UVB Irradiation-induced Activator Protein-1 Activation Correlates with Increased c-fos Gene Expression in a Human Keratinocyte Cell Line*

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The effects of UVB irradiation on transcription factor activator protein-1 (AP-1) DNA binding and AP-1 trans-activation were studied in a human keratinocyte cell line, HaCaT. UVB-induced AP-1 binding to a consensus AP-1 binding site was observed by gel shift assays with maximum stimulation at 12 h after UVB irradiation. A promoter region of the human collagenase-1 gene containing the same AP-1 binding sequence linked to a luciferase reporter gene was stably transfected into HaCaT cells. UVB irradiation significantly increased luciferase activity in these stably transfected cells, with maximum activity observed at 24 h after UVB irradiation. c-Fos and Jun D were identified by antibody clearing assays as the main components of the bound AP-1 complexes. Inhibition of transcription with actinomycin D and inhibition of protein synthesis with cyclohexamide significantly abrogated the effect of UVB on AP-1 DNA binding, indicating that transcription and translation were required for AP-1 activation. Northern and Western analyses revealed a correlation between increased AP-1 activity and accumulation of c-fos mRNA and c-Fos protein after UVB irradiation. UVB irradiation increased c-fos transcription in HaCaT cells stably transfected with a plasmid containing the human c-fos promoter driving a luciferase reporter gene. These results suggest that increased c-fos expression may play an important role in UVB-induced AP-1 activation in HaCaT cells.

The major cause of non-melanoma skin cancer is exposure to sunlight, most notably to the UVB (280–320 nm) part of the spectrum (1). The possible mechanisms of UV radiation-induced skin carcinogenesis are thought to be UV-induced genetic and epigenetic changes (2–4). Genetic changes, such as activation of oncogenes and inactivation of tumor suppressor genes, lead to tumor initiation (2, 3). Epigenetic changes, such as induced expression of certain genes that may be involved in cell proliferation, appear to play a role in tumor promotion (4–6). Although UVC (200–280 nm) is also a potent photocarcinogen, its biological significance may be less important, since it does not reach the earth’s surface (7). However, previous UV studies have been conducted mostly using 254 nm UVC. Those studies showed that UVC could induce the expression of number of genes, including c-fos and c-jun (4).

c-Fos and c-Jun are members of the activator protein 1 (AP-1) family, which is one of several transcription factors that mediate diverse gene expression induced by UVC irradiation (4). AP-1 can also be induced by TPA, growth factors, cytokines, and transforming oncoproteins (4). AP-1 is a protein complex that consists of families of Jun and Fos proteins. There are three Jun proteins (i.e. c-Jun, Jun B, and Jun D) and four Fos proteins (i.e. c-Fos, Fos B, Fra-1, and Fra-2). Jun proteins form homodimers or heterodimers with Fos proteins; however, Fos proteins cannot homodimerize. AP-1 binds to a consensus site, known as the TPA response element (TRE), in the promoters of AP-1-induced genes and mediates transcriptional activation of these genes (4).

Several lines of evidence supported a role for AP-1 in cell proliferation and tumor promotion. Its activity was enhanced when cells were stimulated by agents that promote proliferation (8). AP-1 was activated in tumor promotion-sensitive (P*) mouse JB6 epithelial cells, but not in tumor promotion-insensitive (P*) JB6 cells (9). Blocking tumor promoter-induced AP-1 activity inhibited neoplastic transformation (10). Previously we showed that blocking AP-1 transactivation in two malignant cell lines inhibited their ability to form squamous cell carcinomas upon subcutaneous injection into athymic nude mice (11). It has also been shown that UV irradiation leads to cell proliferation in vivo (12). The consequent effect of UVB-induced cell proliferation might lead to tumorigenesis (13). Huang et al. (14) reported that UVB irradiation induced AP-1 transactivation in a mouse epithelial cell line. In light of the evidence of a functional role for AP-1 activation in epidermal carcinogenesis, AP-1 activation may also play an important role in UVB-induced tumor promotion.

To date, most of the published research dealing with UV-induced signal transduction, as it relates to activation of AP-1, has involved the use of UVC irradiation. Since UVB is more relevant to sun-induced human skin cancers, and keratinocytes are a relevant cell type, this study deals with UVB and a human keratinocyte cell line, HaCaT (15). Although HaCaT is an immortalized cell line, these cells cannot induce tumors when injected into mice. Thus this cell line has been used
extensively in different studies dealing with regulation of the AP-1 family members (16), reactive oxygen species (17), apoptosis (18), and signaling pathways (19). The purpose of this study is to examine whether UVB irradiation induces AP-1 activation in HaCaT cells and to investigate the mechanisms involved in this induction.

**EXPERIMENTAL PROCEDURES**

**Plasmids and Reagents**—The following plasmids were used for transfection: AP-1 luciferase reporter plasmid (14), fos/luciferase plasmid (provided by Drs. Arai and Watanabe, University of Tokyo), pSV2-neo plasmid (20). The following probes were used for Northern blot analysis: a 2.2-kb EcoRI fragment of mouse c-fos cDNA from plasmid psfos-ks. pFos-ks was generated by excising a 2.2-kb EcoRI-SalI fragment of mouse c-fos CDNA from plasmid pc-fos-3 (22) and inserting the 2.2-kb fragment into the multiple cloning site of pBluescript II KS(+/-) (Stratagene, La Jolla, CA): a 0.75-kb PstI-XbaI fragment of human glyceraldehyde-3-phosphate dehydrogenase cDNA from plasmid pTZ-GAP (21). Dulbecco’s modified Eagle’s medium (DMEM), G418, Lipofectin, and LipofectAMINE were from Life Technologies, Inc. Fetal bovine serum was from JRH Biosciences (Lenexa, KS). Antibodies against AP-1 family members were from Santa Cruz Biotechnology (Santa Cruz, CA). Actinomycin D, cycloheximide, and luciferin were from Sigma. LipofectAMINE reagent was from Life Technologies, Inc. Fetal bovine serum was from JRH Biosciences (Lenexa, KS). Antibodies against AP-1 family members were from Santa Cruz Biotechnology (Santa Cruz, CA). Actinomycin D, cycloheximide, and luciferin were from Sigma.

**Cell Culture and UVB Irradiation**—A human keratinocyte cell line, HaCaT (15), was cultured in DMEM medium with 10% fetal bovine serum and 100 units/ml penicillin/streptomycin at 37 °C in an incubator containing 5% CO2. Stably and transiently transfected cells were cultured under the same conditions. For experiments, the cells were cultured to 80% confluence, then serum-starved for 30–36 h. The cells were then washed with phosphate-buffered saline and exposed to UVB without medium. A bank of two SP20 UVB lamps (National Biological Corp., Twinsburg, OH) with a peak emission at 313 nm were used. Control cells were mock-irradiated. After exposure to UVB, the cells were continually cultured in serum-free DMEM until the cells were harvested. Organotypic cultures were constructed as described previously (23) using HaCaT cells stably transfected with an AP-1 luciferase reporter plasmid (described below). Organotypic cultures were constructed and cultured for 7 days at the air-liquid interface to allow for formation of a stratified epithelial layer. Cultures were then switched to serum-free medium for 36 h, UVB-irradiated, and then incubated for a further 20 h in serum-free DMEM. The transfected HaCaT layer was then peeled off from the underlying collagen gel with forceps and then processed for luciferase assays as described below.

**Stable Transfection**—The HaCaT cells were cultured with DMEM in a 60-mm plate until they reached 50% confluence. For generating a stable transfectant containing a sequence from human collagenase-1 gene promoter (−73 to +63) with one endogenous AP-1 binding site driving a luciferase reporter gene, the cells were co-transfected in serum-free medium with 7.5 μg of AP-1 luciferase reporter plasmid and 0.75 μg of pSV2-neo selection plasmid in the presence of 30 μg of Lipofectin reagent. 24 h later, medium was then replaced with DMEM containing serum-free medium after 48 h, serum-starved and then harvested, and gel shift assays performed. The results indicated a significant increase in a dose-dependent manner. The

**Isolation of Nuclear Proteins, Gel Shift Assay, Antibody Clearing Assay**—Isolation of cell nuclear protein was carried out as reported previously (24). Gel shift assays were performed with nuclear protein and [32P]dCTP-labeled double strand 22-mer probes containing the AP-1 binding site TGAAGTCA (called TPA response element, TRE) (8). Detailed procedures were as described previously (24). Antibody clearing assays were performed by preincubating nuclear protein with various concentrations of antibodies against AP-1 family members at 4 °C for 2 h. Then the [32P]dCTP-labeled 22-mer TRE probes were added to the reaction at room temperature, and gel shift assays were performed.

**Luciferase Assay for AP-1 Transactivation or c-fos Gene Transcriptional Activation**—Total cellular protein from transfected cells was extracted with lysis buffer, and the luciferase activity was measured using a Monolight 3010 luminometer (Analytic Luminescence Laboratory, Sparks, MD) or a Beckman LS 5000TD scintillation counter (Beckman Instruments Inc.).

**RNA Extraction and Northern Analysis**—Total RNA was extracted, and Northern analyses were performed as described previously (27).

**Western Analysis**—Western analyses were carried out as reported previously (24). The

**RESULTS**

**UVB Induction of AP-1 DNA Binding**—To determine whether UVB could induce AP-1 binding to its target DNA, gel shift assays were performed with nuclear proteins extracted from UVB-irradiated and unirradiated HaCaT cells using a radiolabeled double strand 22-mer probe containing a consensus AP-1 binding sequence. We first performed a UVB dose response study to ask which UVB dose could induce AP-1 DNA binding using gel shift assays. As shown in Fig. 1A, an AP-1-DNA complex was found to exist in unirradiated cells. With increasing UVB dose, this basal AP-1 DNA binding activity was significantly increased in a dose-dependent manner. The
Elevated AP-1 DNA binding was detectable at 150 J/m² and was further increased at 400 J/m². We then carried out a time course study with an UVB dose of 250 J/m². As shown in Fig. 1B, AP-1 DNA binding was induced as early as 4 h after UVB irradiation with maximum induction occurring at 12 h. This binding gradually decreased to close to basal level within 20 h. The specificity of this complex was determined with competition assays using wild type and mutated TRE probes. The results indicated that the protein-DNA complexes were specific AP-1 protein-DNA complexes (data not shown).

**c-Fos and Jun D Were the Main Components of the UVB-induced AP-1-DNA Binding Complex, whereas Other AP-1 Members Were Minor Components**—Since the same DNA element can be bound by various AP-1 proteins with different affinities (4), we performed antibody clearing experiments to analyze the composition of the bound AP-1 complex(es). Prior to incubation with radiolabeled TRE probe, 4.5 μg of nuclear protein were preincubated for 2 h at 4 °C with various amounts (300, 600, and 900 ng) of antibodies as indicated by the triangles. Controls were preincubated with or without rabbit serum. The gel shift assays were performed. The results indicated that c-Fos and Jun D were the main components of the AP-1 complex and c-Jun, Jun B, Fos B, Fra-1, and Fra-2 were minor components of the AP-1 complex. Co, the sample without adding rabbit serum and antibodies.

Fig. 2. Composition of UVB-induced AP-1 complex that binds to the TRE. HaCaT cells were serum-starved 36 h and then washed with phosphate-buffered saline and irradiated with 400 J/m² UVB or mock-irradiated. At 12 h post-UVB, the cells were harvested. Prior to gel shift assays, 4.5 μg of nuclear protein were preincubated for 2 h at 4 °C with various amounts (300, 600, and 900 ng) of antibodies as indicated by the triangles. Controls were preincubated with or without rabbit serum. The gel shift assays were performed. The results indicated that c-Fos and Jun D were the main components of the AP-1 complex and c-Jun, Jun B, Fos B, Fra-1, and Fra-2 were minor components of the AP-1 complex. Co, the sample without adding rabbit serum and antibodies.

UVB induction of AP-1 transactivation—Although we showed that UVB could induce AP-1 DNA binding (Fig. 1), this did not necessarily mean that AP-1 was activated. To test whether UVB-induced AP-1 DNA binding could result in AP-1 transactivation, HaCaT cells were stably transfected with an AP-1 luciferase reporter plasmid. This plasmid contained a 136-base pair fragment from the human collagenase-1 gene promoter (−73 to +63) with one endogenous AP-1 binding site driving a luciferase reporter gene. An UVB dose response study using the stable transfectant showed induction of reporter gene expression by UVB (Fig. 4A). The pattern of UVB dose response for inducing AP-1 transactivation (Fig. 4A) was very similar to that for inducing AP-1 DNA binding (Fig. 1A). A time course further showed that peak induction occurred at about 24 h after 250 J/m² UVB (Fig. 4B).

All of the above experiments were performed with HaCaT cells growing in monolayer on plastic. To investigate whether the results obtained from the monolayer cultures reflected what was happening in the epidermis, we carried out AP-1 transactivation experiments using the stably transfected HaCaT cells grown in an organotypic culture model (23). This model system generates an epidermal skin equivalent by culturing air-exposed keratinocytes over a bed of collagen embedded with dermal fibroblasts. Similar to what is seen in normal skin, keratinocytes grown under these conditions form fully stratified epithelium. The stably transfected HaCaT cells were cultured over the collagen beds and UVB-irradiated. The results showed that UVB could induce AP-1 transactivation in the organotypic model (Fig. 4C), which indicated relevance to skin. UVB significantly increased c-Fos protein level—Since c-Fos and Jun D were the main components of UVB-induced AP-1-DNA binding complex, whereas other AP-1 members were minor components (Fig. 2), we tested whether UVB-induced AP-1 DNA binding and AP-1 transactivation correlated with expression of these AP-1 proteins. As shown in Fig. 5, Western analyses indicated that UVB significantly increased c-Fos protein levels. However, other AP-1 members did not show significant changes after UVB irradiation. These results implied that...
UVB-induced AP-1 Activation and c-fos Expression

UVB-induced c-fos gene expression might be an important mechanism of UVB-induced AP-1 activation in HaCaT cells.

UVB Significantly Increased mRNA Level and Transcriptional Activation of c-fos Gene—To further determine the mechanism of increased c-Fos protein after UVB, we examined effect of UVB on c-fos mRNA level in HaCaT cells. As shown in Fig. 6, Northern analysis demonstrated that c-fos mRNA significantly increased after UVB, indicating that increased c-Fos protein might be the result of increased c-fos mRNA. The results of UVB increasing both c-fos mRNA and protein (Figs. 5 and 6) were consistent with the observation that RNA and protein syntheses were required for UVB-induced AP-1 DNA binding (Fig. 3). To further determine the mechanism of increased c-fos mRNA after UVB, we stably transfected HaCaT cells with a fos/luciferase plasmid. This vector contains a fragment of the human c-fos promoter (–2404 to +141, including serum response element) driving a luciferase reporter gene. Luciferase activity was examined with total cellular protein isolated from transfected cells after 250 J/m² UVB treatment. The results showed a significantly increased luciferase activity with time after UVB (Fig. 7), supporting the idea that at least part of the increase in c-fos mRNA after UVB is due to transcriptional activation of the c-fos gene.

DISCUSSION

UVB is a major cause of human non-melanoma skin cancer (1). It is well known that UVB acts both as a tumor initiator and tumor promoter (28, 29). The AP-1 transcription factor is believed to be involved in tumor promotion (8–11). In this study, we demonstrated, for the first time, that UVB increased AP-1 DNA binding to a TRE in cultured human keratinocytes (Fig. 1). More significantly, we demonstrated that this in-
c-fos mRNA was significantly increased with the time after UVB (Fig. 6), which suggested a possible reason of UVB-increased c-Fos protein. The observation that requirement for transcription and translation (Fig. 3) correlated with increases in steady state levels of c-fos mRNA and protein (Figs. 5 and 6) indicates that UVB-increased AP-1 activation, including AP-1 DNA binding and AP-1 transactivation, may be primarily due to increased c-fos gene expression. Induction of c-fos transcription by UVC was observed in primary human skin fibroblasts (34). Schreiber et al. (35) reported that c-Fos was an essential component of the mammalian UVC response. They observed that transcriptional induction of the AP-1 target genes by UVC was almost absent in cells lacking c-fos gene, which correlated with a reduced UVC induction of AP-1 DNA binding and transactivation (35). Our findings indicated that increased c-fos expression may play an important role in UVB-induced AP-1 activation in HaCaT cells.

Although UVB irradiation leads to significantly increased c-fos mRNA (Fig. 5), it was not clear whether this increased message was due to transcriptional activation of the c-fos gene or stabilization of c-fos mRNA. To begin to answer this question, we transfected the cells with a plasmid containing a fragment of the human c-fos promoter driving a luciferase reporter gene and analyzed luciferase activity from cell extracts after UVB. Our results showed that UVB significantly stimulated c-fos gene transcription (Fig. 7). Thus, transcriptional activation of the c-fos gene was, at least in part, responsible for the increased c-fos mRNA and protein after UVB. However, we cannot rule out the possibility that c-fos mRNA stabilization could play a role as well. Similar results to ours have been reported in mouse epidermal cells (36).

In contrast to other studies, which reported a fast and transient induction of c-fos gene (37, 38), we observed in our system that c-fos mRNA and protein levels were increased later and stayed elevated for more than 12 h (Figs. 5 and 6). This difference could be explained by the fact that different cell lines (fibroblasts) and different extracellular stimulators (serum, UVC) were used. This observation was supported by Shah et al. (36) who reported similar results to ours using UVB and a mouse epithelial cell line. They observed that UVB induced an immediate early response of c-fos that was down-regulated within 2 h and a strong second phase of c-fos induction, which peaked at 8 h and returned to basal level after 24 h. They suggested that UVB-irradiated cells may release a factor with the ability to induce the second phase of c-fos induction. In addition, continuous expression of the c-fos gene has been reported in normal human skin under physiological conditions (33, 39).

The molecular mechanism of UVB-induced c-fos expression may be similar to that of serum (38, 40). Serum-induced c-fos transcription is through the serum response element, which is located in the promoter region of the c-fos gene (40, 41). It has been shown that the ternary complex factor (TCF), a transcription factor that binds to the SRE, is critical for triggering c-fos transcription by serum (41). Mitogen-activated protein kinase (MAPK) family, which includes ERK, JNK, and p38, plays an important role in activating TCF (41–43). ERK can activate TCF through phosphorylating the protein at serine 383 and serine 389 (41, 43). The activated TCF then induces c-fos transcription (41). Recent studies have shown that both JNK and p38, which are activated by UVC irradiation, are also able to phosphorylate the same major sites in TCF recognized by ERK and activate the TCF (44, 45). Thus, it appears that all three members of the MAPK family may participate in triggering transcription of the c-fos gene. Huang et al. (46) have reported that ERK was activated in UVB-irradiated mouse epithelial
cells. Assesa et al. (47) have shown that UVB caused differential stimulation of ERK and JNK activities in HaCaT cells. Our preliminary data indicated that UVB irradiation resulted in activation of JNK, ERK, and p38 kinases in HaCaT cells. Based on these results we speculate that alterations of activities of MAPK family members might be a possible mechanism through which UVB induces c-fos expression. It has been demonstrated that the atypical protein kinase C (aPKC) family was involved in UVB-induced AP-1 activation by using both Xenopus PKCα and mouse PKCζ dominant negative mutant constructs (14). It appears that MAPK are downstream of aPKC, since PKCζ has been found to bind to Ras, which is located upstream of MAPK (25). Thus it is possible that aPKC-MAPK pathway might be involved in UVB-induced c-fos expression. Experiments in progress are directed at exploring this possibility.

In conclusion, this study provides evidence that in HaCaT cells UVB irradiation can induce significant AP-1 DNA binding and AP-1 transactivation. Accumulation of c-fos mRNA and protein may be the main mechanism of UVB-induced AP-1 activation. Increased c-fos expression may be explained by UVB-induced transcriptional activation of the c-fos gene.

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