Exposure of mammalian cells to UV light causes initial changes in the cell membrane, induces phosphorylation and clustering of growth factor/cytokine receptors, and activates the Jun N-terminal kinase/stress-activated protein kinase (JNK/SAPK) signaling pathway leading to programmed cell death (apoptosis). In this study, we found that an early event in the cell membrane of myeloblastic leukemia (ML-1) cells was the vigorous activation of the voltage-gated K⁺ channel by UV irradiation. The strong enhancement by UV irradiation of K⁺ channel activity in the cell membrane subsequently activated the JNK/SAPK signaling pathway and resulted in myeloblastic leukemia cell apoptosis. Suppression of UV-induced K⁺ channel activation with specific channel blockers prevented UV-induced apoptosis through inhibition of UV-induced activation of the proteins SEK (SPA2 kinase) and JNK. However, suppression of K⁺ channel activity could not protect cells from etoposide-induced apoptosis, which bypasses the membrane event. Elimination of extracellular Ca²⁺ had no effect on the UV-induced and K⁺ channel-mediated JNK/SAPK activation. Thus, we have identified a novel mechanism in which activation of K⁺ channels by UV-irradiation upstream of SEK and SAPK/JNK mediates UV-induced myeloblastic cell apoptosis.

Exposure of mammalian cells to UV irradiation causes programmed cell death and cancers. Early responses to UV irradiation include the activation of transcription factors, Ap-1 and NF-κB (1, 2), and of immediate early genes, c-fos and c-jun (3, 4). This activation, which is known as the UV response, is mediated by activation of intracellular signaling pathways that are shared with growth factors. Erk1/2, JNK/SAPK, and p38 are three mitogen-activated protein kinase pathways that can be activated by UV irradiation (5, 6). The degree of activation, however, varies. UV irradiation strongly increases JNK/SAPK activity but only modestly increases Erk1/2 activity in opposed to growth factors such as epidermal growth factor (7–10).

What upstream events of this signaling transduction are induced by UV irradiation? Ras, a small G protein and transmitting signal from membrane to cytoplasm, is activated by UV irradiation and mediates UV-induced activation of JNK, Erk, and transcription factors (6, 11–14). Src, a nonreceptor tyrosine kinase, is stimulated by UV irradiation (13). Exposure to UV light induces clustering and internalization of cell surface receptors for epidermal growth factor, tumor necrosis factor, and interleukin 1. Inhibition of clustering or receptor down-regulation attenuates the response to UV (7). UV irradiation induces ligand-independent activation of numerous receptor tyrosine kinases such as epidermal growth factor, platelet-derived growth factor and insulin receptors, and protein-tyrosine kinases at the inner side of the plasma membrane (13, 15–18). Other membrane-associated proteins, the protein-tyrosine phosphatases, can be inhibited with UV irradiation by targeting an essential -SH group in the tyrosine phosphatase. This results in inhibition of dephosphorylation and enhancement of autophosphorylation of epidermal growth factor receptor and platelet-derived growth factor receptor (18). It has been demonstrated in enucleated cells that UV activation of NF-κB and JNK does not require a nuclear signal (19). These two observations, the full response of enucleated cells to UV irradiation and the involvement of membrane-associated proteins in the UV response, strongly suggest that important UV-induced cell events probably occur through initiation of conformational changes in the plasma membrane.

Several recent studies have implied that potassium (K⁺) plays an important role in the regulation of programmed cell death. A bacterial pore-forming cytolytic, staphylococcal α-toxin, which selectively permeabilizes plasma membranes for monovalent ions, appeared to induce apoptosis (20). In contrast, diminishing the normal K⁺ electrochemical gradient completely nullified the ability of the anti-Fas antibody to induce apoptosis in Jurkat cells (21). Apoptotic cells and shrunken cells have a much lower intracellular K⁺ concentration compared with normal cells (22–23). Furthermore, both DNA autodigestion and nuclease activity of thymocytes are suppressed by an increase in extracellular K⁺ concentration in a dose-dependent manner. The complete inhibition can be reached at a concentration of 150 mM extracellular K⁺, close to the intracellular K⁺ concentration found in normal cells (23).

The question that naturally arises, then, is in regard to the existence of a relationship between K⁺ channel activity and UV irradiation-induced apoptosis in ML-1 cells. Because voltage-gated K⁺ channel activity involved in cell proliferation (24, 25) is regulated by growth factors (26) and is associated with Src-tyrosine kinase (27), we propose that activation of the K⁺ channel can mediate UV irradiation-induced apoptosis. To address this hypothesis, we first observed the effects of UV-C light on the K⁺ channel in myeloblastic leukemia cells (ML-1) by using whole-cell and cell-attached patch recording techniques. Then, we investigated the role of K⁺ channels in UV-induced cell death. Finally, we examined the effect of K⁺ channel activity on UV-stimulated JNK pathway. Our results show...
that UV irradiation activated K+ channels at both whole-cell and single-channel levels. Blockade of K+ channels with 4-aminoypyridine (4-AP) almost completely prevented UV-induced apoptosis and suppressed UV-stimulated JNK pathway, indicating that UV-activated K+ channels do mediate apoptosis in myeloblastic leukemia cells.

**MATERIALS AND METHODS**

**Cell Culture**—ML-1 cells originally isolated from an acute myeloblastic leukemia patient were received as a generous gift from Dr. R. W. Craig (Dartmouth Medical School, NH). All myeloblastic leukemia cells were grown in Roswell Park Memorial Institute (RPMI) 1640 culture medium containing 7.5% heat-inactivated fetal bovine serum and 25 mM HEPES buffer. Cells were grown in suspension culture in a humidified incubator at 5% CO2, 37°C. FDC-P1 murine myeloid progenitor cells were grown in RPMI 1640 culture medium containing 7.5% heat-inactivated fetal bovine serum and 10% conditioned medium from WEHI-3b cells as a source of interleukin 3.

**Apoptosis Induction**—Myeloblastic leukemia cells at a concentration of 3 × 105 cells/ml were incubated with complete culture medium. K+ channel blockers were added into the culture medium to a final concentration of 2.0 mM. For UV irradiation experiments, cells were placed in a tissue culture hood at a distance of 60 inches from the UV-C light source and exposed at an intensity of 40 mW/cm² for 3 to 8 min (60 to 72 J/m²). For exposure to etoposide (an apoptosis inducer), a stock solution of 10 mg/ml etoposide was added to the culture medium at a final concentration of 20 μM. After etoposide and UV treatments, cells were incubated at 37°C in 5% CO2 for 15 to 24 h. Cell viability was measured using the trypan blue dye exclusion method.

**Apoptosis Detection Assays**—Cell apoptosis was detected by DNA fragmentation and nuclear staining with ethidium bromide/acridine orange. To determine internucleosomal DNA cleavage, myeloblastic cells were washed twice with phosphate-buffered saline. Lysis buffer (200 mM Tris-HCl, pH 8.0, 100 mM EDTA, 1% SDS, and 100 μg/ml proteinase K) was added, and cells were then incubated for 4 h at 55°C. The nuclear lysates were extracted twice with an equal volume of phenol (25/24). DNA was precipitated with 0.6 volume of isopropanol, incubated overnight at −20°C, and centrifuged at 13,000 × g for 10 min at 4°C. The DNA pellet was dried and dissolved in TE buffer (10 mM Tris-HCl, pH 7.5, 1 mM EDTA) containing 20 μg/ml RNase A and incubated for 1 h at 37°C. The DNA was extracted with an equal volume of phenol/chloroform/isomyl alcohol (25/24:1). DNA samples were analyzed by electrophoresis on 1.5% agarose gels, and the results were visualized by staining with 1 μg/ml ethidium bromide. Gel-purified DNA was digested with a restriction enzyme marker. Nuclear staining with ethidium bromide and acridine orange was done by adding 2 μl of dye mixture containing 100 μg/ml each acridine orange and ethidium bromide to 25 μl of cell suspension. Cell populations were scored according to color using a UV-fluorescence microscope (Nikon). Nuclei staining green have not lost membrane integrity. In contrast, myeloblastic cells in which the nuclei stained orange have lost membrane integrity. Apoptotic cells can be distinguished from nonapoptotic cells on the basis of the absence or presence of nuclear condensation/fragmentation.

**Immunoblotting and Kinase Assays**—SEK-1 (SPAK kinase 1) activity was determined by measuring the level of SEK-1 phosphorylation with Western blotting using SEK-1 antibody (1:1000) against phosphorylated SEK-1 (New England Biolabs, Beverly, MA). After proper treatments, 1 × 106 cells (5 × 105 cells/ml) were lysed in 20 μl of Laemmli buffer. Western blotting was performed using the same protocol as described below. Phospho-SEK-1 levels were quantified by measuring film densities with a densitometer.

JNK-1 and p38 activities were measured by an immunocomplex kinase assay with GST-ATF-2 as the substrate (28, 29). Briefly, ML-1 cells (7 × 105 cells) were washed once with ice-cold phosphate-buffered saline, then lysed with 1 ml of lysis buffer (20 mM Tris-HCl, pH 7.5, 137 mM NaCl, 1.5 mM MgCl2, 2 mM EDTA, 10 mM sodium pyrophosphate, 25 mM β-glycero-phosphate, 10% glycerol, 1% Triton X-100, 1 mM sodium orthovanadate, 1 mM phenylmethylsulfonyl fluoride, 10 μg/ml leupeptin). Cell lysates were incubated on ice for 10 min and then precleared by centrifugation at 13,000 × g for 25 min. JNK-1 or p38 proteins were immunoprecipitated with 0.5 μg of rabbit polyclonal antibody against JNK-1 or p38 (Santa Cruz Biotechnology, Santa Cruz, CA) and protein A-Sepharose beads (Sigma). The immunocomplex was washed three times with lysis buffer and twice with kinase buffer (20 mM HEPES, pH 7.4, 1 mM MgCl2, 5 mM β-glycerophosphate, 100 mM sodium orthovanadate, and 2 mM dithiothreitol) and resuspended in 50 μl of kinase buffer. One μg of GST-ATF-2 (Santa Cruz Biotechnology) was added to 30 μl of the immunocomplex. The kinase reaction was initiated by adding 2 μl of ATP mixture (20 μM ATP and 10 μCi of γ-32P/ATP (Amersham Pharmacia Biotech). The reaction proceeded at room temperature for 5 min before it was terminated by adding 30 μl of NaOH (250 mM). Phosphorylated proteins were transferred to a polyvinylidene difluoride membrane (Millipore) and incubated with the same antibodies (1:5000) used for JNK-1 or p38 immunoprecipitations. The membranes were then incubated with goat anti-rabbit immunoglobulin IgG conjugated with alkaline phosphatase (1:10,000) (Santa Cruz Biotechnology). Secondary antibodies were detected with a Phototope-Star Western blot detection kit (New England Biolabs).

**RESULTS**

**UV Irradiation Stimulates K+ Channel Activity**—Changes in cell membrane K+ channel activity can mediate functional adaptation to a variety of chemical and physical stresses through membrane voltage stabilization and maintenance of salt and water balance. We found that cytokine-mediated stimulation of proliferation in myeloblastic ML-1 cells is associated with increases in K+ channel activity. This channel activity is sensitive to inhibition by 4-AP but less sensitive to inhibition by Ba2+ and tetraethylammonium (TEA) (24). Using the nystatin-perforated whole cell technique, the whole-cell current was activated by depolarization of the membrane potential from a holding potential of −60 to +80 mV in 20-mV increments. Upon exposure of ML-1 cells to UV-C light for 1 min, the amplitude of the K+ current increased markedly. UV-evoked K+ current was sensitive to 4-AP and was completely blocked by 2 mM 4-AP (Fig. 1, A and B). The time course showed that the amplitude of the K+ current doubled within 1 min after exposure to UV light and reached the maximal amplitude within 5 min. In the presence of 4-AP, UV stimulation of K+ currents was blocked, following the time course showed (Fig. 1C).

To further confirm the effect of UV irradiation on single K+ channel activity, the cell-attached patch clamp was used. The single-channel current was recorded at a membrane potential of −60 mV in vivo (Fig. 1D). Exposure to UV-C irradiation (−45 J/m²) strongly stimulated K+ channel activity (NP). Activity increased from 9.6 ± 1.6% to 68.0 ± 5.6% within 30 s (Fig. 1E). In seven independent patches with 100 μM 4-AP in the patch.
pipette, UV irradiation failed to activate K$^+$ channel activity, and $N_{P_o}$ remained unchanged at 12.2 ± 3.5% (Figs. 1, D and E). The addition of 20 mM TEA in the patch pipette reduced the UV-activated channel activity to 28.8 ± 4.9% ($n = 4$, Fig. 1E). These results suggest that an early effect of UV irradiation is the direct stimulation of cell membrane K$^+$ channel activity in ML-1 cells.

**Effect of Suppressing K$^+$ Channel Activity on UV-induced Apoptosis**—To determine whether UV-induced K$^+$ channel hyperactivity is a component of the cell signaling pathway mediating UV-induced apoptosis, the effect of blocking K$^+$ channel activity with the K$^+$ channel inhibitor 4-AP was determined by measuring cell viability after UV irradiation in the presence or absence of 4-AP. In the presence of 2 mM 4-AP, cell viability was protected from UV irradiation (99.5 ± 0.5% for control, 96.1 ± 0.7% for 4-AP-treated, 32.0 ± 6.7% for UV-induced, and 92.6 ± 1.6% for UV plus 4-AP) (Fig. 2A). In contrast, 4-AP had no protective effect on cells treated with another apoptosis-inducer, etoposide (an inhibitor of topoisomerase II). With etoposide alone, viability decreased to 59.4 ± 3.2%. This decline was indistinguishable from the effect of etoposide measured in the presence of 4-AP (61.5 ± 0.4%) (Fig. 2A).

The protective effect of 4-AP on UV-induced cells was a time-dependent process. The addition of 4-AP before or at the onset of UV irradiation completely prevented cell death from UV irradiation. However, when 4-AP was added 5 s after the onset of UV irradiation, 30% of the cells died (Fig. 2B). We also found that four other types of myeloblastic cells (FD-C-P1, U937, HL-60, and Himeg-1) exhibited 4-AP-sensitive K$^+$ channel activity (data not shown). After exposure of these cells to UV irradiation, their viabilities decreased to 57.7 ± 3.6%, 8.3 ± 0.6%, 27.0 ± 0.3%, and 31.0 ± 7.0%, respectively. The suppres-

**Fig. 1. Activation of a 4-AP-sensitive K$^+$ channel by UV irradiation.** A, effect of UV-irradiation on the 4-AP-sensitive K$^+$ current. Whole-cell currents were activated by exposure of ML-1 cells to UV light in the absence and presence of 4-AP. The membrane potential was depolarized from a holding potential of −60 mV to +80 mV at 20-mV increments. B, current-voltage relationship of the 4-AP-sensitive K$^+$ current activated by UV light. C, time course of UV-activated K$^+$ current in the absence and presence of 4-AP. Currents were normalized as $I_{UV}/I_C$ where $I_{UV}$ and $I_C$ represent amplitudes of the K$^+$ current measured before and after UV irradiation, respectively. D, single channel recording of K$^+$ channel in ML-1 cells. Outward current recorded as an upward deflection was obtained from cell-attached patches at a membrane potential of −60 mV. UV-C irradiation was directly applied to the patch chamber to activate K$^+$ channels in the same patch. The bottom trace demonstrates that UV irradiation induced an increase in K$^+$ channel activity that was blocked by application of 100 μM 4-AP in the patch pipette. Channel activity ($N_{P_o}$) was plotted as a function of time in the lower panel. E, statistics of K$^+$ channel activity stimulated by UV irradiation and blocked by 100 μM 4-AP or by 20 mM TEA. Vertical bars represent mean K$^+$ channel activity (horizontal bars represent S.E.). An asterisk represents a significant difference (statistical tests: ANOVA and Tukey, $p < 0.001$). Data were collected from seven independent experiments.
The effects of blocking channel activity on UV- and etoposide-induced cell death were evaluated using DNA fragmentation and nuclear staining methods. Suppression of $K^+$ channel activity with 4-AP completely prevented UV-induced DNA fragmentation in ML-1 cells but did not prevent etoposide-induced DNA fragmentation (Fig. 2C). The suppression of UV-induced DNA fragmentation was also observed in four other myeloid leukemia cell lines (Fig. 2E). The protective effect of 4-AP against UV- and etoposide-induced apoptosis was evaluated based on the extent of nuclear staining with ethidium bromide/acridine orange. Exposure of cells to UV irradiation and etoposide resulted in orange-stained nuclei indicating nuclear death (Fig. 2F). Suppression of $K^+$ channel activity with 4-AP protected the cells against UV irradiation-induced nuclear death, whereas it was ineffective in preventing etoposide-induced nuclear death. These results reveal that UV irradiation elicits $K^+$ channel hyperactivity, which, in turn, mediates apoptosis. The ability of etoposide to induce apoptosis despite the presence of 4-AP is consistent with its known inhibition of topoisomerase II activity at the level of the nucleus.

**Effect of Suppressing $K^+$ Activity on UV-activated JNK Signaling Pathway**—Many cells respond to UV irradiation by activating their JNK signaling pathway. To determine whether UV irradiation-induced $K^+$ channel hyperactivity is an essential component in the UV-activated JNK signaling pathway, JNK-1 activity was measured after suppression of $K^+$ channel activity. JNK-1 was strongly activated after 5 min of UV irradiation (Fig. 3A). In contrast, activation of JNK-1 by UV irradiation was almost completely prevented when $K^+$ channel activity was suppressed with 2 mM 4-AP. In addition, UV-induced JNK activation was partially inhibited, falling to 62
and 24% of its original activity when K⁺ channel activity was suppressed with either 10 mM TEA or 5 mM Ba²⁺, respectively (Fig. 3A). The fact that 4-AP was the most potent protective agent is consistent with its rank as the most potent inhibitor of this particular type of K⁺ channel activity in these cells (24, 26). The suppression by 4-AP of K⁺ channel activity and of JNK-1 activation was dose-dependent and reached its maximum inhibitory effect at 1 mM (Fig. 3B). The suppressive effect of 4-AP on UV-induced JNK activity closely corresponds to its dose-dependent inhibition of the K⁺ current in ML-1 cells (26).

SEK is a specific protein kinase in the JNK signaling cascade that phosphorylates and activates JNK (30, 31). To confirm the involvement of UV-stimulated K⁺ channel hyperactivity in mediating events upstream from SEK, the relationship between

**Fig. 2.** Protection from UV irradiation-induced apoptosis by suppressing K⁺ channel activity with 1 mM 4-AP in myeloblastic leukemia cells. A, viability of ML-1 cells treated with UV irradiation or etoposide in the presence or absence of 4-AP blockade. Cell viabilities were determined 24 h after UV irradiation or etoposide (Eto) induction. An asterisk indicates a significant difference (statistical tests: ANOVA and Tukey, p < 0.01, n = 12). B, time course of protection from UV irradiation-induced death by the addition of 4-AP in the culture medium. The inset shows an expanded time scale with 5 s/division. C, protection from UV irradiation by 4-AP blockade in various myeloid cells. Cell viabilities were determined 24 h after UV irradiation. An asterisk indicates that significant differences were found (statistical tests: ANOVA and Tukey, p < 0.01, n = 9–12). D, effect of 4-AP blockade on UV- and etoposide-induced DNA fragmentation of ML-1 cells. Internucleosomal DNA cleavage was determined at 8 and 15 h after apoptotic inductions. PstI-digested λ-DNA was used as a molecular weight marker. E, protection from UV-induced DNA fragmentation by 4-AP blockade in various myeloid cells. Internucleosomal DNA cleavage was analyzed 15 h after UV irradiation. F, effect of UV irradiation and etoposide on nuclear condensation/fragmentation in the presence and absence of 4-AP blockade in ML-1 cells. Untreated ML-1 cells served as controls. Assessment of damage was by the ethidium bromide/acridine orange method. Photographs were taken at a magnification of 400×.
the phosphorylation state of SEK and K⁺ channel activity was characterized. The SEK-1 protein was strongly phosphorylated after a 5-min exposure to UV irradiation (Fig. 3C). Suppression of UV-induced K⁺ channel activity with either 4-AP or Ba²⁺ inhibited SEK-1 phosphorylation by 70 and 16%, respectively. These results indicate that suppression of UV-induced K⁺ channel activity specifically inhibits the early events in the cell membrane upstream from JNK.

Another stress-activated MAP kinase, p38, is also activated in response to UV irradiation (32, 33). To test for K⁺ channel-mediated p38 activation in response to UV irradiation in ML-1 cells, the effect of UV irradiation was measured on p38 activity in the presence and absence of K⁺ channel blockers. Activation of p38 occurred irrespective of the presence or absence of 4-AP (Fig. 3D). Our results strongly suggest that UV-stimulated K⁺ channel hyperactivity is an essential upstream component of the JNK signaling pathway; however, p38 activation is not linked to stimulation of K⁺ channel activity. The mechanism underlying UV-induced p38 activation and apoptosis remains to be elucidated.

**Effects of Osmotic Stress and Ca²⁺ Influx on JNK Activity in K⁺ Channel-suppressed Cells**—To further support the notion that 4-AP is not a nonspecific inhibitor of JNK pathways, we examined the effect of 4-AP on JNK-1 activation induced by hyperosmolarity in ML-1 cells. Hyperosmotic shock (600 mM sorbitol) strongly activated JNK-1. 4-AP had no effect on JNK activity (Fig. 4A). This result indicates that 4-AP has a specific inhibitory effect on UV-induced JNK activation. In addition, it
suggests that the effect of 4-AP on UV-induced JNK-1 activation is likely through blockage of $K^+$ channel activity and that activation of JNK-1 by hyperosmotic shock in these cells may not be a $K^+$ channel activity-mediated process.

Recent studies have shown that an increase of $Ca^{2+}$ influx may be a component of the signaling mechanism for mediating UV-induced apoptosis. Accordingly, we examined whether UV irradiation could induce JNK stimulation when extracellular $Ca^{2+}$ concentration was reduced by the addition of EGTA. Our results showed that at a very low $Ca^{2+}$ concentration (0.5 mM EGTA) or in a nominally $Ca^{2+}$-free medium (5 mM EGTA) JNK activation still occurred in response to UV irradiation (Fig. 4B). In addition, suppression of $K^+$ channel activity with 4-AP inhibited UV-induced JNK activation in $Ca^{2+}$-free medium. Therefore, $Ca^{2+}$ influx did not play a significant role in the JNK signaling pathway mediating UV-induced apoptosis in ML-1 cells.

**DISCUSSION**

We provide evidence for a novel mechanism of UV irradiation-induced apoptosis in myeloblastic leukemia cells. An important early component of the signaling process mediating UV-induced apoptosis is strong activation of cell membrane $K^+$ channels. There is growing evidence showing that $K^+$ channel activities are probably involved in programmed cell death. Various investigations have shown that $K^+$ channel activity can be affected by apoptosis inducers, including reactive oxygen species (34–37), Fas ligand and tumor necrosis factor (38, 39), and anticancer drugs (40, 41). The $K^+$ channel blocker 4-AP inhibits the shrinkage of human eosinophils undergoing apoptosis induced by cytokine withdrawal (42), and a combination of two $K^+$ channel blockers, TEA and 4-AP, inhibited interleukin 1b release from lipopolysaccharide-stimulated monocytes (43). Neurons undergoing apoptosis exhibited an up-regulation of outward $K^+$ currents. This enhancement of outward $K^+$ current, induced by serum deprivation and staurosporine, can be prevented by the $K^+$ channel blocker TEA and by increasing the extracellular $K^+$ concentration. It has also been observed that the $K^+$ channel opener cromakalim induces neuronal apoptosis (44). Thus, it appears that the activation of $K^+$ channels is responsible for $K^+$ efflux and the consequent membrane hyperpolarization and decrease in cell volume, thereby activating a particular signaling system leading to $1\beta$-converting enzyme activation and apoptosis.

The stimulation of $K^+$ channel activity could result in the quick loss of intracellular $K^+$. The loss of intracellular $K^+$ activates interleukin 1$\beta$-converting enzyme (21, 43, 45). Some evidence suggests that interleukin 1$\beta$-converting enzyme can affect upstream events in the JNK pathway at the JNK level (46). UV-induced activation of interleukin 1$\beta$-converting enzyme and JNK-1 could occur subsequent to the stimulation of $K^+$ channel activity and the loss of intracellular $K^+$. This mechanism has been implicated in apoptosis in neuronal cells (47, 48). Alternatively, cell shrinkage that occurs as a result of a quick fall in intracellular $K^+$ concentration, may trigger apoptosis. Accordingly, suppression of $K^+$ channel activity may prevent a quick loss of intracellular $K^+$ ions resulting from UV-induced $K^+$ channel hyperactivity. This possibility is supported by recent findings that UV irradiation-induced JNK activation can be mimicked by hypertonic stress in HeLa cells (7). In addition, cytokine receptors can be activated by either UV irradiation or hypertonic stress. It is speculated that cytokine receptor activation induced by hypertonic stress occurs as a consequence of cell shrinkage.

UV-induced apoptosis in ML-1 cells is dependent on stimulation of SEK/JNK and p38 pathways in ML-1 cells. We found that activation of 4-AP-sensitive $K^+$ channel activity occurs upstream from the stimulation of the SEK/JNK pathway and that p38 stimulation is a component of the cell signaling systems responsible for UV-induced apoptosis. Activity of p38, however, resides in a signaling pathway parallel to that of SEK/JNK, as shown by the observation that inhibition of $K^+$ channel activity with 4-AP has no effect on p38 activity. This result suggests that p38 stimulation may not be linked to activation of this type of $K^+$ channel activity. Our finding that UV-induced $K^+$ channel hyperactivity precedes SEK and JNK stimulation documents for the first time a role for membrane ion channels in mediating radiation- and cytokine-induced signal transduction and apoptosis. This process, as well, has been shown to account for serum deprivation-induced neuronal cell apoptosis and occurs in the absence of $Ca^{2+}$ influx across the cell membrane (44). Some studies have shown that JNK acti-
UV-activated K+ Channel Mediates Apoptosis Of ML-1 Cells

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