Activation of c-Jun-NH₂-Kinase by UV Irradiation Is Dependent on p21ras

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We have demonstrated previously that Jun-NH₂-kinase (JNK) activation in vitro is potentiated by association with the p21ras protein. To determine if in vivo activation of JNK also depends on p21ras, we have used M1311 cells that carry the cDNA for the neutralizing antibody to p21ras, Y13-259, under a dexamethasone-inducible promoter. The ability of UV to activate JNK gradually decreased over a 4-day period of cell growth in dexamethasone. This decrease coincides with weaker transcriptional activation measured via gel shift and chloramphenicol acetyltransferase assays. Peptides corresponding to amino acids 96–110 on p21ras were shown to block Ras-JNK association, inhibited UV-mediated JNK activation in mouse fibroblast 3T3-4A cells as well as in M1311 cells, further supporting the role of p21ras in UV-mediated JNK activation. Overall, the present studies provide in vivo confirmation of the role p21ras plays in JNK activation by UV irradiation.

Jun-NH₂-kinase (JNK) represents a family of stress-activated protein kinases that phosphorylate serine/threonine in the NH₂-terminal domain of transcription factors c-Jun, ATF2, ELK1, and p53 (1–4). JNK activation has been shown to occur in response to various types of external stress such as UV, x-rays, heat shock, and inflammatory cytokines (1, 5, 6). Alternative cellular pathways are involved in JNK activation, as demonstrated for heat shock and UV irradiation (7). The ability of UV irradiation to activate signal transduction components requires cell surface receptors, as shown for epidermal growth factor receptor and insulin receptor (8), followed by the activation of Src-related tyrosine kinases (9). Several G proteins, including growth factor receptor binding protein 2, SOS Ras and Rac, also play an important role in transmitting the proper signal to protein kinases, such as MEKK and JNKK, which, in turn, activate JNK (10, 11). A focal point in the activation of diverse signal transduction pathways is p21ras, which appears to serve as a docking site for the binding of Raf-1 (12) JNK and its substrate c-Jun (13). Although the Raf-1-mitogen-activated protein kinase pathway results in the activation of transcription factors other than those activated by the MEKK and JNKK pathway (i.e. c-Fos and c-Jun, respectively), certain cross-talk between the two pathways appears to exist (14).

We have recently found that the p21ras protein stimulates phosphorylation of JNK and enhances JNK-catalyzed phosphorylation of c-Jun (13). We obtained additional evidence that p21ras interacts directly with both c-Jun and JNK proteins. This interaction is inhibited by specific peptides, corresponding to the effector domains of p21ras (residues 96–110 and 115–126) identified in molecular modeling studies (13, 15–17). All of these peptides block oncopgenic p21-induced oocyte maturation (18).

Since p21ras appears to be involved in the JNK-Jun signaling pathway, we have undertaken a study to determine whether in vivo activation of these two proteins is p21ras-dependent. For this purpose, we have used the cell line M1311, NIH-3T3 cells that carry the cDNA for the neutralizing antibodies to p21ras, Y13-259. Although the heavy chain of these antibodies is constitutively expressed in M1311 cells, the light chain cDNA is under a dexamethasone-inducible promoter; thus, upon exposure to dexamethasone, there is expression of functional Y13-259 antibodies that are capable of reverting the transformed phenotype in these cells (19). Using the M1311 cell system as a model, we demonstrate the contribution of p21ras to UV-mediated JNK activation.

EXPERIMENTAL PROCEDURES

Cell Lines—M1311 cells are NIH-3T3 derivatives that were transfected with cDNA for the heavy and light chains of Y13-259 antibodies against the p21ras protein (19). While the heavy chain cDNA is constitutively expressed, the light chain cDNA is under a dexamethasone-inducible promoter; thus, upon exposure to dexamethasone, the light chain cDNA is under a dexamethasone-inducible promoter; thus, upon exposure to dexamethasone, there is expression of functional Y13-259 antibodies that are capable of reverting the transformed phenotype in these cells (19). Using the M1311 cell system as a model, we demonstrate the contribution of p21ras to UV-mediated JNK activation.

UV Irradiation—Cells were exposed to UV irradiation as indicated previously (7). Briefly, prior to irradiation, the cells were washed with phosphate-buffered saline and, with the lids off, placed in marked areas in the tissue culture hood, which had been precalibrated for the required dose of UV using the germicidal lamp (254 nm) with the aid of a UV-C probe (UVP, San Diego, CA). The media that were removed prior to irradiation were added again after UV exposure, and the cells were harvested at the indicated time points.

Preparation of Whole-cell Extract Proteins—3T3-4A cells (1.5 × 10⁷) were lysed in lysis buffer (20 mM HEPES buffer, pH 7.5, 350 mM NaCl, 23304
25% glycerol, 0.25% Nonidet P-40, 1 mM sodium vanadate, 0.5 mM phenylmethylsulfonyl fluoride, aprotinin, and leupeptin, each present at a concentration of 1 μg/ml. Lysate was clarified by centrifugation for 15 min at 14,000 × g. The protein concentrations were determined, and aliquots of the proteins were stored at −80 °C.

**Oligonucleotide and Peptide Synthesis**—Oligonucleotides representing the dimer of the UV response element (URE) (ACTATGACAA-CACCATGACAA-CAGT) or the API (CTGACTCATCCTGACTACTG) target sequences were synthesized in-house with the aid of a Cyclone Plus DNA synthesizer (Milligen Biosearch, Bedford, MA). Complementary DNA strands were purified and annealed by standard procedures. Peptides synthesized in this study were purified to >99% as verified by high-performance liquid chromatography analysis, as described previously (18).

**Antibodies**—Antibodies against p21ras were purchased (Oncogene Science, Uniondale, NY). Antibodies to c-Jun were purchased from Santa Cruz Biotechnology (Santa Cruz, CA). Antibodies to JNK (clone 1-99) were obtained from PharMingen (San Diego, CA) (7).

**SDS-Polyacrylamide Gel Electrophoresis and Western Blotting**—Whole-cell extracts (100 μg) were incubated at 100 °C for 15 min in the presence of Laemmli sample buffer prior to separation on 15% SDS-polyacrylamide gel electrophoresis. The gels were transferred to a polyvinylidene difluoride membrane (Millipore) in Tris-glycine buffer with 90 volts for 1 h at 4 °C using an electroblotter (Bio-Rad). Membranes were then blocked with Trition X-100 (0.5%) and nonfat milk (5%) and blotted with antibodies either to p21 (Y13-259; Oncogene Science; 1:2000 dilution), to JNK (PharMingen; 1:3000 dilution), or to c-Jun (Santa Cruz Biotechnology; 1:2000 dilution). Binding of each antibody was detected by a chemiluminescence detection kit (ECL) according to the manufacturer’s recommendations (Amersham Corp.). The secondary antibody provided with the kit was diluted 1:15,000. In all cases, protein concentration was carefully evaluated prior to loading and by Ponceau staining after blotting.

**Electrophoretic Mobility Shift Assay (EMSA)**—The synthetic URE or API target sequence was labeled with [γ-32P]ATP (3000 Ci/mmol) using polyethylene imine (Promega Corp., Madison, WI) according to standard procedures. The labeled DNA (0.4 ng, 4400 cpm) was incubated with nuclear proteins (0.8 μg, as specified under “Results”) for 20 min at room temperature in the presence of 100 ng of poly(dI-dC) oligomer (Boehringer Mannheim) and DNA binding buffer, as described previously (7). The complexes were then separated on 7.5% polyacrylamide gel and autoradiographed. Each of these experiments was reproduced three times, using independently prepared protein extracts.

**Electrophorations and CAT Assays**—Thirty μg of the mammalian expression vector, as indicated under “Results,” were cotransfected with 3 μg of β-galactosidase construct by electroporation into 5 × 106 cells using 270 volts, 1050 microfarads, 25 mm HEPES, pH 7.1, 0.25 mM NaHPO4, and 140 mM NaCl. Correction for transfection efficiency was based on normalization of values obtained for the pURECAT relative to the values obtained for β-galactosidase activity. Levels of CAT activity were determined through standard thin-layer chromatography, and the percentage of conversion of chloramphenicol to the acetylated form was quantitated with the aid of a radioimaging blot analyzer (AMBIS, San Diego, CA).

**Protein Kinase Assays**—To assay JNK activity, the fusion protein glutathione S-transferase-Jun beads were used as the substrate for JNK as described previously (7, 13). Briefly, aliquots of 50 μg were incubated with [γ-32P]ATP (50 cpm/nmol; DuPont NEN) for 15 min. Following extensive washing, the phosphorylated glutathione S-transferase-Jun-bound beads were boiled in SDS sample buffer, and the eluted proteins were separated on a 15% SDS-polyacrylamide gel. The gel was dried, and phosphorylation of the Jun substrate was determined by quantitative autoradiography using a computerized radioimaging blot analyzer.

**RESULTS**

**Interaction Between Ras and JNK and c-Jun in Cellular Extracts**—To demonstrate direct interaction of p21ras with JNK, we have immunoprecipitated whole-cell extracts from 3T3-4A cells with the anti-Ras antibody, Y13-259. The immunoprecipitated proteins were subjected to Western blotting with either anti-JNK (Fig. 1, lane 3) or anti-Jun antibody (Fig. 1, lane 6), revealing that both JNK and Jun proteins coprecipitated with p21ras. Immunoprecipitation of cellular proteins with antibod-
shown that the presence of p21<sup>ras</sup> is sufficient to potentiate JNK activation in vitro (13). To this end, we have used M1311 cells that were maintained under normal growth conditions with or without dexamethasone. In the presence of dexamethasone, the expression of Y13-259 light chain cDNA is induced to enable the formation of functional antibodies that neutralize p21<sup>ras</sup> (19). UV irradiation was chosen as an external source of stress to induce JNK since it has been well studied with respect to cellular requirements to achieve proper activation of the kinase, including membrane components and nuclear DNA lesions (22). Exposure of M1311 cells to UV irradiation led to a noticeable increase in JNK activation (Fig. 5A), which resembled the pattern seen with other cell types (7, 13, 22). However, JNK activity progressively decreased as a function of the time of exposure of the cells to dexamethasone over a 5-day period (Fig. 5A). After 5 days of exposure, UV irradiation caused a very weak activation of JNK. Unlike its effect on UV-mediated JNK activation, neutralizing p21<sup>ras</sup> by dexamethasone-induced expression of anti-Ras antibodies did not impair the ability of heat shock to activate JNK (data not shown). Heat shock is an alternate form of stress shown to use cellular pathways other than UV, which are not dependent on membrane integrity and thus considered Ras-independent (7). As a control for the possible effect of dexamethasone itself, we have also maintained 3T3-4A cells, which are well characterized for JNK inducibility, in dexamethasone. As shown in Fig. 5B, dexamethasone did not affect the ability of UV to induce JNK activation, even after 5 days of exposure. As an additional control, we examined a variant of M1311 cells, DL6373 cells (19), that expresses a mutant p21 protein which lacks the Y13-259 binding domain (residues 63–73; Ref. 23) and is, therefore, not inactivated by expression of this antibody (19). When DL6373 cells were subjected to UV irradiation, no changes in the degree of UV-mediated JNK activation were noticed over the 5-day period (Fig. 5B). These results further confirm that the observed changes in M1311 cells are due to p21<sup>ras</sup> inactivation and indicate a requirement for p21<sup>ras</sup> in UV-mediated activation of JNK.

Transcriptional Activities of JNK Substrates in M1311 Cells—To measure transcriptional activities of the JNK substrates Jun and ATF2 in M1311 cells, we used the URE (TGA-CAACA), which has been shown to serve as a target for binding of c-Jun and ATF2 (24) as well as the AP1 target sequence. Previous studies demonstrated correlation between c-Jun phosphorylation by JNK and its DNA binding activities in gel shifts (25), as well as transcriptional activities in CAT assays using c-Jun promoter/target sequences (26). Gel shift assays, with proteins prepared 30 min after UV treatment, demonstrated that the presence of p21<sup>ras</sup> is sufficient to potentiate JNK activity using pGEX-Jun as a substrate in a solid-phase kinase reaction. Indicated antibodies (numbers in superscript indicate regions to which they were developed; poly reflects polyclonal antibodies) were used to immunodeplete the protein extracts, in which case the supernatant was used for the kinase reaction. B, quantification of the kinase reaction shown in A via radioimaging. Column 1, UV; column 2, antibody to JNK<sub>133–305</sub>; column 3, antibody Y13-259 to Ras; column 4, antibody to JNK<sub>168–615</sub>; column 5, polyclonal antibody to JNK; column 6, mouse IgG; column 7, rabbit IgG; column 8, antibody to Rb. Error bars were calculated based on three independent experiments.
that binding to the URE is inhibited in the M1311 cells that were maintained under dexamethasone (Fig. 6A, compare lanes D (−) and C (−) under the M1311 panel). In control DL6373 cells, dexamethasone treatment led to increased binding to the URE target sequence. UV treatment, however, decreased binding to the URE, in both the DL6373 and M1311 cells, a phenomenon we have observed previously in other transformed cells and which is attributed to the induction of a UV-inducible transcriptional inhibitor (27). In all cases, the complex formed was inhibited by an excess of cold URE or AP1 target sequences (Fig. 6A).

As an independent measure for transcriptional activities, we have transfected CAT vectors driven by either URE or AP1 target sequences (Fig. 6A). As shown in Fig. 6B, whereas URE-CAT and AP1-CAT activity measured 32 h after UV treatment was clearly induced after UV irradiation (6–12-fold), dexamethasone did not affect these activities in the DL6373 cells, although it greatly reduced URE-CAT and AP1-CAT transcription in the M1311 cells (Fig. 6B). When tested at earlier times (i.e. 24 h), no transcriptional activity was observed, in agreement with the pattern seen in the EMSA, which was performed on proteins prepared 30 min after UV treatment (Fig. 6A).

Analysis of JNK activities in protein preparations used for EMSA confirmed that dexamethasone-maintained M1311 cells had lost the ability of UV irradiation to properly activate JNK (Fig. 6C). Changes in binding to the URE thus indicate that transcriptional activities in UV-irradiated M1311 cells correlate with alteration by impaired Ras-dependent JNK activities.

**Peptide Inhibition of UV-induced JNK Activation**—Since the p21<sup>WAF1</sup> peptide corresponding to amino acids 96–110 was found to inhibit the binding of p21 to JNK (Fig. 1), we performed experiments in which 3T3-4A and M1311 cells were exposed to UV light in the presence and absence of selected peptides that...
were added to the incubation medium. To insure proper introduction of peptides into the cells, we have used the scrape-loading technique (28); this approach has been shown previously to successfully alter Ras activities (29). As shown in Fig. 7, the presence of the peptide significantly reduced the level of JNK activation in UV-treated 3T3-4A cells. For non-dexamethasone-treated M1311 cells, a significant (50%) reduction in the degree of JNK activation was also observed (Fig. 7). Dexamethasone-maintained M1311 cells (for 1 day, yielding a limited inhibition on UV-mediated activation; see Fig. 2) exhibited the most striking decrease in JNK activation of almost 90%, indicating that this peptide had a synergistic effect on the anti-Ras antibody induced by dexamethasone. Control reactions were performed by incubating these cells with different peptides, including epidermal growth factor receptor, Src, mitogen-activated protein kinase, and a mutant form of the Ras peptide corresponding to amino acids 96–110. None of these peptides was able to elicit inhibition of UV-mediated JNK activation in M1311 cells, nor could they affect the degree of JNK activation in the cells that were maintained in dexamethasone (data not shown).

DISCUSSION

We previously found that p21ras binds to purified bacterially expressed JNK and Jun proteins (13). The present studies further confirm this interaction both in vitro and in functional in vivo-based assays. These studies demonstrate that p21ras-bound JNK is increased after UV treatment, and that depletion of p21ras from protein extracts results in a marked decrease in JNK activity. That the amount of p21ras-bound JNK depends on cellular stress and increases significantly after UV irradiation points to a role for p21ras in UV-mediated JNK activation. Although immunodepletion with antibodies to p21ras resulted in about a 50% decrease in JNK activity, antibodies to JNK reduced this activity twice as efficiently, indicating that about one-half of the cellular JNK is bound to p21ras.

To probe the physiological significance of the direct interaction between p21ras and JNK and Jun, we have used a model cell system in which p21ras activation is blocked by an endogenously produced anti-p21ras-neutralizing antibody. Induction of Y13-259 antibody expression in the NIH-3T3 (M1311) cell line blocked the activation of JNK since JNK-induced phosphorylation of Jun diminished over a 5-day period, corresponding to increased expression of the anti-p21ras antibody (Fig. 2). Expression of ras cDNA, which lacks the recognition site for these antibodies, as seen in the DL8373 cells, restored the ability of UV to activate JNK, further supporting the conclusion that it is Ras inactivation that led to impaired JNK activation in M1311 cells. An independent support for the role of Ras-JNK interaction in JNK activation by UV comes from experiments in which a peptide corresponding to a Ras domain required for interaction with the kinase (amino acids 96–110) was introduced into M1311 cells, where it inhibited JNK activation after UV irradiation (Fig. 7). When dexamethasone was added to the medium allowing expression of Y13-259 antibodies, the inhibition mediated by this peptide was found to be synergistic with that induced by the antibody itself. Further support for p21ras-mediated JNK activation upon UV irradiation comes from the observation that JNK activation by heat shock, an alternate form of stress using different cellular pathways that do not require membrane integrity (7), was not inhibited in dexamethasone-maintained M1311 cells.

Our findings that membrane-bound p21ras binds to JNK and is required for its activation imply that JNK (and Jun) may become activated at or near the cell membrane. Interestingly, protein extracts prepared in the presence of Triton X-114, which was shown to extract p21ras from the membrane, led to the identification of JNK as a p21ras-bound protein.2 Recent studies suggest that JNK binds to growth factor receptor binding protein 2 (11), the adapter protein that links tyrosine kinase receptors to the SOS protein, which, in turn, activates p21ras by promoting GTP/GDP exchange. Although these findings suggest that JNK may be activated in the cytosol near the cell membrane, different JNK isozymes may be activated by alternate pathways, which include nuclear DNA lesions formed after UV irradiation (21). Nuclear localization of JNK was demonstrated recently to occur in UV-treated cells (30).

Expression of the anti-p21ras antibody Y13-259 in the NIH-3T3 (M1311) cells was also found to strongly inhibit transcriptional activation, as evidenced by weaker complexes and decreasing transcriptional activities measured by gel shift and CAT assays using the URE as a target sequence. The latter indicates that p21ras-associated JNK may play an important role in mediating the transcriptional activation of the JNK substrates tested here, viz c-Jun and ATF2.

Because other kinases (i.e. p54 and p38) were also shown capable of phosphorylating ATF2, which forms a heterodimer with c-Jun for binding to the URE (24), we cannot exclude the possibility that the mechanism of inhibition of URE-DNA binding activity, although Ras-dependent, is not solely related to JNK. Similarly, dexamethasone inhibition of URE-CAT activities in M1311 cells may not be confined to JNK inhibition. Further elucidating JNK-related transcriptional activities in Ras-dependent and -independent pathways will allow us to clarify the complex regulation of AP1 and ATF2 activities. Changes in JNK activity are likely to also affect its substrate stability, as shown for c-Jun, which is targeted by JNK for ubiquitination in a phosphorylation-dependent manner (31). In all, the functional significance of UV-mediated Ras-dependent transcriptional activities is expected to affect cell ability to cope with the UV effect via changes at the level of DNA repair, cell cycle, and possibly apoptosis.

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