We have studied a possible role of extracellular zinc ion in the activation of p70S6k, which plays an important role in the progression of cells from the G1 to S phase of the cell cycle. Treatment of Swiss 3T3 cells with zinc sulfate led to the activation and phosphorylation of p70S6k in a dose-dependent manner. The activation of p70S6k by zinc treatment was biphasic, the early phase being at 30 min followed by the late phase at 120 min. The zinc-induced activation of p70S6k was partially inhibited by down-regulation of phorbol 12-myristate 13-acetate-responsive protein kinase C (PKC) by chronic treatment with phorbol 12-myristate 13-acetate, but this was not significant. Moreover, Go6976, a specific calcium-dependent PKC inhibitor, did not significantly inhibit the activation of p70S6k by zinc. These results demonstrate that the zinc-induced activation of p70S6k is not related to PKC. Also, extracellular calcium was not involved in the activation of p70S6k by zinc. Further characterization of the zinc-induced activation of p70S6k using specific inhibitors of the p70S6k signaling pathway, namely rapamycin, wortmannin, and LY294002, showed that zinc activated upstream of mTOR/FRAP/RAFT and phosphatidylinositol 3-kinase (PI3K), because these inhibitors caused the inhibition of zinc-induced p70S6k activity. In addition, Akt, the upstream component of p70S6k, was activated by zinc in a biphasic manner, as was p70S6k. Moreover, dominant interfering alleles of Akt and PDK1 blocked the zinc-induced activation of p70S6k, whereas the lipid kinase activity of PI3K was potently activated by zinc. Taken together, our data suggest that zinc activates p70S6k through the PI3K signaling pathway.

p70 S6 kinase (p70S6k) was originally recognized as the kinase that regulates the multiple phosphorylation of the 40 S ribosomal protein S6 in vivo (1-4). Physiological roles of the kinase have been sought using various molecular and pharmacological methods for the past decade. Most worth noting, the inhibition of agonist-induced p70S6k activation in vivo by either microinjecting neutralizing antibodies (5) or by treatment with the immunosuppressant rapamycin to the cell severely impairs the progression of the cell cycle through the G1 phase (6-8). This strongly supports that p70S6k plays important roles during cell growth in the G1 to S cell cycle transition. Further emphasizing the importance of p70S6k at a molecular level is that the kinase is involved in the selective translational regulation of a unique family of mRNAs (9), presumably by mediating the multiple phosphorylation of 40 S ribosomal protein S6. These mRNAs encode for components of the translational apparatus, including ribosomal proteins and translational elongation factors whose increased expression is essential for cell growth and proliferation (10).

Recently, Thomas’ group (11) has shown that a mutant fly that has lost the p70S6k ortholog displays delayed growth and reduced cell and body size compared with those of the wild type fly. These genetic studies in Drosophila melanogaster clearly demonstrate that p70S6k and its downstream targets are not only involved in growth at the cellular level but also affect the development and growth of organs and the organism as a whole.

Although numerous agonists such as growth factors, cytokines, phorbol esters, calcium, inhibitors of protein synthesis, and hormones can activate p70S6k, still little is known about the direct regulators of p70S6k (1-4). Many studies utilizing either point mutational analysis of platelet-derived growth factor receptor (12), various PI3K mutants (13), or specific inhibitors for PI3K such as wortmannin and LY294002 (12, 14) have shown that PI3K is an upstream regulator of p70S6k. In addition, recent progresses in the understanding of the PI3K signaling have led to the discovery of two upstream regulators of p70S6k. The pleckstrin homology domain containing protein kinase phosphoinositide-dependent protein kinase 1 (PDK1) has been identified as the kinase responsible for phosphorylating threonine 229 in the activation loop of p70S6k (15). Interestingly, PDK1 phosphorylates and activates another pleckstrin homology domain containing protein kinase, Akt, as well (16, 17). Because p70S6k and Akt share PDK1 as a common upstream regulator, it appears that the PI3K signaling pathway is branched at the level of PDK1 in vivo. However, overexpression of constitutively active or dominantly negative forms of Akt also regulates p70S6k accordingly in vivo (18, 19), suggesting that the PI3K signaling pathway is not a typical kinase cascade as exemplified in the mitogen-activated protein kinase pathways.

In addition to these complex mechanisms, another signaling molecule is also involved in the regulation of p70S6k. The immunosuppressant rapamycin strongly inhibits p70S6k in vivo, which is a consequence of the inhibition of the activity of mammalian target of rapamycin (mTOR/FRAP/RAFT) (20-22). Although there are strong evidences implicating mTOR as an upstream regulator for p70S6k in vivo (6-8, 23), the exact...
molecular mechanism by which mTOR regulates p70S6k still remains elusive. In conclusion, such complexity in the regulation of p70S6k is likely due to its activation mechanism, which requires multiple hierarchical phosphorylations by several different kinases.

Zinc is an important trace element in biological systems. It is redox inert and has important roles in modulating the structural and catalytic activities of many cellular proteins. There has been circumstantial evidence suggesting that zinc might be involved in several neurological dysfunctions and other diseases (24, 25). For example, zinc interacts with β-amyloid and its precursor protein, which are believed to be involved in the pathogenesis of degenerative processes in the brain, particularly in Alzheimer’s disease (26). On the other hand, recent experimental evidences support that zinc is involved in cell growth and death in general in vivo (24, 25). For example, zinc potentiates the mitogenic signaling of insulin (27) and activates extracellular signal-regulated kinase-mitogen-activated protein kinase 1 and 2 (28). In addition, tyrosine phosphorylations of epidermal growth factor (EGF) receptor are induced by zinc in human epithelial cell lines (29). These findings prompted us to examine the effects of zinc on p70S6k and the PI3K signaling pathway.

Here, we show that zinc potently activates p70S6k in a biphasic manner. This activation is completely inhibitable by rapamycin, wortmannin, and LY294002 and is independent from PKC and extracellular calcium levels. In addition, co-expression of dominantly interfering alleles of Akt and PDK1 strongly blocks the activation of p70S6k by zinc. Furthermore, zinc can activate the lipid kinase activity of PI3K. Thus, we conclude that zinc activates p70S6k via the PI3K signaling pathway in vivo.

**EXPERIMENTAL PROCEDURES**

**Cell Culture and Transfection**—COS and Swiss 3T3 cells were maintained in Dulbecco’s modified Eagle’s medium supplemented with 10% fetal bovine serum (Life Technologies, Inc.) at 37 °C in a humidified atmosphere with 5% CO2. Transient transfection in COS cells were performed at 60% confluency by a DEAE-dextran method as described in the manufacturer’s manual (Promega).

**Cell Lysate Preparation**—Serum-starved cells were treated with various reagents as indicated in figures; 50 ng/ml EGF (Life Technologies, in the manufacturer’s manual (Promega)).

**Protein Kinase Assay**—The endogenous p70S6k in Swiss3T3 cells was immunoprecipitated by anti-p70S6k polyclonal antibody coupled to protein A-Sepharose (Amersham Pharmacia Biotech). Transiently transfected HA-tagged Akt and p70S6k or Myc-tagged PDK1 and p70S6k were immunoprecipitated by 12CA5 anti-HA or HE10 anti-Myc monoclonal antibody coupled to protein G-Sepharose (Amersham Pharmacia Biotech). The samples were washed twice with Buffer A containing 50 mM Tris- HCl (pH 7.5), 150 mM NaCl, 1 mM MgCl2, 1 mM CaCl2, 10% glycerol, 1% Nonidet P-40, and 500 μM sodium orthovanadate.

**RESULTS**

**Zinc Induces PI3K Cell Signalings**

**Dose- and Time-dependent Activation of p70S6k by Zinc**—To examine the effects of zinc on p70S6k, quiescent Swiss 3T3 cells were treated with ZnSO4 for various doses and time periods, and the S6 phosphotransferase activities of p70S6k of their cell lysates were examined by immune complex kinase assays. As shown in Fig. 1A, the protein kinase activities of p70S6k were slightly induced by up to 50 μM ZnSO4 but strongly activated by 100 μM ZnSO4 to levels comparable with EGF stimulation (Fig. 1A, top and middle panels). In the immunoblots analyses of the same lysates used for the kinase assay, we could detect the slow migrating species of p70S6k in the 100 μM ZnSO4-treated sample (Fig. 1A, bottom panel). As previously reported, such retarded species of p70S6k are also seen following growth factor stimulation and represent the highly phosphorylated and activated forms of the kinase (6).

Next, we examined the activation time course of p70S6k by zinc. Quiescent cells were treated with 100 μM ZnSO4 for various time periods. Unexpectedly, we reproducibly observed that zinc stimulation induces p70S6k activity in a biphasic manner (Fig. 1B). The earlier phase appears between 0 and 60 min and peaked at 30 min, followed by the late phase peaking at 120 min. These time-dependent activities of p70S6k were again tightly co-related with the phosphorylation of the kinase (Fig. 1B, bottom panel).

To confirm that the zinc sulfate-mediated activation of p70S6k is indeed induced specifically by zinc divalent ion, we examined the effects of other similar salts on the S6 kinase activity of p70S6k. As shown in Fig. 2, only ZnSO4 and ZnCl2, but not MgSO4, MgCl2, NaCl, or CaCl2, induced the activities of p70S6k. This result unequivocally demonstrates that zinc ion is specifically responsible for activation of p70S6k.

**Protein Kinase C- and Calcium-independent Activation of p70S6k by Zinc**—The PMA-dependent activation of p70S6k requires PMA-responsive PKC (30). This was demonstrated by rechallenging PMA to cells with PKC down-regulated by chronic pre-exposure (20 h) to PMA. To test the role of PKC in the biphasically induced activation of p70S6k by zinc, we stim-
Zinc Induces PI3K Cell Signalings

FIG. 1. Zinc sulfate activates p70S6k biphasically in Swiss 3T3 cells. Quiescent Swiss 3T3 cells were treated with the indicated concentration of zinc sulfate or EGF for 30 min (A) or 100 μM of zinc sulfate for the indicated time periods (B). Cells were lysed and assayed for p70S6k activity as described under “Experimental Procedures.” Phosphorylated substrates were visualized by autoradiography (middle panel) and quantified with Phosphoimager analyses (top panel). Anti-p70S6k immunoblot analyses were completed from the same cell lysates used for the kinase assay (bottom panel). Arrows indicate the phosphorylated and slowly migrating forms of p70S6k. The values in the top panel represent the mean of three independent cell preparations ± S.D.

FIG. 2. Only zinc ion activates p70S6k in Swiss 3T3 cells. Quiescent cells were treated with 100 μM of various salts as indicated for 30 min. Prepared cell lysates were assayed for p70S6k activity as described under “Experimental Procedures.” Phosphorylated S6 proteins were quantified with Phosphoimager analyses (top panel) and visualized by autoradiography (middle panel). Immunoblot analyses were completed from the same cell lysates used for the kinase assay with anti-p70S6k polyclonal antibody (bottom panel). Arrows indicate the phosphorylated and slowly migrating forms of p70S6k. The values in the top panel represent the means of three independent cell preparations ± S.D.

the possible involvement of calcium in the regulation of p70S6k (31, 32). Therefore, we examined whether calcium plays a role in the activation of p70S6k by zinc. The activation and phosphorylation of p70S6k from Swiss 3T3 cells cultured in a calcium-free Dulbecco’s modified Eagle’s medium (obtained from Life Technologies, Inc.) were strongly induced by zinc (Fig. 4). As a control, the addition of calcium to the cell did not significantly stimulate the S6 kinase activities of p70S6k, despite slightly increasing phosphorylation of the kinase. In addition, when we applied calcium and zinc together, calcium rather slightly inhibited the zinc-mediated activation of p70S6k at higher doses (Fig. 4). These data indicate that extracellular calcium is not involved in the zinc-induced activation of p70S6k.

PI3K- and mTOR-dependent Signaling Pathways Mediate the Activation of p70S6k by Zinc—Our immunoblot analyses clearly show that the activation of p70S6k by zinc is mediated by phosphorylations, as with activation by other agonists. As described in the introduction, p70S6k is regulated by the PI3K signaling pathway and the mTOR-dependent pathway in vivo. Therefore, we examined the effects of rapamycin, a specific inhibitor of mTOR, or wortmannin and LY294002, two structurally unrelated PI3K inhibitors, on the activation and phosphorylation of p70S6k by zinc. As shown in Fig. 5, the zinc-induced activation and phosphorylation of p70S6k were strongly inhibited by these drugs. These results strongly suggest that the zinc-mediated activation and phosphorylation of p70S6k is dependent on mTOR and PI3K in vivo. Zinc Activates Akt in a Biphasic Manner—To understand how the PI3K pathway mediates the zinc-mediated activation of p70S6k, we first examined the zinc-induced activation of Akt in Swiss 3T3 cells. Akt plays a pivotal role in the PI3K pathway and is activated by phosphorylations at threonine 308 in the activation loop and serine 473 within the C-terminal domain (33). These phosphorylations are tightly correlated with the activities of Akt in vivo (33). As shown in Fig. 6, quiescent Swiss 3T3 cells were stimulated with 100 μM of zinc sulfate for various time intervals as indicated, and the Akt activities were determined by immunoblot analyses with serine 473 phosphospecific Akt antibody. Surprisingly, zinc induced Akt serine 473 phosphorylation in a biphasic manner (Fig. 6), just like p70S6k shown in Fig. 1B. The early phase appears as early as 1 min and peaked at 5 min, followed by the late phase peaking...
Zinc Induces PI3K Cell Signalings

4. Extracellular calcium is not involved in the activation of p70S6k by zinc in Swiss 3T3 cells. Quiescent Swiss 3T3 cells were incubated in the absence (−) or presence (+) of zinc sulfate (100 μM) for 30 min following pretreatment with rapamycin (Rap), wortmannin (Wort), or LY29402 for 30 min. Cell lysates were subjected to immune complex kinase assays for p70S6k (top and middle panels) and immunoblot analyses for p70S6k (bottom panel) as described under “Experimental Procedures.” The values in the top panel represent the means of three independent cell preparations ± S.D.

5. Inhibition of the zinc-induced p70S6k activity by rapamycin, wortmannin, or LY29402 in Swiss 3T3 cells. Quiescent Swiss 3T3 cells were incubated in calcium-free Dulbecco’s modified Eagle’s medium supplemented with 100 μM of zinc sulfate for 30 min following pretreatment with rapamycin (Rap), wortmannin (Wort), or LY29402 for 30 min. Cell lysates were subjected to immune complex kinase assays for p70S6k (top and middle panels) and immunoblot analyses for p70S6k (bottom panel) as described under “Experimental Procedures.” The values in the top panel represent the means of three independent cell preparations ± S.D.

6. Biphasic activation of Akt by zinc in Swiss 3T3 cells. Quiescent cells were treated with zinc sulfate (100 μM) for the indicated time periods. Cell lysates were subjected to immunoblot analyses for Akt serine 473 phosphorylation (top panel) and total Akt protein as described under “Experimental Procedures.” The results shown are representative of three independent experiments.

at 60 min (Fig. 6). This activation pattern of Akt is very similar to that induced by growth factors such as EGF, platelet-derived growth factor, and insulin (34).

Zinc Activates p70S6k via the PI3K Signaling Pathway in Vivo—Because we found Akt to be activated by zinc, we next examined whether other components of the PI3K pathway are affected by zinc in the activation of p70S6k. Recent studies showed that PDK1 (15) and Akt (18, 19) relay the growth factor-induced activation signals from PI3K to p70S6k either directly or indirectly. To confirm their involvement in the zinc-mediated activation of p70S6k in vivo, we co-expressed a dominant negative form of Akt or PDK1, both kinase-dead (KD) mutants, with p70S6k in COS cells. Zinc strongly induced p70S6k activity in COS cells, supporting that the zinc-mediated activation of p70S6k is not a cell type-specific phenomenon (Fig. 7). As expected, co-expression of wild type (wt) Akt (Fig. 7A) or PDK1 (Fig. 7B) with p70S6k slightly augmented the activation of p70S6k by zinc. However, co-expression of dominant negative Akt (Fig. 7A) or dominant negative PDK1 (Fig. 7B) blocked the zinc-induced activation of p70S6k down to the unstimulated control level. These results strongly suggest that PDK1 and Akt play major roles as upstream regulators in the zinc-mediated activation of p70S6k.

Next, we examined whether zinc directly regulates the activities of PDK1 and Akt. As shown in Fig. 8, addition of zinc ion failed to affect the phosphorylase activity of immunoprecipitated PDK1 and Akt in our experimental conditions (Fig. 8, A and B, respectively), which suggests that extracellular zinc regulates component(s) further upstream of PDK1 in the PI3K signaling pathway in vivo. Therefore, we examined...
whether the lipid kinase activity of PI3K was stimulated by exogenous zinc. Indeed, zinc strongly stimulated the lipid kinase activity of PI3K by 7-fold, comparable with EGF stimulation, and this activation was inhibited by wortmannin (Fig. 9).

**FIG. 7.** Inhibition of zinc-induced p70S6K activities by co-expression of dominant interfering alleles of Akt or PDK1. A, COS cells were transiently transfected with pJ3M-p70S6K alone or pJ3M-p70S6K and pCMV5-HA-Akt-wt or -KD. Quiescent cells were stimulated with (+) or without (−) zinc sulfate (100 μM) for 30 min. Cell lysates were subjected to either immune complex kinase assays for Myc-p70S6K (top panel) or immunoblot analyses for Myc-p70S6K (middle panel) and HA-Akt (bottom panel). B, COS cells were transiently transfected with pJ3M-p70S6K alone or pJ3M-p70S6K and pDNA-Myc-PDK1-wt or KD. Quiescent cells were incubated with (+) or without (−) zinc sulfate (100 μM) for 30 min. HA-p70S6K was immunoprecipitated by anti-HA monoclonal antibody and assayed for S6 phosphotransferase activity as described under “Experimental Procedures” (top panel). Immunoblot analyses for HA-p70S6K (middle panel) and Myc-PDK1 (bottom panel) were completed from the same cell lysates used for the kinase assays. The results shown are representative of three independent experiments.

**FIG. 8.** Zinc does not directly activate PDK1 and Akt. COS cells were transiently transfected with pC3DNA3-Myc-PDK1 (A) or pCMV5-HA-Akt (B). Quiescent cells were stimulated with (+) or without (−) EGF for 5 min. PDK1 and Akt were immunoprecipitated by anti-Myc and anti-HA antibody, respectively, and the immunocomplexes were subjected to kinase assays as described under “Experimental Procedures” (top and middle panels). Zinc sulfate (final concentration, 100 μM) was added in the kinase assay mixture. Immunoblot analyses were completed from the same cell lysates used for the kinase assays (bottom panel). The results shown are representative of three independent experiments.

**FIG. 9.** Activation of the lipid kinase activity of PI3K by zinc. Quiescent Swiss 3T3 cells were pretreated with (+) or without (−) wortmannin (Wort) and further treated with zinc (100 μM) or EGF (50 ng/ml) for 2 min. Cell lysates were prepared as described under “Experimental Procedures,” and anti-phosphotyrosine antibody was added to the cleared cell lysates. Immune complexes were subjected to lipid kinase assays for PI3K, and phospholipids were extracted and separated by thin layer chromatography. The quantitated 32P incorporation into phosphatidylinositol 3-phosphate (PIP) (bottom panel) was shown as a bar graph (top panel) that represents the means of three independent experiments ± S.D.

**DISCUSSION**

Zinc is present in nearly all body tissues, especially in the thyroid, pancreas, brain, and reproductive organs (25). This mineral is involved in the body’s enzymatic reactions, protein synthesis, and carbohydrate metabolism, etc. In addition, zinc is essential for cell growth and is required for healing and maintaining healthy tissues. It has been understood that these important physiological roles of zinc might stem from the co-factor-like roles of the divalent ion in the cell. However, a recent output of research, mainly focusing on zinc-mediated neurotoxicity, has implied that zinc itself may be directly involved in various cell signalings (24). However, no systematic research has been conducted on how zinc is involved in the regulation of cell growth and survival at the molecular level. Here, we first demonstrate the involvement of zinc in the cell signaling activity of p70S6K through the PI3K signaling pathway. Because the PI3K pathway has important roles in regulating cell growth, apoptosis, and development, our present results not only provide a novel mechanism in the regulation of the p70S6K and the PI3K pathway but also instate zinc as a major player in cell signal transduction.

Several groups have proposed that zinc can enter cells through calcium channels along with calcium (35, 36), and Kiss and co-workers (37) reported that extracellular calcium-induced stimulation of DNA synthesis and p70S6K activity in NIH 3T3 was dependent on zinc, leading us to first suspect that zinc regulates p70S6K through calcium- and PKC-dependent mechanisms. However, our results clearly showed that an increase in extracellular zinc strongly stimulates p70S6K in a manner that is independent of both PKC and extracellular calcium (Figs. 3 and 4). These interesting effects of zinc on...
p70S6k are very similar to those seen following growth factor-mediated cell stimulation (30).

A decade ago, Thomas’ group (38) showed that the EGFstimulated p70S6k activities exhibit biphasic activation kinetics; the early phase of activation appears at 10–15 min, followed by the late phase at between 30–60 min, which is sensitive to PKC down-regulation. Our data demonstrated that zinc also induces p70S6k and Akt in a biphasic manner (Figs. 1B and 6). The early peak of p70S6k activity appears at 30 min, and the late peak appears at 120 min following zinc stimulation. Interestingly, the p70S6k activities detected during the early peak is partially (about 30%) sensitive to down-regulation of PKC and to a specific PKC inhibitor, but the late peak is completely insensitive to PKC down-regulation (Fig. 3). This interesting pattern of PKC dependence of the zinc-induced p70S6k activity is highly consistent with our previous results from the platelet-derived growth factor-dependent activation of p70S6k (12); p70S6k is regulated by the PKC-dependent pathway and the PI3K-dependent pathway in a 3:7 ratio.

In this paper, we confirmed that zinc stimulates p70S6k activity through the PI3K-dependent pathway using specific inhibitors of PI3K, wortmannin, and LY294002 (Fig. 5) and a model that zinc induces the generation of reactive oxygen species; the early phase of activation appears at 10–15 min, followed by the late phase at between 120–180 min. This model suggests that zinc activates PI3K and on the precise mechanisms through which the PI3K/p70S6k signaling pathway acts to modulate the response

to zinc, are needed to fully understand this newly discovered role of zinc in the cell.

REFERENCES
1. Grammer, T. C., Cheatham, L., Chou, M. M., and Blenis, J. (1994) Cancer Surv. 27, 271–292
2. Proud, C. G. (1996) Trends. Biochem. Sci. 21, 181–185
3. Belham, C., Wu, S., and Avruch, J. (1999) Curr. Biol. 9, 93–96
4. Dufner, A., and Thomas, G. (1999) Exp. Cell. Res. 253, 100–109
5. Lane, H. A., Fernandez, A., Lamb, N. J., and Thomas, G. (1995) Nature 363, 170–172
6. Chung, J., Kuo, C. J., Crabtree, G. R., and Blenis, J. (1992) Cell 69, 1227–1236
7. Kuo, C. J., Chung, J., Fiorentino, D. F., Flanagan, W. M., Blenis, J., and Crabtree, G. R. (1992) Nature 358, 70–73
8. Price, D. J., Grove, J. R., Calvo, V., Avruch, J., and Birer, B. E. (1992) Science 257, 973–977
9. Jeffries, H. B., Furmagalli, S., Dennis, P. B., Reinhard, C., Pearson, R. B., and Thomas, G. (1997) EMBO J. 16, 3693–5704
10. Alamed, A., and Pierandrei-Alamed, P. (1997) Prog. Mol. Subcell. Biol. 18, 1–17
11. Montagne, H., Stewart, M. J., Stocker, H., Hafen, E., Kozma, S. C., and Thomas, G. (1999) Science 285, 2126–2129
12. Chung, J., Grammer, T. C., Lemon, K. P., Kazlauskas, A., and Blenis, J. (1994) Nature 370, 71–75
13. Weng, Q. P., Andrabhi, K., Klippel, A., Kozlowski, M. T., Williams, L. T., and Avruch, J. (1999) Proc. Natl. Acad. Sci. U. S. A. 96, 5744–5748
14. Cheatham, B., Vlahos, C. J., Cheatham, L., Wang, L., Blenis, J., and Kahn, C. R. (1994) Mol. Cell. Biol. 14, 4902–4911
15. Pullen, N., Dennis, P. B., Andjelkovic, M., Dufner, A., Kazlauskas, S. C., Hemmings, B. A., and Thomas, G. (1998) Science 279, 707–710
16. Alesse, D. R., James, S. R., Downes, C. W., Holmes, A. B., Gaffney, P. R., Reese, C. B., and Cohen, P. (1997) Curr. Biol. 7, 261–269
17. Shepherd, L., Anderson, K., Stokoe, D., Erdjument-Bromage, H., Painter, G. F., Holmes, A. B., Gaffney, P. R., Reese, C. B., McCormick, F., Tempest, P., Coadwell, J., and Hawkins, P. T. (1998) Science 279, 710–714
18. Burgering, B. M., and Coffer, P. J. (1995) Nature 376, 599–602
19. Koh, A. D., Summermen, S. A., Birnbaum, M. J., and Roth, B. A. (1996) J. Biol. Chem. 271, 31372–31378
20. Brown, R. J., Albers, M. W., Skin, T. B., Ichikawa, K., Keith, C. T., Lane, W. S., and Schreiber, S. L. (1995) Nature 377, 441–446
21. Choi, D. W., and Koh, J. Y. (1998) Annu. Rev. Neurosci. 21, 347–375
22. Cuaqugno, M. P., and Lees, G. J. (1997) Neurobiol. Dis. 4, 137–169
23. Bush, A. I., Multhaup, G., Mor, R. D., Williamson, T. G., Small, D. H., Rumble, B., Bullwein, P., Breytercher, K., and Masters, C. L. (1993) J. Biol. Chem. 268, 16109–16112
24. Kiss, Z., Crilly, K. S., and Tomono, M. (1997) FEBS Lett. 415, 71–74
25. Park, J. A., and Koh, J. Y. (1999) J. Neurochem. 73, 459–456
26. Wu, W., Graves, L. M., Jackson, J. P., Devlin, R. B., Reed, W., and Samet, J. M. (1999) Am. J. Pathol. 154, L924–L931
27. Chung, J., Chen, R. H., and Blenis, J. (1991) Mol. Cell. Biol. 11, 1868–1874
28. Green, L. M., He, Y., Lambert, J., Hunter, D., Li, X., and Ehr, H. S. (1997) J. Biol. Chem. 272, 1920–1928
29. Conus, N. M., Hemmings, B. A., and Pearson, R. B. (1998) J. Biol. Chem. 273, 4776–4782
30. Alesse, D. R., Andjelkovic, M., Caudwell, B., Cron, P., Morrice, N., Cohen, P., and Hemmings, B. A. (1996) EMBO J. 15, 6541–6551
31. Franke, T. F., Yang, S. I., Chan, T. O., Datta, K., Kazlauskas, A., Morrison, D. K., Kaplan, D. R., and Tsichlis, P. N. (1996) Cell 81, 727–736
32. Koh, J. Y., and Choi, D. W. (1994) Neuroscience 109, 1049–1057
33. Weiss, J. H., Hartley, D. M., Koh, J. Y., and Choi, D. W. (1993) Neuron 10, 45–49
34. Huang, J. S., Mukherjee, J. J., Chung, T., Crilly, K. S., and Kiss, Z. (1999) Eur. J. Biochem. 266, 943–951
35. Susa, M., Olivier, A. R., Fabbro, D., and Thomas, G. (1989) Cell 57, 817–824
36. May, J. M., and Contoreggi, C. S. (1982) J. Biol. Chem. 257, 4362–4368
37. Wang, X., McCulloch, K. D., Franke, T. F., and Huber, N. A. (2000) J. Biol. Chem. 275, 14624–14631
38. Van der Kaay, J., Beck, M., Gray, A., and Downes, C. P. (1999) J. Biol. Chem. 274, 35063–35068
39. Sonada, Y., Watanabe, S., Matsumoto, Y., Aizu-Yokota, E., and Kasahara, T. (1999) J. Biol. Chem. 274, 10566–10570
40. Abe, J., Takahashi, M., Ishida, M., Lee, J. D., and Berk, B. C. (1997) J. Biol. Chem. 272, 20389–20394
Extracellular Zinc Activates p70 S6 Kinase through the Phosphatidylinositol 3-Kinase Signaling Pathway
Sunhong Kim, Youngsun Jung, Dohoon Kim, Hyongjong Koh and Jongkyeong Chung

J. Biol. Chem. 2000, 275:25979-25984.
doi: 10.1074/jbc.M001975200 originally published online June 12, 2000

Access the most updated version of this article at doi: 10.1074/jbc.M001975200

Alerts:
• When this article is cited
• When a correction for this article is posted

Click here to choose from all of JBC's e-mail alerts

This article cites 44 references, 19 of which can be accessed free at
http://www.jbc.org/content/275/34/25979.full.html#ref-list-1