Irradiation of mammalian cells with ultraviolet-B radiation (UV-B) triggers the activation of a group of stress-activated protein kinases known as c-Jun NH2-terminal kinases (JNKs). UV-B activates JNKs via UV-B-induced ribotoxic stress. Because oxidative stress also activates JNKs, we have addressed the question of whether the ribotoxic and the oxidative stress responses are mechanistically similar. The pro-oxidants sodium arsenite, cadmium chloride, and hydrogen peroxide activated JNK1 with slow kinetics, whereas UV-B potentiated the activity of JNK1 rapidly. N-acetyl cysteine (a scavenger of reactive oxygen intermediates) abolished the ability of all oxidative stressors tested to activate JNK1, but failed to affect the activation of JNK1 by UV-B or by another ribotoxic stressor, the antibiotic anisomycin. In contrast, emetine, an inhibitor of the ribotoxic stress response, was unable to inhibit the activation of JNK1 by oxidative stressors. Although UV-A and long wavelength UV-B are the spectral components of the ultraviolet solar radiation that cause significant oxidative damage to macromolecules, the use of a filter to eliminate the radiation output from wavelengths below 310 nm abolished the activation of JNK1 by UV. Our results are consistent with the notion that UV-B and oxidative stressors trigger the activation of JNK1 through different signal transduction pathways.

Both in cultured mammalian cells and in the in vivo mouse skin experimental system, the nongenomical intermediate wavelength ultraviolet part of the solar radiation (UV-B, λ = 280–320 nm) elicits biological responses such as cytotoxicity, mutagenicity, carcinogenicity, and gene activation. Similar to the short wavelength ultraviolet radiation (UV-C, λ = 200–280 nm), UV-B produces oxygen-independent damage to DNA, RNA, and proteins. Similar to the long wavelength ultraviolet radiation (UV-A, λ = 320–400 nm), UV-B also induces oxidative damage to diverse cellular substrates. Murine fibroblasts exposed to UV-B generate superoxide anion radicals (O2-), which are, in turn, dismutated to hydrogen peroxide (H2O2) by superoxide dismutases (1). Thus generated, H2O2 further participates in the Fenton reaction (H2O2 + Fe2+ → ‘OH + OH− + Fe3+) to generate the highly reactive hydroxyl radical (‘OH) (2). Apart from fibroblast cultures, the Fenton reaction has also been detected in UV-B-irradiated mouse skin (3). Hydroxyl radicals contribute to cellular damage by inducing lipid peroxidation. In addition to the generation of ‘OH, H2O2 can react with hypochlorous acid (HOCl) to generate singlet oxygen (1O2). Indeed, 1O2 has been detected in UV-B irradiated mammalian cells (4). Furthermore, a substantial component of the oxygen-dependent damage to DNA (formation of the 7,8-dihydro-8-oxo-2′-deoxyguanosine lesion) in response to UV-B has been attributed to the generation of O2- (5).

The cytoprotective, survival reaction of cells to UV-C and UV-B involves the rapid activation of the pre-existing transcription factor AP-1, a dimer composed of members of the c-Fos and c-Jun families of gene products. AP-1 activation is mediated by a profound (10–100-fold) increase in the activity of a group of related serine/threonine protein kinases collectively termed c-Jun NH2-terminal kinases (JNKs) (reviewed in Ref. 6). JNKs phosphorylate and activate c-Jun, as well as the transcription factors TCF/Elk-1 and ATF-2 that positively regulate the expression of the c-fos and c-jun genes, respectively (reviewed in Ref. 7). The mechanisms of UV-C- and UV-B-induced activation of JNKs have been subjects of considerable investigation and debate over the last few years (8–11).

We have recently discovered a novel signaling pathway to JNK1 that is initiated in, or in close proximity to, the functional center of actively translating eukaryotic ribosomes (12). This center contains the 3′-end of 28 S rRNA and its proteinaceous environment and is responsible for aminoacyl-tRNA binding, peptidyl transfer, and ribosome translation. This region of the 28 S rRNA is the target of the antibiotics anisomycin and blasticidin S and of the enzymatic ribotoxins ricin A chain and α-sarcin, all of which strongly activate JNK1 (see Ref. 12, and a detailed list of references therein). The activation of JNK1 by the foregoing agents was termed the ribotoxic stress response and is characterized by the absolute requirement for the presence of actively translating ribosomes at the moment of cellular encounter with the 28 S rRNA-acting antibiotic or ribotoxin. Cells whose ribosomes are not engaged in translational elongation fail to activate JNK1 in response to these agents. In contrast, the activation of JNK1 by nonribotoxic stressors, such as inflammatory cytokines, osmotic stress, and some DNA-damaging drugs, is intact in cells containing nontranslating ribosomes (12). Interestingly, both UV-C and UV-B require the presence of active ribosomes to activate JNK1; furthermore, nucleotide- and position-specific damage to the 3′-end of 28 S rRNA was detected in UV-C- or UV-B-irradiated cells (10). We concluded, therefore, that both UV-C and UV-B trigger the ribotoxic stress response that leads to the activation of JNK1. Our previous work, however, has not addressed the possibility that the ribotoxic stress response trig-

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**Different Mechanisms of c-Jun NH2-terminal Kinase-1 (JNK1) Activation by Ultraviolet-B Radiation and by Oxidative Stressors**

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gated by UV-C or UV-B may be mediated by UV-induced oxidative damage (for instance to RNA or protein components of ribosomes). Such a possibility is plausible because the damage to the 28S rRNA incurred in response to UV-C involved guanosine-specific lesions (potentially 7,8-dihydro-8-oxo-guanosines) (10). Indeed, oxidative stressors are potent activators of JNK activity. Sodium arsenite, the carcinogenic form of trivalent arsenic (As3+), has been found to induce elevated levels of OH through depletion of cellular reduced glutathione (GSH) (13). Arsenite interacts directly with the sulfhydryl group of both GSH and proteins, leading to the formation of mixed protein-As-GS complexes (14, 15). Several groups have reported that arsenite is a potent activator of JNK activity (16–19). H2O2, a precursor of OH (see above), was found to activate JNK as well (20–23). Cadmium chloride, an agent that, similar to sodium arsenite, depletes the cellular levels of reduced GSH (13), has also been found to activate JNK (19, 24).

In this investigation we have employed Rat-1 fibroblasts (the cells used initially to describe the ribotoxic stress response) to address the question of whether UV-B, on the one hand, and three oxidative stressors (sodium arsenite, cadmium chloride, and H2O2), on the other hand, share common signal transduction pathways to induce the activation of JNK. We present several lines of evidence that suggest that UV-B does not activate JNK1 through oxidative damage. First, sodium arsenite, cadmium chloride, and H2O2 activated JNK1 with relatively slow kinetics, whereas UV-B potentiated JNK1 activity rapidly. Second, pretreatment of cells with N-acetyl cysteine (NAC, a potent scavenger of H2O2, OH, and HOCl (25, 26) and a precursor for the biosynthesis of GSH (27–30)) at physiological pH abolished the ability of all oxidative stressors tested to activate JNK1, but failed to affect the activation of JNK1 by UV-B or by another ribotoxic stressor, the antibiotic anisomycin. Third, etemine, an immediate inhibitor of ribosomal translocation and of UV-B- and anisomycin-induced activation of JNK1 (10, 12), was unable to inhibit the activation of JNK1 by the oxidative stressors. Fourth, eliminating more than 90% of the spectral output below 310 nm (i.e., the wavelengths that produce more direct, oxygen-independent damage to macromolecules than oxidative damage) abolished the activation of JNK1 by UV. Taken together, these results strongly argue that, although oxidative damage plays a role in the long-term effects of UV-B, it does not participate in the immediate-early cellular response that involves the activation of JNK.

EXPERIMENTAL PROCEDURES

Anisomycin, sodium arsenite, cadmium chloride, and N-acetyl cysteine were from Sigma. Recombinant mouse IL-1α was from Genzyme (Cambridge, MA). H2O2 was from Fisher Chemicals (Fair Lawn, NJ). The cell culture and all experimental techniques employed in this work have been previously described in Iordanov et al. (12). Briefly, JNK1 activity was determined by a coupled immunoprecipitation/immunocomplex kinase assay using an anti-JNK1 antibody (Santa Cruz Biotechnology Inc., sc-474) to precipitate the active kinase and GST-Elk1 recombinant protein as a substrate for phosphorylation (12). The phosphorylated GST-Elk1 was quantified from dried gels using a Molecular Dynamics PhosphorImager and IP Lab Gel software (12). The activation of SEK1/MKK4 was determined in a Western blot procedure using an antibody directed against SEK1/MKK4 protein phosphorylated at Thr223 (New England BioLabs Inc., Beverly, MA, 91518). The antibody was used following the instruction of the manufacturer (12). After hybridization with the phospho-specific antibody, the same membrane was hybridized with an anti-SEK1/MKK4 antibody (Santa Cruz Biotechnology Inc.). The UV-B source and the method of UV-B irradiation of cells have been described in Iordanov et al. (10). The A18 glass filter was from Eastman-Kodak.

For the NAC pretreatment of cells, cell culture medium was made to contain 30 mM NAC freshly before use. The pH of the NAC-containing medium was then adjusted with NaOH to the pH value of the medium without NAC. Either NAC-free or NAC-containing medium (after equilibrating in humidified incubator at 37 °C and 5% CO2) was then used to exchange the old cell culture medium 30 min before treatment with UV-B or another agent.

RESULTS

Kinetics of JNK1 Activation by UV-B and by Oxidative Stressors—In Rat-1 cells irradiated with UV-B, the activity of JNK1 was markedly elevated as early as 15 min after the irradiation and remained elevated throughout the next 2 h, as determined in immunocomplex kinase activity assays (12) (Fig. 1, compare lanes 1–4 with lanes 9–12). This kinetics of activation resembled that observed in anisomycin-treated cells (Fig. 1, compare lanes 1–4 with lanes 25–28). In contrast, the activity of JNK1 in cells treated with sodium arsenite was not substantially elevated 15 min after the treatment and displayed a slow, graded, increase during the 2 h postincubation period (Fig. 1, compare lanes 1–4 with lanes 17–20). Similarly, cadmium chloride-treated cells displayed a slow, graded, dose-dependent, increase in JNK1 activity (Fig. 2B, lanes 1–8, and not shown). The response of JNK1 in Rat-1 cells treated with H2O2 appeared to be complex; activation of JNK1 was not observed in cells treated with doses below 1 mM (not shown) as well as in cells treated with 10 mM H2O2 (Fig. 2A, lanes 6–9). Potent activation of JNK1 was observed only in cells treated with 1 mM H2O2 and, in addition, reproducibly only at 4 h after the treatment (Fig. 2B, lanes 2–5). These results demonstrate that three oxidative stressors (sodium arsenite, cadmium chloride, and H2O2) are slow activators of JNK1, whereas the ribotoxic stressors UV-B and anisomycin are rapid JNK1 activators.

Differential Effect of NAC on the Activation of JNK1 by Ribotoxic and by Oxidative Stressors—NAC exerts an antioxidant role via its dual capability to act both as a potent direct scavenger of H2O2, OH, and HOCl (25, 26) and as a precursor...
for the biosynthesis of GSH (27–30). To investigate whether UV-B-induced activation of JNK is dependent on reactive oxygen intermediates, we employed pretreatment of Rat-1 cells with NAC (30 mins) for 30 min before challenging the cells with UV-B or other stimuli. Because NAC acidifies the cell culture medium (not shown), we adjusted the pH of the medium containing NAC to physiological values (pH 7.0 at 5% CO₂). Under these conditions, NAC specifically abolished the ability of sodium arsenite (Fig. 1, compare lanes 17–20 with lanes 21–24), cadmium chloride (Fig. 2B, compare lanes 1–8 with lanes 9–16), and H₂O₂ (Fig. 2A, lower panel) to activate JNK1. However, neither UV-B- nor anisomycin-induced JNK1 activities were affected by NAC pretreatment (Fig. 1, compare lanes 9–12 with lanes 13–16 and lanes 25–28 with lanes 29–32). Furthermore, the activation of JNK1 in response to IL-1β was not affected by NAC (Fig. 1, compare lanes 33–36 with lanes 37–40). We considered the possibility that NAC might have failed to inhibit rapid JNK activators (such as UV-B and anisomycin) because of the insufficient time of pretreatment with NAC (30 min, see Fig. 1). Rat-1 cells were therefore pretreated with NAC for 4 h and then challenged with UV-B for 15 min. Even under these conditions NAC failed to inhibit the activation of JNK1 by UV-B, whereas, in the same experiment, NAC completely inhibited cadmium chloride-induced JNK1 activity (Fig. 3A). Next, we considered the possibility that the failure of NAC to inhibit UV-B-induced JNK1 activity might result from the high (presumably, saturating) doses of radiation (1200 J/m²) UV-B). However, NAC also failed to inhibit JNK1 activities induced by significantly lower doses of UV-B radiation (150, 300, or 600 J/m², Fig. 3B). In fact, NAC slightly potentiated the UV-B-induced activity of JNK1, especially at lower UV-B doses (Fig. 3B). The ability of NAC to potentiate the activation of JNK1 by UV-B, however, might be because of the slightly elevated levels of JNK1 basal activity in the presence of NAC (Fig. 3B, see 0 J/m², and also see Figs. 2A and 3A, graphs).

Ribotoxic Stressors, Oxidative Stressors, and NAC Regulate the Activity of the JNK1 Cascade at a Level Upstream of MKK4/SEK1—We have recently reported that agents that induce ribotoxic stress activate the JNK1 cascade through signal transduction pathways that are independent (downstream) of cell surface cytokine receptors but are upstream of the dual specificity protein kinase MKK4/SEK1 (also known as JNK kinase-1, JNKK1) (10, 12). To investigate whether MKK4/SEK1 is activated by oxidative stressors as well, we monitored the phosphorylation of threonine 223 of this kinase, an event indicative of MKK4/SEK1 activation by upstream kinases such as MEKK1 (31, 32). Similar to the ribotoxic stressor UV-B (Fig. 4, lanes 5–7), both cadmium chloride and sodium arsenite induced a clear pattern of MKK4/SEK1 phosphorylation (Fig. 4, lanes 11–14, and not shown for sodium arsenite) as detected in immunoblot assays using an antibody specific for MKK4/SEK1.
protein phosphorylated at threonine 223. The kinetics of MKK4/SEK1 phosphorylation by either UV-B or cadmium chloride correlated closely with the kinetics of JNK1 activation by the same agents (compare Fig. 1, lanes 9–12, to Fig. 4, lanes 5–7, and Fig. 2B, lanes 1–8, to Fig. 4, lanes 11–14). In agreement with the results obtained using JNK1, NAC was unable to reduce the UV-B-induced MKK4/SEK1 phosphorylation (Fig. 4, compare lanes 5–7 with lanes 8–10) but was very efficient in inhibiting the phosphorylation of the kinase induced by cadmium chloride and sodium arsenite (Fig. 4, compare lanes 11–14 with lanes 15–18, and not shown for sodium arsenite). We concluded, therefore, that the ribotoxic stress and the oxidative stress-induced signal transduction pathways to JNK1 are separate, but converge at, or upstream of, MKK4/SEK1.

**Inability of Ribosomal Inactivation to Reduce the Responsiveness of JNK1 to Oxidative Stressors**—We have previously demonstrated that the most characteristic feature of the ribotoxic stress-induced signaling to JNK1 is its absolute requirement for ribosomes actively engaged in translational elongation to elicit a signaling cascade to JNK1 (10, 12). Rat-1 cells, pretreated with emetine (and inhibitor of translational elongation), cannot activate JNK1 in response to ribotoxic stress, but possess a full capacity to activate JNK1 in response to cytokines, osmotic stress, and DNA-damaging agents (10, 12). The possible effects of ribosomal inhibitors on the oxidative stress-induced JNK1 activation have not, however, been investigated. Fig. 5 demonstrates the ability of emetine pretreatment to abolish the activation of JNK1 by UV-B. However, neither sodium arsenite- nor cadmium chloride-induced activation of JNK1 was inhibited by emetine pretreatment (Fig. 5). We concluded, therefore, that oxidative damage-induced signal transduction to JNK1 is ribosome-independent.

**Failure of UV-B (280–310 nm) to Activate JNK1—Both in vitro and in living cells, the ratio of oxidative damage (e.g. the 7,8-dihydro-8-oxo-2′-deoxyguanosine lesion, 8-oxodGuo) to direct damage (e.g. the cyclobutyl pyrimidine dimers, CPD) caused by UV increases with the wavelength. For instance, at equal doses, the 8-oxodG/CpD ratio for UV-A (320–400 nm)-irradiated HeLa cells was found to be approximately 10-fold higher than that for UV-B (280–320 nm) or UV-C (200–280 nm)-irradiated HeLa cells (33).** If UV-induced oxidative damage is an important intermediate in the signal transduction pathways that lead to the activation of JNK1, the action spectrum of UV (measured by JNK1 activation) should be shifted toward wavelengths with high 8-oxodG/CpD ratios (i.e. UV-A). Because the UV-B source employed in our work has a substantial portion of UV-A spectral output (Fig. 6A), it became possible to address this question experimentally. We observed that the A-18 glass filter from Eastman-Kodak retains more than 90% of the UV wavelengths shorter than 310 nm (Fig. 6A). By appropriately adjusting the irradiation time, we were able to deliver to cells equal doses of radiant energy containing either 100% of the original 280–310 nm spectral output (irradiation without the A-18 filter) or less than 10% of the original 280–310 nm spectral output (irradiation through the A-18 filter). Fig. 6B demonstrates that the use of the A-18 filter to eliminate more than 90% of the 280–310 nm spectral output abolished the ability of UV to activate JNK1 (compare lanes 1–6 with lanes 7–11). Thus, the JNK1-activating spectral portion of the UV source used belongs to the wavelengths below 310 nm that have lower 8-oxodG/CpD ratios than UV-A. This finding is consistent with the previous results (Figs. 1–5) indicating that UV-B activates JNK1 through mechanisms that do not involve UV-induced oxidative damage.

**DISCUSSION**

Ultraviolet radiation and oxidative agents are relevant environmental hazards for eukaryotic organisms with cytotoxic, carcinogenic, and tumor-promoting properties. Whereas the biochemistry of reactive oxygen intermediates is relatively well understood, the modes of biological action of UV are considerably more complex, as they involve both oxygen-dependent and oxygen-independent (direct) damage to biomolecules. Although some of the biological activities of UV might be attributed to UV-induced oxidative stress, the question of the role of oxidative stress in the cellular transcriptional responses to UV (that involve the activation of cytoplasmic tyrosine- and serine/threonine-directed protein kinases) has not been extensively addressed. Recently, JNKs have emerged as important mediators of the transcriptional stress responses in mammalian cells to both UV and oxidative stressors. Because of their responsiveness to both UV and oxidative stressors, JNKs constitute biologically relevant end points to investigate the dependence of UV-induced signal transduction on UV-induced oxidative dam-
age. Previously, we have been able to demonstrate that an invariant requirement for the successful activation of JNK1 by either UV-C or UV-B is the presence, at the moment of UV irradiation, of ribosomes actively engaged in translational elongation (10). This finding placed UV in the distinct group of JNK1 activators that share the requirement for active ribosomes to activate JNK1 and that are collectively termed ribotoxic stressors (10, 12, 34). This group includes agents that either bind to the functional center of 28S rRNA (anisomycin, blastidicin S, and gougerotin) or cause covalent damage to the ribosomes (10, 36). Taken together, our results and the work of Knebel et al. (35) present evidence that the activation by UV of the extracellular signal-regulated kinases (ERKs) correlates with the UV-induced inhibition of EGF-R dephosphorylation. It must be noted, however, that of all the members of the MAP kinase superfamily (that also includes the JNKs and the p38 MAP kinase families of kinases), ERKs are kinases that are the weakest in their responsiveness to UV (10, 36). Taken together, our results and the work of Knebel et al. contribute to an emerging picture of the UV response through the MAP kinase superfamily of protein kinases in which the UV-induced oxidative damage plays a role in the activation of ERK family of kinases, but in which oxygen-independent and ribosome-dependent mechanisms predominate in the activation by UV of the stress-activated protein kinases of the JNK and p38 MAP kinase families.

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REFERENCES

1. Masaki, H., and Sakurai, H. (1997) J. Dermatol. Sci. 14, 207–216
2. Masaki, H., Atsumi, T., and Sakurai, H. (1995) Biochem. Biophys. Res. Commun. 206, 474–479
3. Taira, J., Mimura, K., Yoneya, T., Hagi, A., Murakami, A., and Makino, K. (1992) J. Biochem. (Tokyo) 111, 693–695
4. Dalle Carbonare, M., and Pashak, M. A. (1992) J. Photochem. Photobiol. B 14, 105–124
5. Zhang, X., Rosenstein, B. S., Wang, Y., Lee, M., and Wei, H. (1997) Free Radical Biol. Med. 23, 880–885
6. Ip, Y. T., and Davis, R. J. (1998) Curr. Opin. Cell Biol. 10, 205–219
7. Whitmarsh, A. J., and Davis, R. J. (1996) J. Mol. Med. 74, 589–607
8. Adler, V., Schaffer, A., Kim, J., Dolan, L., and Ronai, Z. (1995) J. Biol. Chem. 270, 26071–26077
9. Adler, V., Polotsakaya, A., Kim, J., Dolan, L., Davis, R., Pincus, M., and Ronai, Z. (1996) Carcinogenesis 17, 2073–2078
10. Iordanov, M. S., Pribnow, D., Magun, J. L., Dinh, T. H., Pearson, J. A., and Magun, B. E. (1998) J. Biol. Chem. 273, 15794–15803
11. Rosette, C., and Karin, M. (1996) Science 274, 1194–1197
12. Iordanov, M. S., Pribnow, D., Magun, J. L., Dinh, T. H., Pearson, J. A., Chen, S. L., and Magun, B. E. (1997) Mol. Cell. Biol. 17, 3373–3381
13. Applegate, L. A., Luscher, P., and Tyrrell, R. M. (1991) Cancer Res. 51, 974–978
14. Winski, S. L., and Carter, D. E. (1995) J. Toxicol. Environ. Health 46, 379–397
15. Jennette, K. W. (1981) Environ. Health Perspect. 20, 233–252
16. Cavalli, E., and Verderio, E. (1981) Eur. J. Biochem. 119, 587–595
17. Liu, Y., Guyton, K. Z., Gorsse, M., Xu, Q., Lee, J. C., and Holbrook, N. J. (1996) Free Radical Biol. Med. 21, 771–781
18. Lim, C. P., Jain, N., and Cao, X. (1998) Oncogene 16, 2915–2926
19. Elrifi, K. K., Whitmarsh, A. J., Davis, R. J., and Bonkovsky, H. L. (1998) J. Biol. Chem. 273, 8922–8931
20. Dhar, V., Adler, V., Lehmann, A., and Ronai, Z. (1996) Cell Growth Diff. 7, 841–846
21. Lo, Y. Y. C., Wong, J. M. S., and Cruz, T. F. (1996) J. Biol. Chem. 271, 15703–15707
22. Tournier, C., Thomas, G., Pierre, J., Jacquesmin, C., Pierre, M., and Saunier, B. (1997) Eur. J. Biochem. 244, 587–595
23. Wang, X., Martindale, J. L., Liu, Y., and Holbrook, N. J. (1998) Biochem. J. 333, 291–300
24. Matsuoka, M., and Igisu, H. (1998) Biochem. Biophys. Res. Commun. 251, 527–532
25. Gillissen, A., Scharling, B., Jaworska, M., Bartling, A., Rasche, K., and Schultze-Werninghaus, G. (1997) Res. Exp. Med. (Berlin) 196, 389–398
26. Aruoma, O. I., Halliwell, B., Hoey, B. M., and Butler, J. (1989) Free Radical Biol. Med. 6, 593–597
27. Miners, J. O., Drew, R., and Birkett, D. J. (1984) Biochem. Pharmacol. 33, 2995–3000
28. Shattuck, K. E., Rassin, D. K., and Grinnell, C. D. (1998) J. Parenter. Enteral Nutr. 22, 228–233
29. Moldeus, P., Cotgreave, I. A., and Berggren, M. (1986) Respiration 1, 31–42
30. Sala, R., Moriggi, E., Corvasce, G., and Morelli, D. (1993) Eur. Respir. J. 6, 440–446
31. Derijard, B., Raingeaud, J., Barrett, T., Wu, I. H., Han, J., Ulevitch, R. J., and Davis, R. J. (1995) Science 267, 682–685
32. Yan, M., Dai, T., Deak, J. C., Kyriakis, J. M., Zon, L. I., Woodgett, J. R., and Templeton, D. J. (1994) Nature 372, 798–800
33. Zhang, X., Rosenstein, B. S., Wang, Y., Lebwohl, M., Mitchell, D. M., and Wei, H. (1997) Photochem. Photobiol. 65, 119–124
34. Iordanov, M. S., and Magun, B. E. (1998) J. Biol. Chem. 273, 3528–3534
35. Knebel, A., Rahmsdorf, H. J., Ulrich, A., and Herrlich, P. (1996) EMBO J. 15, 5314–5325
36. Derijard, B., Hibi, M., Wu, I. H., Barrett, T., Su, B., Deng, T., Karin, M., and Davis, R. J. (1994) Cell 76, 1025–1037