Phosphorylation of 4E-BP1 Is Mediated by the p38/MSK1 Pathway in Response to UVB Irradiation*

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In resting cells, eIF4E-binding protein 1 (4E-BP1) binds to the eukaryotic initiation factor-4E (eIF-4E), preventing formation of a functional eIF-4F complex essential for cap-dependent initiation of translation. Phosphorylation of 4E-BP1 dissociates it from eIF-4E, relieving the translation block. Studies suggested that insulin- or growth factor-induced 4E-BP1 phosphorylation is mediated by phosphatidylinositol 3-kinase (PI3-kinase) and its downstream protein kinase, Akt. In the present study we demonstrated that UVB induced 4E-BP1 phosphorylation at multiple sites, Thr-36, Thr-45, Ser-64, and Thr-69, leading to dissociation of 4E-BP1 from eIF-4E. UVB-induced phosphorylation of 4E-BP1 was blocked by p38 kinase inhibitors, PD169316 and SB202190, and MSK1 inhibitor, H89, but not by mitogen-activated protein kinase kinase inhibitors, PD98059 or U0126. The PI3-kinase inhibitor, wortmannin, did not block UVB-induced 4E-BP1 phosphorylation, but blocked both UVB- and insulin-induced activation of PI3-kinase and phosphorylation of Akt. 4E-BP1 phosphorylation was blocked in JB6 Cl 41 cells expressing a dominant negative p38 kinase, p85 subunit, PD169316 and SB202190, and MSK1 inhibitor, H89, but not by mitogen-activated protein kinase kinase inhibitors, PD98059 or U0126. The PI3-kinase inhibitor, wortmannin, did not block UVB-induced 4E-BP1 phosphorylation, but blocked both UVB- and insulin-induced activation of PI3-kinase and phosphorylation of Akt. 4E-BP1 phosphorylation was blocked in JB6 Cl 41 cells expressing a dominant negative p38 kinase or dominant negative MSK1, but not in cells expressing dominant negative ERK2, JNK1, or PI3-kinase p85 subunit. Our results suggest that UVB induces phosphorylation of 4E-BP1, leading to the functional dissociation of 4E-BP1 from eIF-4E. The p38/MSK1 pathway, but not PI3-kinase or Akt, is required for mediating the UVB-induced 4E-BP1 phosphorylation.

The eIF4E-binding protein 1 (4E-BP1) is a 12-kDa polypeptide that in resting cells binds tightly to eIF4E on the mRNA cap, thus preventing formation of a functional eIF-4F complex (1). Phosphorylation of 4E-BP1 induced by certain extracellular stimuli, including growth factors, hormones, and mitogens, dissociates the binding of 4E-BP1 to eIF-4E and relieves the translation block. Therefore, 4E-BP1 is thought to be important in the regulation of protein synthesis (2, 3). Intensive studies have suggested that insulin- or growth factor-induced 4E-BP1 phosphorylation is mediated by phosphatidylinositol 3-kinase (PI3-kinase) and its downstream protein kinase, serine/threonine kinase Akt (4).

UV ultraviolet; B, DN, dominant negative mutant; MSK1, mitogen- and stress-activated protein kinase 1; ERK, extracellular-regulated kinase; JNK, c-Jun NH2-terminal kinase; MOPS, 4-morpholinepropanesulfonic acid; mTOR, mammalian target of rapamycin.

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MATERIALS AND METHODS

Cell Culture and Reagents—The JB6 mouse epidermal cell line CI 41 and its stable transfectants, dominant negative mutants of p38 kinase (CI 41 DN-p38), JNK1 (CI 41 DN-JNK1), ERK2 (CI 41 DN-ERK2), PI3K p85 subunit (CI 41 DN-p85), and pCMV-FLAG-MSK1 A195-N-terminal kinase-dead (N-DN-MSK1), pCMV5-FLAG-MSK1 A565/C-terminal kinase-dead (C-DN-MSK1), or pCMV5-FLAG-wild type MSK1 (wild-MSK1), were constructed as described previously (7–13). The cells were cultured in monolayers at 37 °C, 5% CO2 using Eagle’s minimal essential medium containing 5% fetal bovine serum, 2 mM L-glutamine, and 25 μg of gentamicin/ml. Fetal bovine serum and minimal essential medium were from BioWhittaker (Walkersville, MD); wortmannin was from BIOMOL Research Laboratories, Inc. (Plymouth Meeting, PA); PD169316, SB202190, PD98059, U0126, rapamycin, and insulin were from Sigma; H89 was from Alexis Corp. (San Diego, CA); antibodies against 4E-BP1 and eIF-4E were from Santa Cruz (Santa Cruz, CA); antibodies against Akt, MAP kinases ERKs, JNKs, and p38, and specific antibodies against phosphorylated sites of 4E-BP1 at Thr-36, Thr-45, Ser-64, and Thr-69, Akt at Ser-473, and ERKs, JNKs, and p38 kinase were from Cell Signaling (Beverly, MA).

Immunoprecipitation and Western Immunoblotting—Mouse epidermal JB6 CI 41 and its dominant negative mutant cell lines were cultured as described above. The cells were starved for 24 h in 0.1% fetal bovine serum minimal essential medium at 37 °C in a 5% CO2 incubator and then treated for 30 min with different inhibitors at the concentrations indicated. They were then exposed to UVB radiation (4 kJ/m2) or insulin (2.5 μg/ml) followed by culturing for another 1 h. Western blot analysis was carried out using antibodies against phosphorylated sites of 4E-BP1 (Thr-36, Thr-45, Ser-64, and Thr-69), Akt (Ser-473), and phosphorylation of the MAP kinase family as described previously (14, 15). Antibodies against total 4E-BP1, Akt, or the members of MAP kinase family were used as internal controls to determine loading efficiency. CI 41 cells were also treated with UVB and then 4E-BP1 in the cells was immunoprecipitated using an antibody against 4E-BP1 and captured by A/G PLUS-agarose/Sepharose beads. The samples were resolved by Western blotting and 4E-BP1 or eIF-4E was

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detected with antibodies against 4E-BP1 or eIF-4E.

**p38/MSK1 Mediates UVB-induced Phosphorylation of 4E-BP1**

**PI3-kinase Assay—**PI3-kinase activity was assessed as described previously (16). In brief, JB6 Cl 41 cells and the dominant negative mutant cell line for the PI3-kinase p85 subunit were cultured in monolayers in 100-mm dishes and incubated at 37 °C in a 5% CO2 incubator. When cells reached 90% confluence, they were starved for 1 h by culturing them in serum-free minimal essential medium for another 12 h. The cells were then either treated or not treated for 30 min with 0.1 μM wortmannin and then exposed to insulin (2.5 μg/ml) for 10 min or UVB (4 kJ/m2) followed by another 15 min incubation. The cells were then disrupted with 400 μl of lysis buffer (20 mM Tris-HCl, pH 7.4, 137 mM NaCl, 1 mM MgCl2, 10% glycerol, 1% Nonidet P-40, 1 mM diethiothreitol, 1 mM sodium orthovanadate, 1 mM phenylmethylsulfonyl fluoride, 10 μM aprotinin, 10 μM leupeptin, and 10 μM pepstatin), kept on ice for 30 min, and then sonicated (3 s). The lysates were centrifuged (14,000 rpm at 4 °C for 10 min) and the supernatant fraction (200 μl of protein) was incubated with 20 μl of agarose-conjugated anti-PI3-kinase p85α antibody (Z-8, Santa Cruz) overnight at 4 °C with gentle mixing. The enzyme-antibody-agarose complex was washed twice with 500 μl of each of the following buffers: 1) phosphate-buffered saline: 1% Nonidet P-40, 1 mM diethiothreitol, 0.1 mM sodium orthovanadate; 2) 100 mM Tris-HCl, pH 7.6, 0.5 mM LiCl, 1 mM diethiothreitol, 0.1 mM sodium orthovanadate; 3) 10 mM Tris-HCl, pH 7.6, 0.1 mM NaCl, 1 mM diethiothreitol, 0.1 mM sodium orthovanadate. The supernatant fraction was carefully removed from the enzyme-antibody-agarose complex and buffer 3 (20 μl) was added and the complex was incubated for 5 min on ice. Substrate buffer (20 μl of 50 mM HEPES, pH 7.6, 1 mM EGTA, 1 mM NaH2PO4, 0.5 mg/ml phosphatidylinositol (Sigma, purity >98%) previously sonicated for 10 min was added and the mixture was incubated for 5 min at room temperature. Reaction buffer (10 μl of 10 mM Tris-HCl, pH 7.6, 60 mM MgCl2, and 250 μM ATP containing 10 μCi of [γ-32P]ATP) was added and the mixture incubated for 10 min at 30 °C in a shaking incubator. The reaction was stopped by addition of 15 μl of 4 N HCl and 130 μl of chloroform/methanol (1:1), vortexed for 30 s, and kept for 5 min at room temperature. The chloroform phase (30 μl) was spotted onto 1% potassium oxalate-coated Silica Gel H (Uniplate) previously baked at 110 °C for 1 h. The plate was developed in chloroform/methanol/NH4OH/dH2O (60:47:4:11.3; v/v) and dried at room temperature. Radiolabeled spots were detected using the Storm 840 PhosphorImage System (Molecular Dynamics).

**Kinase Activity Assays for p38 Kinase, ERKs, and JNKs—**The activities of JNKs, ERKs, or p38 kinase were determined as described previously (16) following immunoprecipitation using c-Jun, Elk-1, or ATF-2 as substrate, respectively. In brief, serum-starved Cl 41 cells and stable transfectants, DN-p38, DN-JNK1, and DN-ERK2 were exposed to UVB irradiation (4 kJ/m2) followed by culturing for another 30 min. The cells were disrupted with ice-cold lysis buffer (50 mM Tris-HCl, pH 7.4, 1% Nonidet P-40, 0.25% Na deoxycholate, 150 mM NaCl, 1 mM EDTA, 1 mM phenylmethylsulfonyl fluoride, 1 μg/ml aprotinin, 1 μg/ml leupeptin, 1 μg/ml pepstatin, 1 mM Na3VO4, 1 mM NaF) and immunoprecipitated by mixing 500 μg of protein of each cell lysate with antibody against p38 kinase, JNKs, or ERKS overnight at 4 °C on an orbital shaker. The immunocomplex was captured by adding 100 μl of protein A/G PLUS-agarose/Pharose beads and gently rocked on an orbital shaker for another 4 h at 4 °C. The following components were then added: 10 μl of assay dilution buffer (20 mM MOPS, pH 7.2, 25 mM β-glycerophosphate, 5 mM EDTA, 1 mM Na3VO4, and 1 mM diethiothreitol); 0.5 μg of substrate, and 10 μl of [γ-32P]ATP (1 μCi/μl mixture). Tubes were incubated at 30 °C for 30 min and then 30 μl of the mixture was spotted on individual pieces of p81 paper (2 cm2). The assay squares were washed twice with 0.75% phosphoric acid and once with acetone and then transferred to scintillation vials with 5 ml of scintillation mixture and counted in a scintillation counter. The results were presented as cpm.

**In Vitro 4E-BP1 Phosphorylation Assay—**In vitro phosphorylation of 4E-BP1 by active p38 kinase, MSK1, Akt kinase (Upstate Biotechnology, Lake Placid, NY), or immunoprecipitated mTOR was assessed as described previously (16). In brief, Cl 41 cells were treated with SB202190 or rapamycin at the concentrations indicated for 30 min and then exposed to UVB. After incubation for another hour, mTOR in the cells was immunoprecipitated using an antibody against mTOR (Onco- gene, MA) and captured by A/G PLUS-agarose/Pharose beads. 4E-BP1 substrate (Stratagene, La Jolla, CA) was incubated with active p38 kinase, MSKI, Akt kinase, or immunoprecipitated mTOR beads and 200 μM ATP in 50 μl of kinase buffer (25 mM Tris, pH 7.5, 5 mM β-glycerophosphate, 2 mM diethiothreitol, 0.1 mM Na3VO4, and 10 mM MgCl2) for 30 min at 30 °C. The samples were resolved by 12% SDS-polyacrylamide gel electrophoresis and phosphorylated 4E-BP1 was detected with antibodies against 4E-BP1 or eIF-4E.

**RESULTS**

**UVB Irradiation Leads to 4E-BP1 Phosphorylation at Multiple Sites and Dissociation of 4E-BP1 from eIF-4E**—Phosphorylation of 4E-BP1 is an important step in controlling the rate of initiation of translation in mammalian cells (17). Some extracellular stimuli can induce proliferation and neoplastic transformation through phosphorylation of 4E-BP1 (1, 3, 17). Our results showed that UVB-induced phosphorylation of 4E-BP1 at multiple sites, Thr-36, Thr-45, Ser-64, and Thr-69, in both time- and dose-dependent manners (Fig. 1, A and B). To further investigate whether UVB-induced 4E-BP1 phosphorylations lead to functional dissociation of 4E-BP1 from eIF-4E, a co-immunoprecipitation experiment and Western blot analysis was performed. In samples immunoprecipitated with anti-4E-BP1 antibody following UVB treatment, eIF-4E could be detected by Western blot in the control and 30 min after UVB, but not at 60 min (Fig. 1C) after UVB, indicating that 4E-BP1 was dissociated from eIF-4E by 60 min after UVB irradiation.

These data suggest that UVB irradiation induces phosphorylation of 4E-BP1 at multiple sites that results in the functional dissociation of 4E-BP1 from eIF-4E.

**PD169316 or SB202190, but Not PD98059 or U0126, Suppress UVB-induced 4E-BP1 Phosphorylation—**UVB irradiation is known to cause activation of ERKs, JNKs, and p38 kinases (14–16). Therefore we examined the influence of specific MAP
kinase inhibitors on UVB- or insulin-induced 4E-BP1 phosphorylation. Both PD169316 and SB202190, specific inhibitors of MAP kinase p38, suppressed UVB-induced phosphorylation of 4E-BP1, but had no effect on insulin-induced phosphorylation of 4E-BP1 (Fig. 2, A and B). Neither MEK1 specific inhibitor, PD98059 nor U0126, had an effect on either UVB- or insulin-induced phosphorylation of 4E-BP1 (Fig. 2, C and D). PD98059 or U0126 also had no effect on UVB-induced phosphorylation of p38 kinase (Fig. 2, C and D). In these experiments, insulin failed to induce phosphorylation of p38 kinase (Fig. 2).

UVB-induced phosphorylation of 4E-BP1 is blocked in dominant negative mutant MAP kinase p38 cells, but not in dominant negative mutant MAP kinase ERK2 or JNK1 cells. JB6 Cl 41 and its stable transfectant dominant negative mutant of p38 kinase, ERK2, or JNK1 were cultured and treated as described under “Materials and Methods.” Western immunoblotting was performed three times using samples from different cell preparations. Similar results were obtained at phosphorylation sites Thr-45 and Thr-69 (data not shown). A representative gel is shown for A, B, and C.

p38/MSK1 Mediates UVB-induced Phosphorylation of 4E-BP1
that the dominant negative mutant cells were effective mutants (Fig. 4, A-C).

UVB-induced Phosphorylation of 4E-BP1 Is Suppressed by H89, or Blocked in DN-MSK1 Cl 41 Cells—MSK1 is a downstream kinase of p38 kinase. It is activated by UV irradiation and is involved in the phosphorylation of some transcription factors and nucleosomel components (13, 18). To further examine whether MSK1 might be involved in mediating UVB-induced phosphorylation of 4E-BP1, we used a dominant negative mutant cell line for MSK1, which is established and well characterized in our laboratory (13), to study phosphorylation of 4E-BP1 induced by UVB. UVB-induced phosphorylation of 4E-BP1 were blocked in either the C-DN-MSK1 or N-DN-MSK1 cell line compared with control Cl 41 (CMV-neo or wild-MSK1) cells (Fig. 5A). UVB-induced phosphorylations of 4E-BP1 were also inhibited by H89, a selective inhibitor of cAMP and cGMP-dependent protein kinases that has been demonstrated to inhibit UVB- or EGF-induced activation of MSK1 (13, 18), in a dose-dependent manner (Fig. 5B). These results indicate that both p38 kinase and its downstream kinase MSK1 may be involved in UVB-induced phosphorylation of 4E-BP1.

4E-BP1 Is Phosphorylated in Vitro by Active p38 Kinase or MSK1—We have demonstrated that p38 kinase or MSK1 is required for mediating UVB-induced phosphorylation of 4E-BP1. To further investigate whether activated p38 kinase or MSK1 phosphorylates 4E-BP1 directly, in vitro phosphorylation of 4E-BP1 was tested. Results indicate that 4E-BP1 was phosphorylated by activated p38 kinase or MSK1 in vitro, and was also weakly phosphorylated by active Akt (Fig. 6). Interestingly, the phosphorylation sites showed a differential response to the activation of different kinases. Active p38 kinase induced strong phosphorylation of 4E-BP1 at sites Thr-36 and Thr-45, but only phosphorylated Ser-64 weakly (Fig. 6). On the other hand, MSK1 induced a strong phosphorylation at Ser-64, but only weak phosphorylation at Thr-36 and Thr-45 (Fig. 6). At a similar dose, Akt could only induce a weak phosphorylation of 4E-BP1 compared with p38 kinase or MSK1 (Fig. 6). These results suggested that both p38 kinase and its downstream kinase, MSK1, are mediators for activation of 4E-BP1. However, the mechanisms of the activation are still not clear.

Wortmannin or DN-p85 Cells Had No Effect on UVB-induced 4E-BP1 Phosphorylation but Blocked UVB-induced PI3-kinase Activation and Akt Phosphorylation—Insulin has been reported to induce 4E-BP1 activation through a PI3-kinase dependent pathway (17, 19). To investigate whether UVB-induced 4E-BP1 phosphorylation is also mediated by PI3-kinase, we used a wortmannin, a PI3-kinase inhibitor, to pretreat JB6 C1 41 cells. Results indicated that wortmannin did not block UVB-induced phosphorylation of 4E-BP1 although it blocked insulin-induced phosphorylation of 4E-BP1 (Fig. 7A). Considering the possibility that wortmannin might be light sensitive, we used medium from the wells of the cells pretreated by wortmannin and exposed to UVB to treat cells for insulin exposure. The medium containing wortmannin did not block UVB-induced phosphorylation of 4E-BP1 but effectively blocked insulin-induced phosphorylation of 4E-BP1 (Fig. 7B). This result demonstrated that wortmannin was still effective after UVB irradiation and the failure of wortmannin to block UVB-induced phosphorylation was not due to the inefficiency of wortmannin after UVB irradiation. DN-p85 expression also had no effect on UVB-induced phosphorylation of 4E-BP1 (Fig. 7B). However, the activation of PI3-kinase induced by either UVB or insulin was blocked by wortmannin or in Cl 41 cells expressing DN-p85 (Fig. 7, C and D). Akt is suggested to act both upstream of 4E-BP1 and downstream of PI3-kinase to...
phosphorylate 4E-BP1 (17). To further verify that observation, we determined whether UVB-induced Akt was influenced by either wortmannin or by expression of DN-p85. The results clearly showed that both UVB- and insulin-activated phosphorylation of Akt was blocked by wortmannin (Fig. 7A) and that UVB-induced phosphorylation of Akt was also blocked in DN-p85 cells (Fig. 7B). These results strongly suggested that, unlike insulin, UVB might induce 4E-BP1 phosphorylation through a PI3-kinase and Akt independent pathway.

UVB-induced Phosphorylation of 4E-BP1 Is Blocked by Rapamycin—The mammalian target of rapamycin (mTOR) has been demonstrated to phosphorylate 4E-BP1 directly (20). To investigate whether UVB-induced 4E-BP1 phosphorylation is mediated by mTOR, we used rapamycin (21) to pretreat JB6 Cl 41 cells followed by exposure to UVB irradiation. Phosphorylation of 4E-BP1 induced by UVB was weakly inhibited by rapamycin in a concentration range that are not cytotoxic (Fig. 8A) (21). UVB-induced phosphorylation of p38 kinase and ERKs was not affected by rapamycin (Fig. 8A), indicating that the effect of rapamycin is not through p38 kinase. When we assessed mTOR activity using 4E-BP1 as substrate, we found that UVB could activate mTOR and this activation was blocked by the p38 kinase inhibitor, SB202190, or rapamycin pretreatment (Fig. 8B). Thus, mTOR may also be involved in UVB-induced 4E-BP1 phosphorylation.

DISCUSSION

UV irradiation is a major risk factor for human skin cancer (22–25). We reported here that UVB could induce a rapid (15 min following UVB exposure) phosphorylation of 4E-BP1 at multiple sites, Thr-36, Thr-45, Ser-64, Thr-69, leading to dissociation of 4E-BP1 from eIF-4E, which is thought to be critical in its function to initiate the protein translation process (26). Considering the important role of 4E-BP1 phosphorylation in cell proliferation and tumorigenesis, this mechanism may also be implicated in the tumor promotion effects of UVB.

UV irradiation has long been known to activate signal transduction pathways mediated by the MAP kinase family (17–19). In the present studies, both p38 kinase-specific pharmacological inhibitors, PD169316 and SB202190, effectively blocked UVB-, but not insulin-induced phosphorylation of 4E-BP1. However, the MEK inhibitors, PD98059 or U0126, which inhibit activation of ERKs, had no inhibitory effects on UVB-induced phosphorylation of p38 kinase or 4E-BP1 phosphorylation. These results indicated that p38 kinase is required for mediating UVB-induced phosphorylation of 4E-BP1, but ERKs are not. This conclusion was further confirmed using dominant negative mutants of p38 kinase, JNK1, or ERK2 cells. UVB-induced 4E-BP1 phosphorylation was blocked in DN-p38 kinase, but not in DN-JNK1 or DN-ERK2 cells. On the other hand, insulin-induced phosphorylation of 4E-BP1 was not blocked in any of the three dominant negative mutant cell lines.

The MAP kinase isoform ERKs is the earliest discovered and by far the most effective kinase that phosphorylates 4E-BP1 in
Thr-69 (data not shown). A representative gel is shown. Similar results were obtained in phosphorylation sites Thr-45 and performed three times using samples from different cell preparations. Western immunoblotting was assessed using 4E-BP1 as substrate (B). mTOR was immunoprecipitated, and mTOR activity was indicated (A). The results agreed well with the observation that the dissociation of 4E-BP1 from eIF-4E occurred between 30 and 60 min (Fig. 1A). All of the phosphorylation sites of 4E-BP1 are conserved in many species (1, 29), suggesting that all may be important in regulating this protein.

An accumulation of evidence supports the hypothesis that the PI3-kinase and Akt pathways are involved in the mediation of insulin- or growth factor-induced phosphorylation of 4E-BP1 (33). However, in our experiments, neither the PI3-kinase inhibitor, wortmannin, nor dominant negative mutant PI3-kinase subunit p85 (DN-p85) cells, was able to block UVB-induced phosphorylation of 4E-BP1, although they both effectively blocked UVB-activated PI3-kinase and Akt. These results indicated that UVB-induced phosphorylation of 4E-BP1 is at least through one pathway that is independent of PI3-kinase and its downstream kinase Akt.

mTOR has been reported to phosphorylate 4E-BP1 directly (19). Our results showed that rapamycin, a specific inhibitor of mTOR, weakly blocked UVB-induced phosphorylation of 4E-BP1, but had no effect on UVB-induced activation of p38 kinase or ERKs. The p38 kinase inhibitor, SB202190, blocked UVB-activated mTOR and subsequent activation of 4E-BP1. These results suggest that mTOR may also be involved in the signaling pathway leading to activation of 4E-BP1. However, whether p38 kinase acts through mTOR or whether other effectors are involved in mediating UVB-induced phosphorylation of 4E-BP1 needs to be further clarified.

We conclude that UVB induces phosphorylation of 4E-BP1 at multiple sites, leading to the functional dissociation of 4E-BP1 from eIF-4E. UVB-induced phosphorylations of 4E-BP1 occur through a pathway involving mTOR and kinases p38/MSK1, but independently of PI3-kinase and Akt (Fig. 9).

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