Phosphorylation of inositol 1,3,4-trisphosphate by inositol 1,3,4,5-tetraphosphate 5/6-kinase is the first committed step in the formation of higher phosphorylated forms of inositol. We have shown that the eight proteins called the COP9 signalosome complex copurify with calf brain 5/6-kinase. Because the complex has been shown to phosphorylate c-Jun in vitro, we tested both the complex and 5/6-kinase and found that both are able to phosphorylate c-Jun and ATF-2 on serine/threonine residues. These findings establish a link between two major signal transduction systems: the inositol phosphates and the stress response system.

Signaling through the inositol phosphate pathway involves a series of kinases and phosphatases that phosphorylate and dephosphorylate the large number of soluble inositol polyphosphates known to exist in eukaryotic cells (1). A branch point in this pathway occurs with the production of inositol 1,3,4-trisphosphate (Ins(1,3,4)P_3), resulting from the hydrolysis of inositol 1,3,4,5-tetraphosphate (Ins(1,3,4,5)P_4) by one of the numerous inositol polyphosphate 5-phosphatase isozymes (2). Ins(1,3,4)P_3 can be dephosphorylated by specific phosphatases, resulting ultimately in the generation of myo-inositol, or it can be phosphorylated further, resulting in the formation of higher phosphorylated forms of inositol. Inositol 1,3,4,5-tetraphosphate 5/6-kinase (5/6-kinase) phosphorylates Ins(1,3,4)P_3 to form both inositol 1,3,4,6-tetraphosphate (Ins(1,3,4,6)P_4) and Ins(1,3,4,5,6)P_5 (3, 4). Ins(1,3,4,6)P_4 is the first intermediate in the pathway leading to the formation of the higher phosphorylated inositol. We have shown that the eight proteins called the COP9 signalosome complex copurify with calf brain 5/6-kinase, assuming that copurification results in the inhibition of nuclear mRNA export (11). The human and calf brain enzymes produce more Ins(1,3,4,6)P_4 than Ins(1,3,4,5)P_4, whereas the ratio of products produced by the plant enzyme is reversed (13). In E. histolytica, the enzyme utilizes both Ins(1,3,4)P_3 and inositol 1,4,5-trisphosphate (Ins(1,4,5)P_3) as substrates. The two tetrakisphosphate products are produced in equal amounts from Ins(1,3,4)P_3, but when Ins(1,4,5)P_3 is the substrate only Ins(1,3,4,5)P_4 is a product. The activity of the amoebae enzyme is very low compared with that of the human and plant enzymes, which may be because of the fact that the inositol polyphosphates found in E. histolytica are not myo-derivatives but are neo-derivatives (14). In addition to producing two distinct isomers of InsP_5 from a single substrate, it has been shown recently that 5/6-kinase can utilize inositol 3,4,5,6-tetrakisphosphate (Ins(3,4,5,6)P_4) as a substrate for 1-kinase activity to produce InsP_5 (15).

Regulation of the activity of 5/6-kinase by cells is not well understood. In adrenal glomerulosa cells, stimulation with angiotensin causes a rise in the level of Ins(1,3,4,6)P_4 (16). A rapid rise in this tetrakisphosphate isomer is also seen after platelet stimulation by thrombin (17). In both cases, the levels of the 5/6-kinase substrate Ins(1,3,4)P_3 are elevated prior to a rise in Ins(1,3,4,6)P_4, and therefore the activity of 5/6-kinase under these conditions may not be changing.

We therefore sought to identify several proteins that copurified with calf brain 5/6-kinase, assuming that copurification may reflect an interaction between these proteins within the cell. We identify these proteins as subunits of a large protein complex called the COP9 signalosome. This complex was described originally in Arabidopsis seedlings in which a COP (constitutive photomorphogenesis) mutant was identified. The mutant, termed cop9, exhibited light-grown morphology when seedlings were grown in the dark. The protein responsible for the cop9 mutation, COP9, was cloned and shown to be a component of a large protein complex, the COP9 signalosome complex (18). The complex consists of eight subunits designated Sgn1 through Sgn8 and is conserved in mammals (19). The only known function of the mammalian complex is the in vitro phosphorylation of IκBα, p105, and c-Jun (20). Overexpression of the COP9 signalosome subunit Sgn2 in HeLa cells results in an increase in complex assembly and an elevation in the cellular levels of c-Jun, which results in increased AP1 transactivation (21). The COP9 signalosome has been shown recently to play a role in the ubiquitin pathway in plants and in fission yeast. The Arabidopsis COP9 signalosome associates with the...
E3 ubiquitin ligase SCFTIR1 and is required for auxin-responsive protein degradation (22). In Schizosaccharomyces pombe, the complex associates with several cullins, ubiquitin ligases that are post-translationally modified by the ubiquitin-like protein NEDD8. COP9 mutants lacking one of the subunits of the complex accumulate NEDD8-modified proteins, indicating that the COP9 complex is required for neddylation (23).

We show here that the calf brain COP9 signalosome complex phosphorylates c-Jun and ATF-2, another transcription factor known to be phosphorylated by stress-activated protein kinases. The calf brain complex contains a small amount of 5/6-kinase, which also phosphorylates c-Jun and ATF-2 in the absence of complex. 5/6-Kinase may represent the as yet unidentified protein kinase activity of the COP9 signalosome complex, which has been referred to as an associated kinase activity (21). Phosphorylation of ATF-2 by 5/6-kinase is concentration dependent, enhanced by Mn++, and unaffected by Ins(3,4,5,6)P4, a potent inhibitor of Ins(1,3,4)P3 phosphorylation and an alternative substrate for 5/6-kinase. Phosphorylation by 5/6-kinase occurs on serine/threonine residues. Fractionation of cytosolic extract from HEK 293 cells stably expressing human 5/6-kinase demonstrates a correlation between the inositol and protein kinase activities of 5/6-kinase. Depletion of 5/6-kinase using a polyclonal antiserum also partially removes the protein kinase activity. Purified, flag-tagged human 5/6-kinase expressed in SF21 cells phosphorylates ATF-2, indicating that these two activities reside within 5/6-kinase or that the two kinases associate very tightly. In either case, this work establishes a link between the inositol and protein kinase activities of 5/6-kinase.

**EXPERIMENTAL PROCEDURES**

**Reagents—**Goat polyclonal antibody against human JAB1, full-length his-tagged ATF-2, rabbit polyclonal antibody against ATP-2, and mouse monoclonal antibody against c-Jun were obtained from Santa Cruz Biotechnology. Recombinant human full-length c-Jun was from Promega. Rabbit polyclonal human 5/6-kinase antibody used for Western blot analysis was generated against the peptide VASLATKASSQ (representing amino acids 404–414 of 5/6-kinase). The rabbit polyclonal antibody used for immunochemicals was prepared against amino acids 124–311 of human 5/6-kinase. Recombinant ATF-2 was expressed in *Escherichia coli* as a GST fusion protein containing the first 109 amino acids of AT.

**Phospho Amino Acid Analysis—**Recombinant full-length his-tagged ATF-2 (4 μg) and recombinant full-length c-Jun (4 μg) were incubated with 390 ng of calf brain 5/6-kinase in a reaction volume of 75 μl containing 45 μCi of [γ-32P]ATP for 30 min at 37 °C. Samples were run on SDS-polyacrylamide gel electrophoresis sample buffer, run on 12% SDS gels, and transferred to polyvinylidene difluoride membranes (Millipore), and protein was precipitated by the addition of ammonium sulfate to 60% saturation, dialyzed against buffer A containing 3 mM MgCl2, and loaded onto a 1-ml Mono Q column (Amersham Pharmacia Biotech). A 20-ml linear gradient of 0–0.3 M NaCl in buffer A was used for elution. Fractions (1 ml) were aliquoted and stored at −80 °C.

**RESULTS**

**The COP9 Signalosome Co-purifies with Ins(1,3,4)P3 5/6-Kinase—**During the purification of calf brain Ins(1,3,4)P3 5/6-kinase, several proteins co-chromatographed with the enzyme preparation through a number of steps including affinity purification with InsP3 (24). The final contaminants, removed using a Mono Q column, were comprised predominantly of eight proteins, 10 ng of 5/6-kinase (as determined by enzymatic activity). Purification of Human 5/6-Kinase from SF21 Cells—Full-length human 5/6-kinase expressed in SF21 cells was used as an enzyme source. Mono Q fraction 14 (10 μl, 2.2 μg of total protein, and 5 ng of 5/6-kinase) was incubated with 10 μg of bovine serum albumin and 6 μl of preimmune or immune rabbit serum in the presence or absence of protein A-Sepharose (43 μl of a 50% slurry) overnight at 4 °C. Samples were spun, and supernatants were assayed for kinase activity.

**Immunodepletion of 5/6-Kinase—**Partially purified human 5/6-kinase expressed in 293 cells was used as an enzyme source. Mono Q fraction 14 (10 μl, 2.2 μg of total protein, and 5 ng of 5/6-kinase) was incubated with 10 μg of bovine serum albumin and 6 μl of preimmune or immune rabbit serum in the presence or absence of protein A-Sepharose (43 μl of a 50% slurry) overnight at 4 °C. Samples were spun, and supernatants were assayed for kinase activity. Phosphorylation of c-Jun and ATF-2 by 5/6-Kinase—Western blot of 200 ng of Mono Q fraction 13 blotted with anti-JAB1 antibody.

10 μg of penicillin/ml, and 100 μg of streptomycin/ml. Expression was induced with 0.1 μg of tetracycline/ml.

For partial purification of human 5/6-kinase, 100 150-mm dishes of cells were plated at 50% confluence in the presence of tetracycline. Cells were harvested after 3 days in culture using homogenization buffer containing 20 mM Heps, pH 7.2, 1 mM EDTA, 1 mM ATP, 10 mM benzanidene, 250 mM sucrose, 200 μg of soybean trypsin inhibitor/ml, 40 mM iodoacetamide, 2 mM pepstatin A, 40 mM bestatin, 1 mM phenylmethylsulfonyl fluoride, 40 mM leupeptin, 1 mM dithiothreitol, 1 mM EGTA, 50 mM NaF, 0.5 mM sodium vanadate, and 5 μg each of calpain inhibitors I and II/ml. The cells were sonicated and spun to remove particulate matter. A total of 360 mg of protein was obtained, which contained 16 μg of 5/6-kinase as determined by enzymatic activity. Filtered crude extract was loaded onto a 60-ml heparin-agarose column (Sigma) in 20 mM bis-Tris, pH 7.2, 1 mM ATP, 1 mM dithiothreitol, and 1 mM EGTA (buffer A). The column was elastomeric and protein was precipitated by the addition of ammonium sulfate to 60% saturation, dialyzed against buffer A containing 3 mM MgCl2, and loaded onto a 1-ml Mono Q column (Amersham Pharmacia Biotech). A 20-ml linear gradient of 0–0.3 M NaCl in buffer A was used for elution. Fractions (1 ml) were aliquoted and stored at −80 °C.

Immunodepletion of 5/6-Kinase—Partially purified human 5/6-kinase expressed in 293 cells was used as an enzyme source. Mono Q fraction 14 (10 μl, 2.2 μg of total protein, and 5 ng of 5/6-kinase) was incubated with 10 μg of bovine serum albumin and 6 μl of preimmune or immune rabbit serum in the presence or absence of protein A-Sepharose (43 μl of a 50% slurry) overnight at 4 °C. Samples were spun, and supernatants were assayed for kinase activity.

**Immunodepletion of 5/6-Kinase—**Partially purified human 5/6-kinase expressed in 293 cells was used as an enzyme source. Mono Q fraction 14 (10 μl, 2.2 μg of total protein, and 5 ng of 5/6-kinase) was incubated with 10 μg of bovine serum albumin and 6 μl of preimmune or immune rabbit serum in the presence or absence of protein A-Sepharose (43 μl of a 50% slurry) overnight at 4 °C. Samples were spun, and supernatants were assayed for kinase activity.

**Immunodepletion of 5/6-Kinase—**Partially purified human 5/6-kinase expressed in 293 cells was used as an enzyme source.
JAB1 (Jun activation domain-binding protein 1), which was part of the COP9 signalosome complex has been shown to phosphorylate c-Jun. The purified calf brain complex contains a small amount of 5/6-kinase, an enzyme that phosphorylates c-Jun. A representative autoradiogram from one of four experiments. Phosphorylation of c-Jun by 5/6-kinase is not caused by the purified inositol kinase preparation used contains no JAB1. Therefore, phosphorylation of c-Jun by 5/6-kinase is not caused by the purified calf brain 5/6-kinase, or 78 ng of 5/6-kinase alone. Shown is a representative autoradiogram from one of four experiments.

**Fig. 2.** Phosphorylation of c-Jun. A, autoradiography of in vitro kinase reactions with c-Jun incubated with 800 ng of COP9 signalosome complex mixed with 78 ng of purified calf brain 5/6-kinase, or 78 ng of 5/6-kinase alone. Shown is a representative autoradiogram from one of four experiments. B, silver-stained SDS gel of 160 ng of purified calf brain 5/6-kinase (Mono Q fraction 10). C, Western blot (W. blot) analysis of calf brain 5/6-kinase (39 ng) and COP9 signalosome complex (800 ng) blotted with an antibody against JAB1 and human 5/6-kinase.

**Phosphorylation of c-Jun and ATF-2 by 5/6-Kinase**

Phosphorylation of c-Jun and ATF-2 by 5/6-kinase has been shown to be inhibited by Ins(3,4,5,6)P4 in rat parotid acinar cells (34), rat liver (35), and porcine brain (36). Consistent with these reports, calf brain 5/6-kinase is inhibited by Ins(3,4,5,6)P4 with a Ki of 30 mM (data not shown). We therefore tested the effects of this InsP4 isomer on the phosphorylation of ATF-2 by 5/6-kinase. In contrast to the inositol kinase activity, the addition of 0.5 µM Ins(3,4,5,6)P4 to the protein kinase assay has no effect on phosphorylation of ATF-2 (Fig. 4A, lanes 2 and 3). No phosphorylation was observed when either 5/6-kinase or ATF-2 were omitted from the reaction (Fig. 4A, lanes 1 and 4, respectively).

Phosphorylation by many protein kinases is enhanced by or even dependent on the presence of MnCl2. We therefore tested whether the addition of MnCl2 to the two assays would have any effect. Inositol kinase assays were done in the presence of 6 mM MgCl2 alone and with 6 mM MgCl2 plus 5 mM MnCl2 (Fig. 4B). The addition of MnCl2 to the assay results in 37% inhibition of Ins(1,3,4)P3 phosphorylation by 5/6-kinase. By contrast, the addition of 5 mM MnCl2 to the protein kinase assay resulted in enhanced phosphorylation of full-length ATF-2, indicated by the arrow in Fig. 4C.

**Protein Kinase Activity of Human 5/6-Kinase**

To determine whether human 5/6-kinase can function also as a protein kinase, HEK 293 cells stably transfected with human 5/6-kinase were used as an enzyme source. Soluble extract from 293 cells induced with 3 days with tetracycline was fractionated on a heparin-agarose column followed by a Mono Q column. Fractions from the Mono Q column (1–20) were assayed for phosphorylation of Ins(1,3,4)P3 and GST-AFT-2 (Fig. 5A). Fractions 1–8 contained little protein and no 5/6-kinase (data not shown). Shown in the top panel is a Western blot of fractions 9–20 using an antibody against a carboxyl-terminal peptide of 5/6-kinase. The middle panel represents in vitro kinase assays of the same fractions using GST-AFT-2 as a substrate. On the bottom panel, Ins(1,3,4)P3 phosphorylation is plotted for these fractions. There is a strong correlation between inositol kinase phosphorylation and GST-AFT-2 activity.
activity and phosphorylation of ATF-2. Some phosphorylation of ATF-2 can be visualized in fractions 11 and 12, in which no inositol kinase activity is detected. Because this enzyme preparation is far from pure, it is likely that these fractions contain an additional kinase capable of phosphorylating ATF-2.

Immunodepletion of 5/6-kinase was done using Mono Q fraction 14 as an enzyme source and a polyclonal rabbit antiserum generated against a 188-amino acid peptide of human 5/6-kinase as antibody. In vitro kinase assays were done using antibody-treated 5/6-kinase and GST-ATF-2 as a substrate (Fig. 5B, upper). Phosphorylation of ATF-2 by 5/6-kinase was reduced in the absence of protein A-Sepharose (lane 2) and in the presence of protein A-Sepharose (lane 4). Similarly, the addition of immune serum reduced inositol kinase activity by 65% in the absence of protein A-Sepharose and by 93% in the presence of protein A-Sepharose (Fig. 5B, lower). Therefore, partial removal of 5/6-kinase as measured by the phosphorylation of Ins(1,3,4)P₃ also reduced the phosphorylation of ATF-2. The addition of protein A-Sepharose to the protein kinase assay consistently reduced the activity slightly.

To further establish the link between the two kinase activities of 5/6-kinase, full-length human 5/6-kinase was expressed in sf21 cells as a flag-tagged fusion protein and purified using an immobilized anti-flag antibody. Silver-stained SDS-polyacrylamide gel electrophoresis of the flag peptide-eluted 5/6-kinase preparation shows a single band (Fig. 6A, lane 1). Western blot analysis using either a flag antibody (Fig. 6A, lane 2) or an antibody against 5/6-kinase (Fig. 6A, lane 3) confirms that the protein band purified from sf21 cells represents flag-tagged 5/6-kinase. The specific activity of this preparation using Ins(1,3,4)P₃ as a substrate is 500,000 min⁻¹/mg of protein, comparable with that obtained for the purified calf brain protein (372,217 min⁻¹/mg of protein).

This flag-tagged 5/6-kinase preparation was then used in an in vitro protein kinase assay using full-length ATF-2 as a substrate. As with the calf brain 5/6-kinase, phosphorylation of ATF-2 occurs in a concentration-dependent fashion. ATF-2 phosphorylation by the recombinant fusion protein requires the addition of a much larger amount of enzyme than does phosphorylation by the purified calf brain protein. This could be because of the presence of Nonidet P-40 in the preparation, inappropriate post-translational modification, or the presence of the flag epitope on the protein.

**DISCUSSION**

The first member of the COP9 signalosome complex was identified originally in a genetic screen of Arabidopsis seedlings. The complex subsequently has been found in many organisms, with the exception of S. cerevisiae (19). We show here that the calf brain COP9 signalosome complex co-purifies with Ins(1,3,4)P₃ 5/6-kinase, an enzyme conserved from such diverse sources as plants (13), E. histolytica (12), and humans (24). Similar to the COP9 signalosome complex, there is no 5/6-kinase homologue in S. cerevisiae. The purification scheme of 5/6-kinase used repeated chromatography on heparin agarose (24). The cauliflower COP9 complex also binds heparin (37). Heparin binding alone is unlikely to account for the co-purification, because differential binding in the presence and absence of magnesium as well as affinity elution with InsP₆ were used. Even after the final purification step, some 5/6-kinase was detected in the fractions containing complex. It is therefore likely that 5/6-kinase associates with the COP9 signalosome complex.

The function of the mammalian COP9 signalosome complex is unknown, although it has been shown to phosphorylate several proteins including c-Jun (20). In this report, we show that the complex and 5/6-kinase purified from calf brain phosphorylate c-Jun as well as ATF-2. All preparations of complex used here contain some 5/6-kinase, which may represent the COP9 signalosome-associated kinase activity that to date has not yet been identified. In samples prepared for phospho amino acid analysis, the relative amount of ³²P incorporated into ATF-2 was significantly greater than that of c-Jun. This could indicate that ATF-2 is a better in vitro substrate for 5/6-kinase or that there may be multiple sites of phosphorylation on ATF-2.

Phosphorylation of ATF-2 by 5/6 kinase occurs predominantly on serine residues, with a minor amount of threonine phosphorylation. There is no evidence of tyrosine phosphorylation of ATF-2 by 5/6-kinase. Phosphorylation of ATF-2 by p38 occurs on threonine residues 69 and 71 (33), which results in increased stability of ATF-2 by protection from ubiquitination.
and subsequent degradation (38). ATF-2 has also been shown to be phosphorylated on threonine residues 69 and 71 as well as Ser-90 by stress-activated protein kinases, with phosphorylation depending on UV treatment of the cells (32). Protein kinase C has been reported to phosphorylate ATF-2 on Ser-121 in response to retinoic acid or induction with E1A (39). The consequences of phosphorylation of ATF-2 by 5/6-kinase remain to be determined.

Phosphorylation of a protein substrate by an inositol kinase has been demonstrated by several lipid kinases. PI3-kinase has been shown to phosphorylate the insulin receptor substrate IRS-1 (40), the adapter protein p101 and the protein kinase MEK-1 (41). Autophosphorylation has been reported to occur by PI3-kinase (reviewed in Ref. 46), type I phosphatidylinositol phosphate 5-kinase isozymes (42), and phosphatidylinositol 4-kinase β (43). Phosphorylation of the transcription factors c-Jun and ATF-2 by 5/6-kinase represents the first example of protein phosphorylation by an inositol kinase that utilizes a soluble, as opposed to a lipid, inositol polyphosphate as a substrate.

Ins(3,4,5,6)P₄ is not only a potent inhibitor of Ins(1,3,4)P₃ phosphorylation by 5/6-kinase, but has been reported recently to be a substrate of this enzyme as well (15). While inhibiting the inositol kinase activity of 5/6-kinase, this IP₄ isomer has no effect on phosphorylation of ATF-2 by 5/6-kinase. We also show that MnCl₂ inhibits Ins(1,3,4)P₃ phosphorylation by 5/6-kinase but activates ATF-2 phosphorylation. Therefore, the inositol kinase and the protein kinase activities of 5/6-kinase seem to be regulated differently. Differential regulation of protein ki-
sequence similarity is the ε isofrom of protein kinase C (24). Of the three short stretches of sequence similarity between the two proteins, none of the conserved residues have been implicated in the catalytic activity of the protein kinase C isoforms (reviewed in Ref. 48). Protein kinase Ce has been shown to be activated by phosphatidylinositol (3,4)P$_2$ and phosphatidylinositol (3,4,5)P$_3$ (49), and thus the regions of identity noted between protein kinase Ce and 5/6-kinase are more likely to be involved in inositol head group binding than in protein kinase activity. Mutagenesis of amino acid residues conserved between 5/6-kinase homologues from different species may shed light upon the structural requirements for inositol versus protein kinase activity.

Phosphorylation of the transcription factors c-Jun and ATF-2 by 5/6-kinase implicates this inositol kinase in the stress response pathway. The 5/6-kinase homologue in E. histolytica was identified in a differential display polymerase chain reaction from control versus heat-shocked amoebae, whereby 5/6-kinase mRNA was increased in extracts of heat-shocked parasites (12), lending additional support for the role of 5/6-kinase in the response of cells to stress. The trigger(s) responsible for the activation of 5/6-kinase in cells, and the cellular events following this activation remain to be determined. In addition, the role of the inositol polyphosphate products of 5/6-kinase in the stress response pathway have yet to be elucidated. The two functions of 5/6-kinase could represent a divergence of signals resulting from the activation of a single kinase by different stimuli having multiple cellular consequences.

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