1,000-bp DNA fragments. After centrifugation, the cleared supernatant was incubated with 4 μg of the indicated antibody at 4°C over night. Immune complexes were precipitated, washed, and eluted as recommended. DNA-protein cross-links were reversed by heating, and the DNA fragments were purified and used as a template for PCR amplification. Quantitative real-time PCR was carried out. *15-PGDH* promoter oligonucleotide sequences for PCR primers were forward, 5′-CTCCGCTCTCCTTCTATC-CA-3′, and reverse, 5′-AACCCACGACTGTGTCACCT-3′. This primer set encompasses the *15-PGDH* promoter sequence from nucleotide −366 to −155. PCR was done at 95°C for 30 seconds, 62°C for 30 seconds, and 72°C for 45 seconds for 40 cycles, and real-time PCR was done at 95°C for 15 seconds and 60°C for 60 seconds for 40 cycles. The PCR product generated from the ChIP template was sequenced, and the identity of the *15-PGDH* promoter was confirmed.

PGE₂ production

The amount of PGE₂ released by cells was measured by enzyme immunoassay according to the manufacturer's instructions. Production of PGE₂ was normalized to protein concentration.

Organotypic skin constructs

EpiDerm, an established normal human epithelial keratinocyte model that exhibits *in vivo*–like morphologic features and growth characteristics, was obtained from MatTek Corp. (33). These skin-like tissue structures are highly differentiated and consist of basal, spinous, granular, and cornified layers and exhibit properties similar to those of human epidermis. Cultures were grown in hydrocortisone-free medium. UVR exposure was done after removing the cultures from agarose-containing 24-well plates and allowing them to equilibrate to 5% CO_2 and 37°C for 1 hour in the medium supplied by MatTek. Cell

lysates were prepared by snap freezing and grinding with a mortar and pestle and were then subjected to Western blot analysis as described above.

Human tissue

Following approval by the Rockefeller University and Weill Cornell Medical College Institutional Review Boards, a human study was done. The Declaration of Helsinki protocols were followed. Written informed consent was obtained from 10 healthy subjects with light skin (Fitzpatrick types I-IV). Phototesting using narrow-band UVB (Philips TL-01 lamps) was done to determine the minimal erythema dose (MED) for each subject (34). The test was read 24 hours after exposure of sun-protected skin to graded doses of narrow-band UVB radiation. The area exposed to the lowest dose of UV that yielded perceptible erythema was determined to be the MED. Two 6-mm punch skin biopsies were then performed. An area that received 2 MED of UVB radiation was biopsied and an adjacent, nonirradiated skin site was also biopsied. Tissue was snap frozen and stored at −80°C until analysis.

Statistical analysis

Comparisons between groups were made with a two-tailed Student's *t* test. A difference between groups of $P < 0.05$ was considered significant.

Results

UVR treatment induces COX-2 and suppresses the levels of 15-PGDH in keratinocytes

Initially, we determined the effects of UVR on the levels of COX-2 and 15-PGDH in HaCaT cells. As shown in Fig. 1A, UVR treatment caused dose-dependent induction of COX-2. The levels of COX-2 were markedly increased 6 hours after UVR exposure and then rapidly declined. Because of its importance in PG catabolism, we also evaluated the effects of UVR on the amounts of 15-PGDH. A marked dose-dependent decrease in the amounts of 15-PGDH protein was found 6 and 12 hours after UVR treatment. Consistent with the Western blot findings, exposure to UVR led to a dose-dependent decrease in 15-PGDH activity in cell lysates (Fig. 1B). To determine whether UVR modulated the expression of COX-2 and 15-PGDH by a pretranslational mechanism, quantitative real-time PCR was carried out. Exposure to UVR led to dose-dependent increases in the levels of COX-2 mRNA with a corresponding reduction in the amounts of 15-PGDH mRNA (Fig. 1C). To determine whether UVR-induced changes in the expression of COX-2 and 15-PGDH had functional consequences, we next determined PGE₂ production. As shown in Fig. 2, UVR treatment led to a dose-dependent increase in PGE₂ concentration in the medium.

UVR suppresses *15-PGDH* transcription

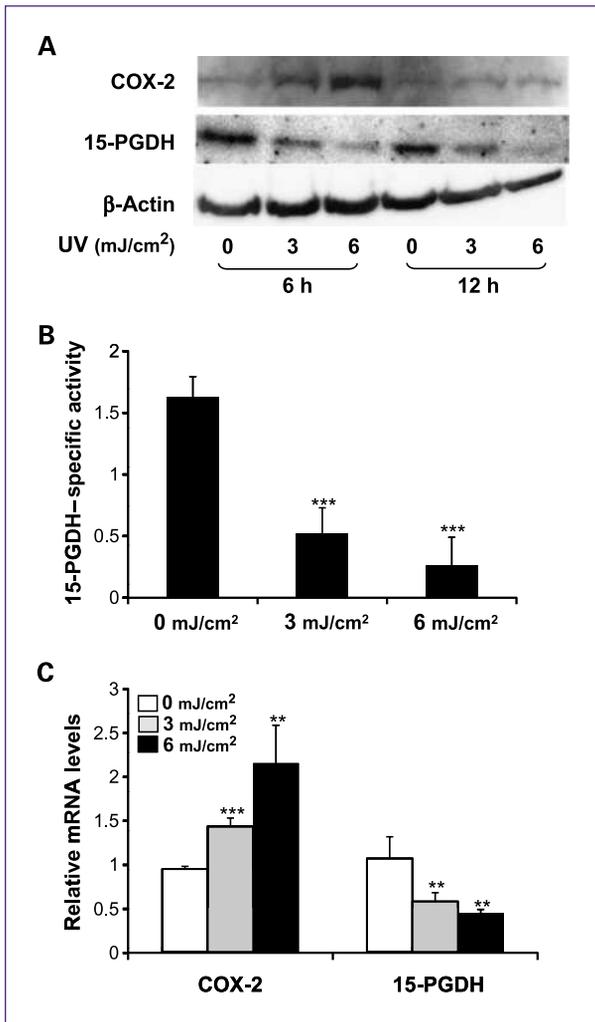Next, we attempted to elucidate the mechanism by which UVR exposure led to reduced expression of 15-PGDH. Slug,

Fig. 1. UVR treatment induces COX-2 and suppresses the levels of 15-PGDH in HaCaT cells. A, cells were sham treated or exposed to 3 or 6 mJ/cm^2 UV and harvested 6 or 12 h later. Cellular lysate protein (50 μg/lane) was loaded onto a 10% SDS-polyacrylamide gel, electrophoresed, and subsequently transferred onto a nitrocellulose membrane. Immunoblots were probed for COX-2, 15-PGDH, and β-actin. B, cells were sham treated or exposed to 3 or 6 mJ/cm^2 UV and harvested 12 h later. Cellular levels of 15-PGDH enzyme activity were determined as described in Materials and Methods. Enzyme activity is expressed as picomoles per minute per milligram of protein. Columns, means ($n = 5$); bars, SD. ***, $P < 0.001$, compared with sham-treated keratinocytes. C, cells were sham treated or exposed to 3 or 6 mJ/cm^2 UV and harvested 6 h later. Total RNA was isolated and quantitative real-time PCR was done. Values for COX-2 and 15-PGDH were normalized to values obtained for β-actin. Columns, means ($n = 4$); bars, SD. **, $P < 0.01$; ***, $P < 0.001$, compared with sham-treated keratinocytes.

a member of the Snail family of transcription factors, has been reported to be induced by UVR (35) and to suppress 15-PGDH transcription in lung cancer (36). Hence, we investigated whether Slug was responsible for UVR-mediated suppression of 15-PGDH in HaCaT cells. UVR led to rapid induction of Slug protein (Fig. 3A). To further evaluate the potential role of Slug in regulating 15-PGDH expression,

we determined whether UVR stimulated the binding of Slug to the 15-PGDH promoter. Repressive transcription factors (e.g., Snail family members) bind to a region of the 15-PGDH promoter that contains E-boxes (36, 37). ChIP assays were carried out using a primer set that included the 15-PGDH promoter segment containing E-boxes. As shown in Fig. 3B, treatment with UVR caused an ~1-fold increase in the binding of Slug to the 15-PGDH promoter. Next, it was important to evaluate whether Slug played a role in UVR-mediated downregulation of 15-PGDH expression. Silencing of Slug blocked UVR-mediated downregulation of 15-PGDH (Fig. 3C). Together, these results suggest that UVR-mediated induction of Slug is responsible for the downregulation of 15-PGDH transcription. Given these findings in HaCaT cells, we also evaluated whether UVR would induce similar effects in a model that more closely mimics human skin. Hence, the EpiDerm skin model, a three-dimensional highly differentiated model of the human epidermis, was used. These organotypic cultures were exposed to 0, 100, or 150 mJ/cm^2 UV and then harvested 6, 12, or 24 hours later. Western blot analysis was done for COX-2 and 15-PGDH (Fig. 4). Consistent with the findings in HaCaT cells, UVR treatment induced COX-2 while suppressing 15-PGDH protein levels. These effects were observed for up to 24 hours following UVR exposure.

UVR induces COX-2 and suppresses the levels of 15-PGDH in human skin

Based on the consistency of the UVR effects in two well-established preclinical models, we next conducted a clinical study to determine if these findings extended to human skin. As detailed in Materials and Methods, 10 subjects
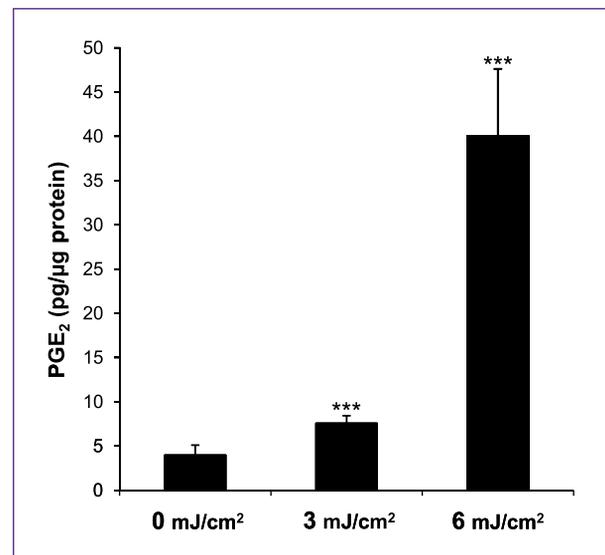

Fig. 2. UVR treatment stimulates PGE$_2$ production by keratinocytes. HaCaT cells were either sham treated or exposed to 3 or 6 mJ/cm^2 UV. The levels of PGE$_2$ were measured in the media 12 h after UV exposure. Columns, means ($n = 6$); bars, SD. ***, $P < 0.001$.
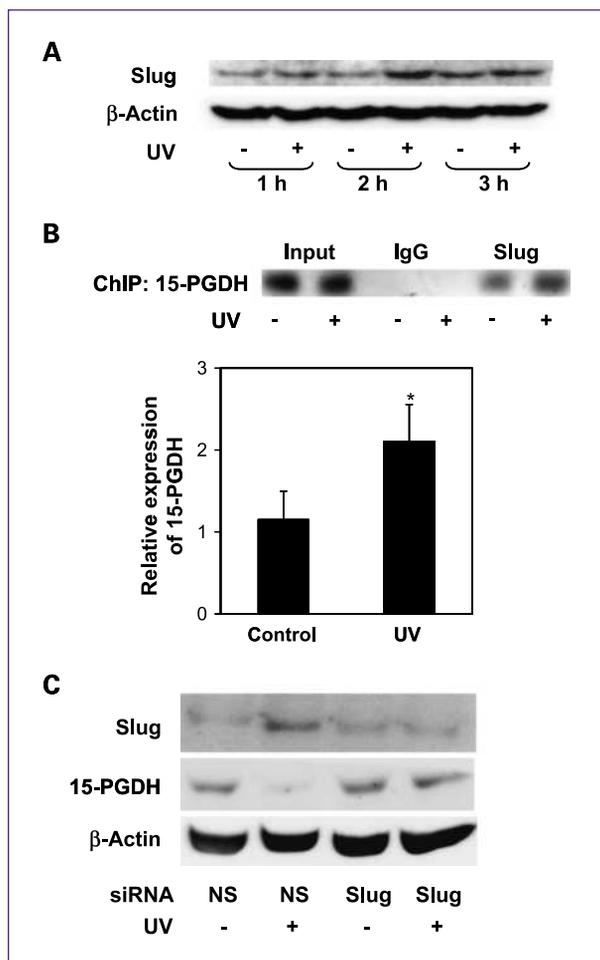
Fig. 3. Slug plays a critical role in UVR-mediated downregulation of *15-PGDH* transcription. A, HaCaT cells were sham treated or exposed to 6 mJ/cm² UV. Cells were harvested 1, 2, or 3 h after UV exposure. Cellular lysate protein (100 μg/lane) was loaded onto a 10% SDS-polyacrylamide gel, electrophoresed, and subsequently transferred onto a nitrocellulose membrane. Immunoblots were probed for Slug and β-actin. B, ChIP assays were done. HaCaT cells were sham treated or exposed to 6 mJ/cm² UV. Three hours later, cells were harvested. Chromatin fragments were immunoprecipitated with antibodies against Slug, and the *15-PGDH* promoter was amplified by PCR (top) or real-time PCR (bottom). DNA sequencing was carried out and the PCR product was confirmed to be the *15-PGDH* promoter. The *15-PGDH* promoter was not detected when normal IgG was used or the antibody was omitted from the immunoprecipitation step (data not shown). Columns, means (n = 3); bars, SD. *, $P < 0.05$. C, HaCaT cells were transfected with 100 pmol of Slug siRNA or nonspecific (NS) control siRNA. Following transfection, cells were sham treated or exposed to 6 mJ/cm² UV. Six hours after irradiation, cells were harvested for Western blot analysis. Cellular lysate protein (100 μg/lane) was loaded onto a 10% SDS-polyacrylamide gel, electrophoresed, and subsequently transferred onto a nitrocellulose membrane. Immunoblots were probed for Slug, 15-PGDH, and β-actin.

with light skin (Fitzpatrick types I-IV) were recruited. The skin was UV irradiated to establish the MED. Twenty-four hours later, each subject underwent biopsies of both unexposed skin (nonirradiated) and skin that most closely cor-

responded to 2 MED. Quantitative PCR was used to determine the amounts of COX-2 and 15-PGDH mRNAs in the biopsies. As shown in Fig. 5, UVR treatment led to marked increases in COX-2 mRNA with a corresponding reduction in the amounts of 15-PGDH mRNA in 9 of 10 subjects. UVR failed to either induce COX-2 or suppress the levels of 15-PGDH in the skin of subject 6. Skin type or the medications used did not provide a potential explanation for the difference in response observed in this subject.

Discussion

In this study, we found that UVR exposure suppressed the expression of 15-PGDH in human skin. This is important because 15-PGDH is the key enzyme for inactivating PGs including PGE₂ (23, 38). UVR is known to cause increased amounts of both COX-2 and PGs in the skin (4, 9, 10). Based on our results, it seems likely that the increased levels of PGs found in the skin following UVR exposure reflect reduced catabolism in addition to increased synthesis. In support of this possibility, a recent human study reported increased levels of PGE₂ in the skin 24 hours after UVB exposure in the absence of a similar increase in 13,14-dihydro-15-keto PGE₂, a catabolic product (10). Future studies will be needed to determine whether or not the UVR-mediated changes in COX-2 and 15-PGDH expression occur in the same cells. Previously, we showed that the levels of 15-PGDH were reduced in inflammatory bowel disease (39). Given that the levels of 15-PGDH are downregulated in both inflammatory bowel disease and UVR-exposed skin, it is highly likely that reduced PG catabolism will be found in a range of inflammatory conditions. Considering the importance of PGs in inflammation and carcinogenesis (3, 10, 40, 41), future studies should be done to evaluate the expression of 15-PGDH in other inflammatory conditions.
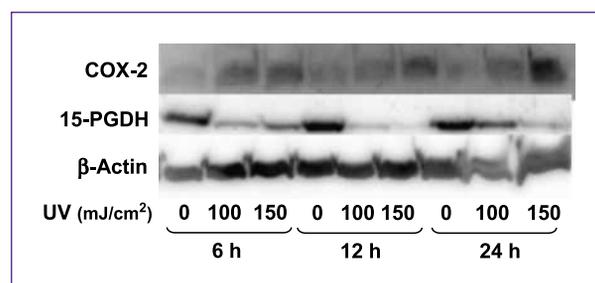

Fig. 4. Treatment with UVR induces COX-2 and suppresses the levels of 15-PGDH in the EpiDerm skin model. Organotypic cultures were exposed to 0, 100, or 150 mJ/cm² UV and then harvested 6, 12, or 24 h later. Cellular lysate protein (50 μg/lane) was loaded onto a 10% SDS-polyacrylamide gel, electrophoresed, and subsequently transferred onto a nitrocellulose membrane. Immunoblots were probed for COX-2, 15-PGDH, and β-actin as indicated.

Fig. 5. UVR induces COX-2 and suppresses 15-PGDH mRNA levels in human skin. Ten subjects with light skin (Fitzpatrick types I-IV) were recruited. The skin was UV irradiated to establish the MED. Twenty-four hours later, each subject underwent biopsies of both unexposed skin (sham-treated) and skin that corresponded to 2 MED (UV-treated). Total RNA was isolated and quantitative real-time PCR was done. Values for COX-2 and 15-PGDH were normalized to the values obtained for β-actin.
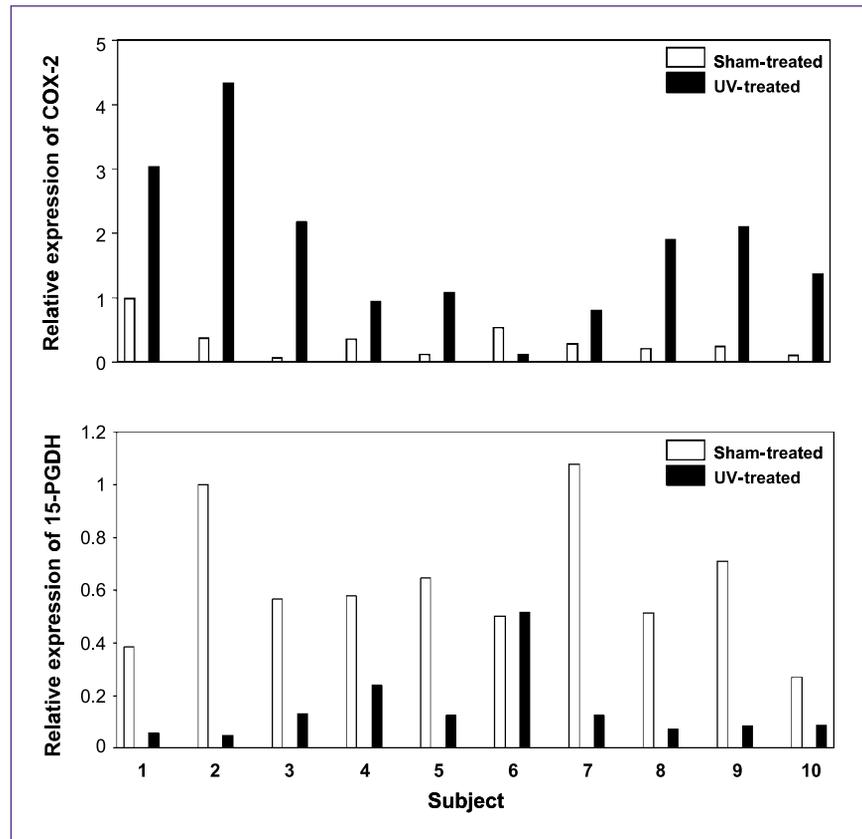
Additional studies were carried out to define the mechanism by which UVR suppressed the levels of 15-PGDH. Our results suggest that UVR suppressed the transcription of *15-PGDH*, leading to reduced levels of 15-PGDH mRNA and protein. We also report that suppression of 15-PGDH reflects UVR-mediated induction of Slug, a Snail family zinc-finger transcription factor. These findings are a logical extension of previous work. UVR is known to induce Slug in keratinocytes (35). Moreover, Slug-mediated suppression of *15-PGDH* transcription is believed to explain the reduced levels of 15-PGDH in non–small cell lung cancer (36). Slug and Snail bind to E-boxes in the *15-PGDH* promoter and thereby inhibit transcription (36, 37). In the current study, ChIP analysis indicated that UVR exposure stimulated the binding of Slug to a region of the *15-PGDH* promoter containing three E-boxes. To evaluate the functional significance of increased Slug binding, siRNA was used. Silencing of Slug blocked UVR-mediated downregulation of 15-PGDH. It is intriguing to note that Slug-knockout mice exhibit an attenuated cutaneous inflammatory response to UVR (42). The current findings suggest the possibility that UVR will cause less suppression of 15-PGDH in *Slug*-knockout mice, resulting in less PG-related skin inflammation.

The fact that coordinated changes in both PG synthetic and catabolic pathways occur in UVR-exposed skin suggests that elevated levels of eicosanoids are likely to play a significant role in the UV response. In fact, there is extensive evidence that UVR-mediated induction of PGE_2 is important in stimulating vasodilation, vascular permeability, and cell proliferation while inhibiting apoptosis and immune function (5, 10, 12, 43–45). Consistent with these effects, increased levels of PGE_2 seem to be important for wound healing (46). Inhibitors of COX-derived PGE_2 production including selective COX-2 inhibitors suppress several components of the acute inflammatory response to UVR exposure (44–47). As mentioned above, there is extensive evidence that PGs also play a significant role in the development of nonmelanoma skin cancer (5–7, 14–18). A number of different mechanisms may contribute to carcinogenesis. For example, it is hypothesized that UVR-mediated induction of PGE_2 levels protects against apoptosis, increasing the likelihood of DNA photoproducts becoming mutations (7). Recent studies have suggested that 15-PGDH behaves as a tumor suppressor for several tumor types (48–50). It is possible, therefore, that UVR-mediated downregulation of 15-PGDH will contribute to increased levels of PGs in the skin and thereby increase the risk of carcinogenesis. Based on this constellation of findings, it will be worthwhile to determine whether knocking out or overexpressing 15-PGDH in the skin affects either the acute or the chronic consequences of

UVR exposure. Inducers of 15-PGDH have been identified (51). Whether inducers of 15-PGDH will alter the acute or the chronic effects of UV exposure should be evaluated. In addition to PGs, some other eicosanoids including lipoxin A_4 are excellent substrates for 15-PGDH. It is possible, therefore, that downregulation of 15-PGDH will have significant effects independent of changes in PG levels. Taken together, it is likely that short-term elevation of PGE_2 in the skin following UVR exposure is an adaptive mechanism that enhances wound healing, whereas chronic elevation of PGE_2 promotes the development of nonmelanoma skin cancer. The results of the current study highlight the potential significance of UVR-mediated downregulation of PG catabolism in mediating these effects.

Disclosure of Potential Conflicts of Interest

Grant Support

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