Ultraviolet-induced junD Activation and Apoptosis In Myeloblastic Leukemia ML-1 Cells

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The exposure of mammalian cells to UV irradiation induces the expression of immediate early genes such as c-jun and c-fos and activates the transcription factors AP-1 and NF-κB. JunD is one of the three members of the Jun family and shares some functional characteristics with c-Jun. In the present study, we found that the exposure of myeloblastic leukemia ML-1 cells to UV light (UVC) caused a significant increase in junD mRNA expression within 5 min that persisted for a period of 3 h. The activation of protein kinase C (PKC) with 12-O-tetradecanoylphorbol-13-acetate (TPA) also induced increases in junD expression similar to those of UV irradiation. In addition, UV irradiation- and TPA-induced increases in junD expression were completely abolished by GF-109203X, a PKC-specific inhibitor. UV irradiation activated intracellular signaling pathways including extracellular regulated kinase-2 (Erk-2), c-Jun N-terminal kinases-1 (JNK-1), and p38. However, TPA-induced activation of PKC affected only Erk-2 activity, and GF-109203X (a PKC inhibitor) markedly suppressed UV-induced Erk-2 activation. To further investigate the effect of UV-induced Erk-2 activation on the expression of junD mRNA, cDNA encoding mitogen-activated protein kinase kinase (MEK1) was overexpressed in ML-1 cells. The overexpression of MEK1 enhanced substantially junD expression in response to UV or TPA. In contrast, the suppression of Erk activation with PD98059, a specific inhibitor of MEK1, inhibited UV- and TPA-induced junD mRNA expression, UV-induced increases in caspase-3 activity and cell death. In addition, the overexpression of junD enhanced the UV irradiation-induced increases in caspase-3 activity and cell death. We conclude that UV irradiation-induced increases in junD expression in ML-1 cells are mediated through activation of the PKC-coupled Erk-2 signaling pathway and play an important role in ML-1 cell apoptosis.

The exposure of mammalian cells to UV light elicits a rapid transcriptional activation of immediate-early genes such as c-jun and c-fos (1). New products of c-jun and c-fos genes form a multimier known as transcriptional factor AP-1 as activator protein 1 (2–4). The activated AP-1 regulates expressions of its target genes including c-jun itself. The multimer of AP-1 is not only composed of c-Jun and c-Fos but also other members of the Jun and Fos family such as JunB (5), JunD (6, 7), and FosB. Similar to c-jun, the transcription of junB is activated when the cells are exposed to UV irradiation (8). However, little is known about either the effects of UV irradiation on junD expression or the involvement of specific cell signaling pathways in mediating this response.

Earlier studies suggest that the JunD protein shares some functional similarities with other members of the Jun family. First, this protein can form a heterodimeric complex with c-Fos and homodimeric complexes with other jun products (4, 6, 7). Second, it has the ability to bind to the cAMP response element (CRE) and to AP-1 consensus DNA sequences (4, 6, 7). Finally, some stimuli such as ionizing radiation, hypoxic-ischemic injury, okadaic acid, insulin-like growth factors, and alkylating mutagens can activate c-jun and junB expressions as well as junD expression (8–11). Our previous studies have demonstrated that the activation of protein kinase C (PKC) by TPA can induce junD expression (12). PKC isoforms have been divided into three categories on the basis of their structure and biochemical properties, including conventional PKC (cPKC), novel PKC (nPKC) and atypical PKC (aPKC). Recently, it has been shown that UV-induced cellular responses involve PKC activation (13, 14). Therefore, it is important for us to examine whether UV irradiation can cause overexpression of junD.

The activation of distinct cellular signaling pathways in many different cell types usually regulates gene expression through the activation of transcription factors. Recent studies have focused on identifying signaling molecules that are involved in UV irradiation-induced increases in transcription factor expressions. It has been shown in different cell types that UV irradiation activates three intracellular signaling cascades, e.g. extracellular regulated kinase (Erk), c-Jun N-terminal kinase (JNK), and p38 mitogen-activated protein kinase (15–17). JNK has been found to play a major role in transmitting signaling events from the cell membrane to the nucleus in a UV-induced rise in c-jun expression. JNK activation is much stronger than that of Erk or p38 in response to UV irradiation (16, 18–20). UV-induced activation of JNK results in an increase in c-jun gene expression and activation of the c-Jun protein (21–23). Erk is also involved in UV-induced immediate-early gene activation because the UV-induced increase in c-jun

PKC: Erk, extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinase; PBS, phosphate-buffered saline; TPA, 12-O-tetradecanoylphorbol-13-acetate; MAP, mitogen-activated protein; MAPK, MAP kinase; MEK, MAPK/Erk kinase; GST, glutathione S-transferase; ATF-2, activating transcription factor 2; MBP, maltose-binding protein; CMV, cytomegalovirus.

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§The abbreviations used are: AP-1, activator protein 1; PKC, protein kinase C; cPKC, conventional PKC; nPKC, novel PKC; aPKC, atypical PKC; Erk, extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinase; PBS, phosphate-buffered saline; TPA, 12-O-tetradecanoylphorbol-13-acetate; MAP, mitogen-activated protein; MAPK, MAP kinase; MEK, MAPK/Erk kinase; GST, glutathione S-transferase; ATF-2, activating transcription factor 2; MBP, maltose-binding protein; CMV, cytomegalovirus.
expression can be inhibited by pretreatment of cells with PD98059, a specific inhibitor of the Erk signaling pathway (24). Thus, it is necessary to identify which signaling pathway(ies) mediates UV irradiation-induced increases in junD expression. In the present study, we investigated the signaling pathway in myeloblastic ML-1 cells that mediates increases in junD mRNA expression in response to UV irradiation and TPA stimulation. Our results indicate that the PKC-coupled Erk-2 signaling pathway is responsible for the transmission of UV-induced signaling events resulting in a high level of expression of junD mRNA.

EXPERIMENTAL PROCEDURES

Cell Culture and Treatment—Human myeloblastic leukemia ML-1 cells were cultured in conditions as described (12). Briefly, ML-1 cells were cultured in RPMI 1640 medium containing 7.5% heat-inactivated fetal bovine serum (Invitrogen) in a humidified incubator supplied with 5% CO2 at 37 °C. Cells were passed at a seeding density of 3 × 105 cells/ml. Before treatment with UV irradiation or drugs, cells were synchronized by serum-deprivation in RPMI 1640 medium containing 0.3% fetal bovine serum for 36 h. They were then exposed to UVC light for 5 min and terminated by proteinase K digestion. Cell number was determined with a detection assay kit (CLONTECH). ML-1 cells (1 × 106) were exposed to UVC light. This similarity suggests that UV-induced rise in junD expression may require activation of a PKC-linked signaling pathway.

UV Irradiation-induced junD mRNA Expression—We first determined whether UV irradiation affected junD mRNA expression in ML-1 cells following serum deprivation for 36 h, which synchronized the cell cycle at the G1 phase. This was done because previous studies revealed that junD expression level was low under this condition (12). Using Northern analysis, junD expression was detected at 5, 30, 60, and 180 min after UV exposure. UV irradiation markedly increased junD mRNA expression compared with that in the control cells (Fig. 1).
109203X, a selective inhibitor of cPKC. In both cases, UV- and TPA-induced \textit{junD} expressions fell close to the basal level in cells pre-incubated with 1\(\mu\)M GF-109203X (Fig. 2, B and C), indicating that PKC activation is a component of the signaling pathway mediating UV- and TPA-induced increases in \textit{junD} expression.

Effects of UV Irradiation and TPA on Intracellular Signal Pathways—To further characterize downstream events involved in a UV-induced rise in \textit{junD} expression, JNK, Erk, and p38 kinase activities were measured in response to UV irradiation. We found that all three limbs of the MAP kinase cascade were activated by UV irradiation. JNK-1, ERK-2, and p38 Kinase activities quickly increased within 5 min after UV irradiation. However, the time courses of activation were variable. JNK-1 and p38 reached peak levels at 30 min followed by declines lasting from 1 to 3 h (Fig. 3, A and B). However, UV increased Erk-2 activity to a high level that remained stable during the entire observation period (Fig. 3, C). It should be noted that the time courses for UV-induced Erk-2 activation and increases in \textit{junD} expression are very similar to one another (Fig. 1).

Previous studies showed that PKC activation by TPA stimulates JNK, Erk, and p38 signaling pathways. Unlike UV irradiation, TPA induces in some cell types a much stronger activation of Erk kinase than that of JNK or p38 (13). To determine whether a specific MAP kinase pathway mediates UV-induced \textit{junD} expression, the difference was determined between TPA- and UV-induced MAP kinase activations. When ML-1 cells were treated with 1 nM TPA, Erk-2 activity dramatically increased throughout the entire observation period (Fig. 4, A) with a pattern very similar to that induced by UV (Fig. 3, C). However, TPA had a much weaker activation effect on both JNK-1 and p38 (Fig. 4, B and C). These results strongly suggest that the MAPK signaling pathway containing Erk-2 kinase is possibly a mediator of UV-induced increases in \textit{junD} expression situated downstream from PKC stimulation.

Effect of Suppressing MEK on Erk-2 Activation and \textit{junD} Expression—In the Erk signaling pathway, Erk is directly activated by MAPK kinase (MEK1), whereas MEK1 is activated induced Erk-2 activation (Fig. 5B). However, UV-induced JNK-1 and p38 activation were unaffected by the inhibition of PKC activity by GF-109203X (Fig. 5, C and D). These results further indicate that PKC (possibly cPKC) plays an important role in mediating UV-induced Erk activation in ML-1 cells.

Effect of Suppressing MEK on Erk-2 Activation and \textit{junD} Expression—In the Erk signaling pathway, Erk is directly activated by MAPK kinase (MEK1), whereas MEK1 is activated...
further upstream by Raf-1. Upstream activators of Raf-1 in this pathway include Ras-1 and PKC. To further determine the involvement of the Erk signaling pathway in UV-induced junD expression, PD98059 (25 μM), a selective inhibitor of MEK1 activation, was applied to ML-1 cells for 20 min prior to UV or TPA exposure. The inhibition of MEK1 activity decreased both UV- and TPA-induced Erk-2 activation to the control level (Fig. 6, A and B). However, a blockade of MEK1 activation had no effect on the UV-induced rise in JNK-1 and p38 activities (Fig. 4).
These results are fairly consistent with previous data showing that the inhibition of PKC activity by GF-109203 did not affect JNK-1 and p38 activities. In addition, the inhibition of MEK1 activity by PD98059 completely suppressed UV- and TPA-induced \textit{junD} expression (Fig. 6, E and F). These results provide additional support for the hypothesis that Erk-2 activation is a signaling event situated downstream from PKC stimulation in the signaling pathway that mediates the UV-induced rise in \textit{junD} expression.

**Effect of Overexpression of MEK1 on \textit{junD} Expression**—To confirm the role of the Erk signaling pathway in UV-induced increases in \textit{junD} expression, an exogenous MEK1 gene was inserted and overexpressed in ML-1 cells. First, a β-galactosidase control vector was transfected into ML-1 cells by electroporation to determine the expression efficiency. Galactosidase activity in transfected ML-1 cells was significantly increased compared with control cells, indicating that the transfection method was appropriate for these cells (Fig. 7A). Thus, a full-length MEK1 sequence contained in the pcDNA III (FL-MEK1-EE) vector was inserted with electroporation. Following transfection, basic Erk-2 activity was obviously elevated relative to that in non-transfected cells, and the baseline expression of \textit{junD} was also significantly increased (Fig. 7, B and C). Moreover, UV-induced increases in Erk-2 activity and \textit{junD} expression in MEK1-transfected cells were significantly larger than in non-transfected cells (Fig. 7, B and C). However, MEK1 overexpression did not affect JNK-1 activity (Fig. 7D) and p38 activity (data not shown). In comparison, the transfection of a constitutive positive JNKK1 gene (\textit{γJNKK1-KD}, constructed in pcDNA III) into ML-1 cells resulted in the overexpression of JNKK1 directly upstream from JNK but had no significant effect on \textit{junD} expression, although it increased the baseline activity of JNK-1 (Fig. 7, D and E). All of these results consistently showed that the overexpression of MEK1 selectively enhanced Erk-2 activity and \textit{junD} expression. The results provide further evidence in ML-1 cells that the Erk signaling pathway is a downstream mediator of PKC activation in UV-induced \textit{junD} expression.

**Effects of the Suppression of Erk Activation and the Overexpression of \textit{junD} on UV-induced ML-1 Cell Death**—The effect of the suppression of Erk activation on UV irradiation-induced cell death was studied by treating the cells with a MEK1 inhibitor. PD98059 (25 μM) was added 20 min prior to UV irradiation. Cell viability was determined 8 h after UV irradiation using trypan blue exclusion to evaluate the rate of cell death. The inhibition of Erk activation markedly reduced cell death induced by UV irradiation (Fig. 8, A). In addition, cellular apoptotic response was evaluated based on measurements of caspase-3 activity. A time course of UV irradiation-induced caspase-3 activation is shown in Fig. 8B. The apoptotic response to UV irradiation in the presence and absence of Erk inhibition was determined 6 h after UV irradiation. UV-in-
duced increases in caspase-3 activity were significantly decreased when cells were pretreated with the MEK inhibitor (Fig. 8C). The functional role of junD on UV irradiation-induced cell death was observed by the overexpression of full-length cDNA encoding JunD. CMV-junD was inserted into ML-1 cells by electroporation, and the empty CMV vector was also transfected into ML-1 cells as a control. After culturing for 48 h, transfected cells were exposed to UV irradiation. The UV-induced death rate of junD transfected cells was markedly increased, and UV-induced caspase-3 activity was also significantly increased in junD transfected cells compared with empty vector transfected cells (Fig. 8, D and E). Results obtained from these experiments were consistent with the expression pattern of junD induced by UV irradiation, suggesting that Erk activation-linked increases in junD expression play an important role in UV irradiation-induced ML-1 cell apoptosis.

**DISCUSSION**

In the present study, we demonstrated that the exposure of ML-1 cells to UV irradiation significantly increased junD
mRNA expression. The pattern of this increase is similar to the increases in \textit{junD} expression resulting from PKC activation by TPA. Both UV- and TPA-induced \textit{junD} expression can be blocked by the pretreatment of cells with a PKC inhibitor, GF-109203X. These results indicate that certain membrane-linked PKC isoforms are components of UV- and stress-induced signaling pathways. PKC isoforms are divided into cPKC (including PKC\textgreek{a}, PKC\textgreek{b}I, PKC\textgreek{b}II, and PKC\textgreek{g}), nPKC (including PKC\textgreek{b}, PKC\textgreek{h}, PKC\textgreek{\eta}, PKC\textgreek{i}, and PKC\textgreek{\epsilon}), and aPKC (including PKC\textgreek{\zeta} and PKC\textgreek{\lambda}). Recent studies have shown that PKC is involved in UV-induced cellular responses. For example, UV irradiation can cause the translocation of some PKC subtypes (PKCe and PKCb) to the cell membrane, which is required for UV-induced activation of Erk and JNK (13). In addition, UV-induced AP-1 activation can be blocked by the expression of a dominant negative mutant PKC\textgreek{\alpha} (14). Although the present study did not identify which PKC isoform(s) must be activated for UV exposure to induce activation of \textit{junD} expression, both cPKC and nPKC (especially cPKC) seem to play an essential role in this event. First, the UV-induced \textit{junD} expression pattern was similar to that in TPA-stimulated cells (Figs. 1 and 2A) (27, 28). Second, pretreatment with GF-109203X selectively blocked cPKC activity and completely prevented UV-induced \textit{junD} expression (Fig. 2C) (29). Finally, UV-induced Erk-2 activation was also blocked by the PKC inhibitor GF-109203X (Fig. 5A). In addition, the hypothesis is supported by a recent report that demonstrates that cPKC and nPKC activation are involved in mediating a cellular response to hyper-osmotic stress (28). However, further investigation is necessary to identify which PKC isoforms are involved in UV-induced \textit{junD} expression.

Previous studies of \textit{c-jun} gene expression suggest that UV irradiation can strongly activate the JNK signaling pathway resulting in increases in \textit{c-jun} expression (17, 30). JNK activation contributes in turn to both \textit{c-jun} transcriptional activation and protein phosphorylation (28, 31, 32). Indeed, JNK, Erk, and p38 signaling pathways were activated by UV irradiation in ML-1 cells. However, our results indicate that JNK and p38 may not play roles in events downstream from PKC to mediate UV-induced activation of \textit{junD} expression. In fact, the time course of UV-induced Erk activation matches the time course of UV-induced \textit{junD} expression (Figs. 1 and 3C). On the other hand, even though a PKC inhibitor, GF-109203X, nearly completely blocked Erk activation induced by UV irradiation and TPA as well as \textit{junD} expression, it had no inhibitory effect on UV-induced increases in JNK and p38 activity. Our evidence to support the hypothesis that Erk is the downstream mediator of PKC activation includes the following facts. 1) Down-regulation of PKC with GF-109203X selectively blocked Erk activation in response to UV and TPA stimulation. 2) Selective inhibition of the Erk signaling pathway by PD98059, a selective inhibitor of MEK (a MAPK kinase immediate upstream of Erk), suppressed Erk-2 activity to the basal level and prevented UV- and TPA-induced increases in \textit{junD} expression (Fig. 6). 3) The overexpression of the exogenous MEK1 gene in ML-1 cells increased Erk activity and enhanced \textit{junD} expression in both
control and UV- and TPA-induced cells (Fig. 7). In addition, the inhibition of Erk activation by PD98059 effectively suppressed UV irradiation-induced caspase-3 activity and ML-1 cell death (Fig. 8). These results consistently demonstrate that the Erk signaling pathway is located downstream from PKC and plays an important role in mediating UV-induced junD expression in ML-1 cells.

Our conclusion is consistent with recent studies showing the involvement of the Erk signaling pathway in c-jun activation. In NIH 3T3 cells the application of wortmannin, an inhibitor of phosphatidylinositol 3-kinase, blocks UV-induced JNK activation without affecting UV-induced increases in c-jun expression (24). The inhibition of the Erk signaling pathway with PD98059 suppresses UV-induced increases in c-jun mRNA level and c-Jun protein expression (24). The overexpression of wild type Erk-2 causes 46–140-fold increases in UV-induced AP-1 activity. Conversely, the introduction of a dominant negative Erk-2 into cells suppressed both UV-induced Erk and AP-1 activation (14).

A remaining question is how does PKC stimulation by UV result in Erk activation. The pathway that leads to Erk activation can be triggered by a variety of stimuli (including UV irradiation). It is known that membrane activation of Ras and PKC during UV exposure occurs earlier than Erk stimulation. Therefore, it is possible that UV irradiation induces Erk activation by either stimulating Ras or PKC or both. Our data imply that, in ML-1 cells, PKC activation instead of the Ras pathway may be an essential mediator in the transmission of UV stimulation to Erk because Erk activation by UV irradiation was completely abolished when PKC activity was inhibited by GF-109203X (Fig. 5A). This conclusion is consistent with other studies (27, 33, 34), indicating that PKC is involved in the transmission of other stress stimuli such as oxygen-stress (33, 34) and hyperosmotic stress (27), resulting in activation of the Erk pathway.

As a member of the Jun protein family, JunD shows functional similarity to c-Jun (4, 6, 7). The overexpression of c-jun...
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induces apoptosis in growth factor-deprived cells (35). The expression of the dominant negative mutant of c-Jun or the inhibition of c-Jun by specific antibodies can protect neuronal cells from apoptosis induced by growth factor withdrawal (36, 37). It is also known that UV irradiation induces inhibition of c-Jun function by specific antibodies can protect expression of the dominant negative mutant of c-Jun or the induction of apoptosis in growth factor-deprived cells (35). The experiment shows that increases in junD expression of ML-1 cells may play a compensatory role in eliciting UV-induced apoptosis despite c-jun deficiency, although the effect of UV-induced junD expression on cellular function was not determined here. Nevertheless, this question warrants future investigation. We found that the overexpression of junD enhances UV-induced increases in caspase-3 activity and cell death (Fig. 8). This result indicates a functional role of increased junD expression in response to UV irradiation.

In conclusion, our results indicate that, in ML-1 cells, UV irradiation-induced activation of junD expression and its activation are mediated by a PKC-coupled Erk signaling pathway. The sequential responses to UV irradiation result in ML-1 cell death. These findings also extend our knowledge about the cellular signaling mechanisms that mediate UV-induced increases in immediate early gene expression.

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