Reactive oxygen species are involved in the mitogenic signal transduction cascades initiated by several growth factors and play a critical role in mediating cardiovascular diseases. Interestingly, H$_2$O$_2$ induces tyrosine phosphorylation and trans-activation of the platelet-derived growth factor receptor and the epidermal growth factor receptor in many cell lines including vascular smooth muscle cells. To investigate the molecular mechanism by which reactive oxygen species contribute to vascular diseases, we examined a signal transduction cascade involved in H$_2$O$_2$-induced platelet-derived growth factor receptor activation in vascular smooth muscle cells. We found that H$_2$O$_2$ induced a ligand-independent phosphorylation of the platelet-derived growth factor-$\beta$ receptor at Tyr$^{1021}$, a phospholipase C-$\gamma$ binding site, involving the requirement of protein kinase C-$\delta$ and c-Src that is distinct from a ligand-dependent autophosphorylation. Also, H$_2$O$_2$ induced the association of protein kinase C-$\delta$ with the platelet-derived growth factor-$\beta$ receptor and c-Src in vascular smooth muscle cells. These findings will provide new mechanistic insights by which enhanced reactive oxygen species production in vascular smooth muscle cells induces unique alleys of signal transduction distinct from those induced by endogenous ligands leading to an abnormal vascular remodeling process.

Several cardiovascular diseases are characterized by a state of excess oxidative stress associated with enhanced production of reactive oxygen species (ROS)$^5$ within the arterial wall. ROS including superoxide anion, hydrogen peroxide (H$_2$O$_2$), and hydroxyl radical are generated in a variety of cells stimulated with cytokines, growth factors, and agonists of G-protein-coupled receptors and are important chemical mediators that regulate signal transduction. Because it has recently become clear that ROS may mediate specific cellular functions such as cell growth, hypertrophy, and apoptosis, understanding the intracellular signaling of vascular smooth muscle cells (VSMCs) induced by ROS should provide further insight into the pathogenesis of cardiovascular diseases (1–4).

We and others have demonstrated that ROS enhance the activation of non-receptor tyrosine kinases such as JAK2 (5, 6), Src (7), and PYK2 (8), and receptor tyrosine kinases such as epidermal growth factor (EGF) receptor (9, 10) and platelet-derived growth factor (PDGF) receptor (11). ROS also activate certain proliferation-associated signaling pathways such as extracellular signal-regulated kinase (ERK) (12) and Akt (13) via a growth factor receptor-dependent manner in VSMCs (10, 14). Moreover, PDGF has long been implicated in atherosclerosis, and the PDGF receptor stimulation leads to potent proliferation and migration of VSMCs (15–17). Therefore, the activation of PDGF receptor by ROS could specifically be involved in vascular remodeling associated with cardiovascular diseases.

It has been reported that ROS such as H$_2$O$_2$ induces tyrosine phosphorylation of cellular proteins, which is strongly potentiated by a combination treatment with vanadate. The mechanism was believed to be attributed in part to the inhibition of tyrosine phosphatase or activation of tyrosine kinase or both (18). However, the precise mechanism by which ROS induce PDGF receptor activation remains unknown. PDGF initially activates the intrinsic tyrosine kinase of the receptors, leading to their dimerization and autophosphorylation. Many Src homology 2-containing proteins such as Ras-GTPase-activating protein, phospholipase C-$\gamma$ (PLC-$\gamma$), phosphatidylinositol 3-kinase, and Grb-2 bind to specific tyrosine phosphorylation sites in the activated PDGF receptor (19). Among these proteins, PLC-$\gamma$ is an enzyme that produces inositol triphosphate and diacylglycerol. These hydrolysis byproducts of PLC-$\gamma$ mobilize Ca$^{2+}$ from intracellular stores and activate protein kinase C (PKC), respectively (20). PLC-$\gamma$ binds to phosphorylated Tyr$^{1021}$ in the C-terminal tail of the PDGF-$\beta$ receptor, and the activation of PLC-$\gamma$ is involved in both cell growth and chemotaxis in certain circumstances (19).

In this study, we explored the mechanisms involved in the activation of PDGF-$\beta$ receptor by H$_2$O$_2$ stimulation in VSMCs. We found that H$_2$O$_2$ enhances the Tyr$^{1021}$ phosphorylation of PDGF-$\beta$ receptor distinct from the ligand-dependent manner. Furthermore, the activation of non-receptor kinases, c-Src and PKC$\delta$, and their complex formation are required for H$_2$O$_2$-
induced PDGFβ receptor activation. Taken together, our findings indicate that H2O2 activates the PDGFβ receptor via signal transduction pathways utilizing Src and PKCβ, and the requirement of c-Src/PKCβ distinguishes H2O2-induced PDGFβ receptor activation from the ligand-induced activation by the autophosphorylation mechanism in VSMCs. The activation of this particular signaling pathway involved in the regulation of cell growth and migration may explain the significance of ROS in cardiovascular diseases.

EXPERIMENTAL PROCEDURES

Materials—BB2116 was kindly provided by Dr. Helen Mills (British Biotech). CGS27023, AG1295, Go6976, rottlerin, PP2, and PP3 were purchased from Calbiochem. H2O2 was purchased from Sigma. Rat recombinant PDGF-BB was obtained from R&D Systems (Minneapolis, MN). Anti-PLCγ antibody was kindly provided by Dr. Graham Carpenter (Vanderbilt University). Phosphospecific antibody for Tyr1021-phosphorylated PDGFβ receptor, anti-PDGFβ receptor antibody, anti-EGF receptor antibody, and anti-PKCβ antibody were purchased from Santa Cruz Biotechnology, Inc. (Santa Cruz, CA). Anti-phosphotyrosine antibody (4G10) and anti-c-Src antibody were from Upstate Biotechnology (Lake Placid, NY). Phosphospecific antibodies for Tyr44696-phosphorylated EGF receptor and Tyr113-phosphorylated c-Src were from Biosource International (Camarillo, CA).

Cell Culture—VSMCs were prepared from the thoracic aorta of Sprague-Dawley rats by the explant method as described previously (21). Subcultured cells from passages 3–12 were used in the experiments and showed 99% positive immunostaining with smooth muscle a-actin antibody (Sigma).

Replication-deficient Adenovirus Generation—The generation and characterization of adenovirus encoding dominant negative mutant of PKCβ were as described previously (22). The dominant negative PKCβ cDNA contained a lysine to arginine mutation in the ATP binding domain at amino acid position 376. The recombinant adenovirus was plaque-purified, expanded, and titered in HEK293 cells using the agarose gel overlay method. VSMCs were infected with adenovirus for 2 days as described previously (6).

Immunoprecipitation and Immunoblot Analysis—After stimulation, VSMCs were lysed with ice-cold immunoprecipitation lysis buffer (150 mM NaCl, 50 mM HEPES, pH 7.5, 1% Triton X-100, 1 mM EDTA, 10 mM NaF, 10 mM sodium pyrophosphate, 2 mM sodium orthovanadate, 10% glycerol, 10 mg/ml aprotonin, and 1 mM phenylmethylsulfonyl fluoride). The cell lysates were centrifuged, and supernatant was immunoprecipitated with the antibody and A/G-agarose for 16 h at 4 °C as described previously. Cell lysates or immune complex were subjected to SDS-PAGE, transferred to a nitrocellulose membrane, and immunoblotted using an ECL detection kit (Amersham Biosciences) as described previously (23).

Reproducibility of Results—Unless stated otherwise, results are representative of at least three separate experiments yielding similar results.

RESULTS

H2O2 Stimulates Tyrosine Phosphorylation of PDGFβ Receptor at the PLCγ Binding Site—To determine whether H2O2-induced tyrosine phosphorylation of PDGFβ receptor is similar to the ligand-dependent phosphorylation, the effects of H2O2 or PDGF-BB on Tyr1021 phosphorylation of PDGFβ receptor were studied. 20 μM H2O2 increased Tyr1021 phosphorylation of PDGFβ receptor within 3 min, peaked at 10 min, and sustained the phosphorylation up to 30 min (Fig. 1A). In contrast, PDGF-BB caused rapid Tyr1021 phosphorylation of PDGFβ receptor as early as 1 min and sustained the phosphorylation up to 10 min (Fig. 1B). When the cell lysates were immunoprecipitated with anti-PDGFβ receptor antibody and immunoblotted with anti-phosphotyrosine antibody, H2O2 also induced tyrosine phosphorylation of PDGFβ receptor maximally at 10–30 min. Moreover, H2O2 enhanced PLCγ association with the PDGFβ receptor in a similar time course as the H2O2-induced tyrosine phosphorylation of PDGFβ receptor (Fig. 1C).

H2O2-induced Tyrosine Phosphorylation of PDGFβ Receptor Does Not Involve Metalloprotease-dependent Trans-activation—Because several G-protein-coupled receptors induce trans-activation of the EGF receptor through metalloprotease-dependent generation of its ligand (24–27), we determined the role of metalloprotease in H2O2-induced PDGFβ receptor phosphorylation. Treatment with metalloprotease inhibitors, BB2116 or CGS27023, did not alter tyrosine phosphorylation of PDGFβ receptor by H2O2. In contrast, both BB2116 and CGS27023 strongly inhibited tyrosine phosphorylation of the EGF receptor induced by H2O2 (Fig. 2).

Role of PDGFβ Receptor Kinase Activity in Tyrosine Phosphorylation of PDGFβ Receptor—To evaluate whether PDGFβ receptor kinase activity contributes to the tyrosine phosphorylation of PDGFβ receptor induced by H2O2, we used AG1295, a potent and selective inhibitor of this kinase (28). AG1295 (12.5–50 μM) strongly inhibited PDGF-BB-induced Tyr1021 phosphorylation of PDGFβ receptor in VSMCs (Fig. 3A). In contrast, AG1295 had no significant effect on H2O2-induced Tyr1021 phosphorylation of the PDGFβ receptor (Fig. 3B). Also, AG1295 did not alter H2O2-induced tyrosine phosphorylation of the PDGFβ receptor when the receptor was immunoprecipitated and immunoblotted with anti-phosphotyrosine antibody (data not shown).

Role of PKCβ in PDGFβ Receptor Phosphorylation Induced by H2O2—Previous studies have shown that H2O2 induces tyrosine phosphorylation and prolonged activation of PKCβ (29), a member of the novel PKC subgroup that is abundant in VSMCs (30). To determine whether PKCβ is involved in H2O2-mediated phosphorylation of the PDGFβ receptor, we used rottlerin, a selective PKCδ inhibitor (31). Recently, we have demonstrated the specificity of this inhibitor in cultured rat VSMCs (6). Rottlerin inhibited H2O2-induced Tyr1021 phosphorylation of the PDGFβ receptor, whereas Go6976, a PKCα and
PKCβ isoform inhibitor, did not alter H2O2-induced Try\textsuperscript{1021} phosphorylation of the PDGFβ receptor. Similar inhibition by rottlerin but not by Go6976 was observed in the immunoprecipitation of the PDGFβ receptor combined with immunoblotting with anti-phosphotyrosine antibody. In contrast, rottlerin had no effect on PDGF-BB-mediated PDGFβ receptor tyrosine phosphorylation (Fig. 4, A and B). To confirm the involvement of the PKCδ isoform in H2O2-induced tyrosine phosphorylation of the PDGFβ receptor in VSMCs, dominant negative (DN) mutant of PKCδ was expressed using an adenovirus vector. We have performed control studies showing that the transfection of adenovirus of up to 100 multiplicity of infection (plaque-forming unit/cells) had no nonspecific effects on VSMCs by using an adenovirus vector encoding LacZ (6). The infection of VSMCs with DN-PKCδ adenovirus inhibited Try\textsuperscript{1021} phosphorylation of PDGFβ receptor induced by H2O2 but not by PDGF-BB (Fig. 5). To further explore the possibility that PKCδ may associate with the PDGFβ receptor in response to H2O2, co-immunoprecipitation experiments were performed. When H2O2-stimulated cell lysates were immunoprecipitated with anti-PDGFβ receptor antibody and immunoblotted with anti-PKCD antibody, PKCD was detected in the PDGFβ receptor immunoprecipitates. In the reciprocal experiments, PDGFβ receptor was detected in anti-PKCD immunoprecipitates from H2O2-stimulated VSMCs (Fig. 6). These data suggest that H2O2-induced tyrosine phosphorylation of the PDGFβ receptor requires the activation of PKCδ and its association with the PDGFβ receptor.

**Role of c-Src in PDGFβ Receptor Tyrosine Phosphorylation Induced by H2O2**—It has been previously reported that the Src family kinases are involved in signaling events evoked by ROS (5, 7). To determine the role of Src family kinases in H2O2-induced PDGFβ receptor activation, we used PP2, a pyrazolopyrimidine that interacts specifically with Src family kinases together with PP3, a negative control for PP2 (32, 33). PP2 but not PP3 completely inhibited H2O2-induced Try\textsuperscript{1021} phosphorylation of the PDGFβ receptor in VSMCs (Fig. 7). These data suggest that H2O2-induced tyrosine phosphorylation of PDGFβ receptor is mediated by Src kinase activation.

PKCδ has been shown to become tyrosine-phosphorylated in COS-7 cells exposed to H2O2 (29). Also, PKCδ can be tyrosine-phosphorylated by the Src family kinases (34–36). Thus, we
determined whether PKCδ was phosphorylated on tyrosine by H₂O₂ stimulation in VSMCs. H₂O₂-induced tyrosine phosphorylation of PKCδ was initially detected at 3 min and continued up to 10 min (Fig. 8A). H₂O₂-induced tyrosine phosphorylation of PKCδ was inhibited by pretreatment with PP2 but not with PP3 (Fig. 8B). We further examined the activation of c-Src and its possible association with PKCδ in response to H₂O₂. Previous studies showed that full catalytic activity of c-Src requires phosphorylation at Tyr418 (37). We found that H₂O₂ stimulated Tyr418 phosphorylation of c-Src as early as 3 min, peaking at 5 min, whereas it decreased at 10 min. Also, H₂O₂ stimulated a prominent increase in the association of PKCδ with c-Src in VSMCs. The complex formation between PKCδ and c-Src was detected within 3 min and plateaued by 5 min (Fig. 8C). These data indicate that the activation of c-Src and its association with PKCδ by H₂O₂ may lead to the activation of PKCδ and subsequent tyrosine phosphorylation of the PDGFβ receptor in VSMCs.
The principal findings of this study are that H2O2 stimulates Tyr1021 phosphorylation of the PDGFβ receptor on Tyr residues, one of which was identified as Tyr1021 in VSMCs. These results are in good agreement with a recent publication (38) showing that H2O2 induced tyrosine phosphorylation of the PDGFβ receptor as well. Also, our finding is further supported by the fact that PLCγ is recruited to the PDGFβ receptor after H2O2 stimulation and because Tyr1021 phosphorylation is known to provide a high affinity binding site for PLCγ (19).

Trans-activation of growth factor receptors such as EGF or PDGF receptor by stimuli that do not directly interact with the receptor is a current exciting topic of signal transduction research. Recently, an attractive mechanism for the trans-activation of the EGF receptor was discovered. This mechanism involves metalloprotease-dependent production of a mature ligand from its precursor (24–27). Although the ligands for the PDGFβ receptor expressed in VSMCs do not require this metalloprotease-dependent step to become an active ligand, VSMCs may also express a newly identified ligand for PDGF receptors such as PDGF-C or PDGF-D. The proform of these ligands contains a proteolytic cleavage site (39). Because we have shown that angiotensin II-induced EGF receptor trans-activation requires both ROS production and a metalloprotease-dependent ligand production (10, 26), we examined whether a metalloprotease function is required for PDGFβ receptor or EGF receptor trans-activation by H2O2 in this study. We confirmed that EGF receptor trans-activation by H2O2 requires a metalloprotease in this study; however, PDGFβ receptor activation appears to be independent from this mechanism.

Because the ligand-independent activation of this tyrosine kinase receptor may not lead to activation of intrinsic tyrosine kinase, we further asked whether the Tyr1021 phosphorylation of PDGFβ receptor requires its intrinsic tyrosine kinase activity by using a selective PDGF receptor kinase inhibitor, AG1295. Our results clearly demonstrate that AG1295 markedly inhibits PDGF-BB-induced Tyr1021 phosphorylation of the PDGFβ receptor but not the phosphorylation induced by H2O2. These data further confirm that the H2O2-induced PDGFβ receptor activation is ligand-independent and suggest that the Tyr1021 phosphorylation of PDGFβ receptor might involve the inhibition of tyrosine phosphatase as previously proposed (18) or the activation of other tyrosine kinases, which may phosphorylate the receptor.

PKCδ is one of the PKC isoforms shown to be activated by H2O2 and is abundant in VSMCs (29, 30). We have previously shown the requirement of PKCδ in mediating the activation of non-receptor tyrosine kinases, PYK2 and JAK2, by angiotensin II in VSMCs and thereby established the specificities of PKCδ inhibitors, rottlerin and a dominant negative adenovirus, used in this study (6). Here, we have shown for the first time that PKCδ is indispensable for H2O2-induced but not PDGF-induced tyrosine phosphorylation of PDGFβ receptor in VSMCs. This is further supported by the fact that there is an indiscernible complex formation between PKCδ and the PDGFβ receptor in response to H2O2. It has been shown that H2O2 induces the association between PKCa and the PDGF receptor in Swiss 3T3 fibroblasts (40). Although we did not measure the PKCo association in this study, the participation of PKCa in H2O2-induced tyrosine phosphorylation of the PDGFβ receptor is unlikely because of the results using a PKCa and PKCβ inhibitors. We have previously shown that the inhibitor at the concentration used in this study is effective for the PKCδ-dependent event in VSMCs that was further confirmed by overexpression of wild type PKCδ in VSMCs (41).

This study suggests the involvement of c-Src in H2O2-induced tyrosine phosphorylation of the PDGFβ receptor in VSMCs. Because PP2 inhibits PKCδ tyrosine phosphorylation, c-Src probably acts upstream of PKCδ-dependent PDGFβ receptor phosphorylation by ROS. However, a recent report using VSMCs showed that angiotensin II stimulates ROS-dependent PDGFβ receptor tyrosine phosphorylation that is insensitive to a Src kinase inhibitor PP1 (11). This may be attributed to a different agonist (angiotensin II) used or an inhibitor for Src (PP1) used in the study.

In conclusion, we demonstrated here that ROS induced a ligand-independent tyrosine phosphorylation of PDGFβ receptor involving PKCδ and c-Src that is distinct from PDGF-induced PDGFβ receptor activation. Because both ROS and PDGF receptor signal transduction are strongly implicated in vascular diseases, our data add new mechanistic insight into these diseases associated with enhanced ROS action.

Acknowledgments—We thank Kunie Eguchi and Trinita Fitzgerald for excellent technical assistance.

REFERENCES

1. Abe, J. and Berk, B. C. (1998) Trends Cardiovasc. Med. 8, 59–64
2. Griendling, K. K., Sorensen, D., and Ushio-Fukai, M. (2000) Circ. Res. 86, 494–501
3. Irani, K. (2000) Circ. Res. 87, 179–181
4. Finkel, T., and Holbrook, N. J. (2000) Nature 406, 239–247
5. Abe, J., and Berk, B. C. (1999) J. Biol. Chem. 274, 21003–21010
6. Frank, G. D., Saito, S., Motley, E. D., Sasaki, T., Ohba, M., and Inagami, T. (2002) Mol. Endocrinol. 16, 357–377
7. Devary, Y., Gottlieb, R. A., Smeal, T., and Karin, M. (1992) Cell 71, 1081–1091
8. Frank, G. D., Motley, E. D., Inagami, T., and Eguchi, S. (2000) Biochem. Biophys. Res. Commun. 276, 761–765
9. Rao, G. N. (1996) Oncogene 13, 713–719
10. Frank, G. D., Eguchi, S., Inagami, T., and Motley, E. D. (2001) Biochem. Biophys. Res. Commun. 280, 1116–1119
11. Hesemann, S., Hasendler, J., Saito, Y., Ishida, M., and Berk, B. C. (2000) J. Biol. Chem. 275, 15926–15932
12. Frank, G. D., Eguchi, S., Yamakawa, T., Tanaka, S., Inagami, T., and Motley, E. D. (2000) Redox Report 2, 3120–3126
13. Ushio-Fukai, M., Alexander, R. W., Akers, M., Yin, Q., Fujio, Y., Walsh, K., and Griendling, K. K. (1999) J. Biol. Chem. 274, 22099–22704
14. Ushio-Fukai, M., Griendling, K. K., Hidaka, H., Huh, N., and Marks, F. (1994) Biochem. Biophys. Res. Commun. 205, 898–905
15. Ross, R. (1993) Nature 362, 801–809
16. Schwartz, S. M. (1997) J. Clin. Invest. 100, 887–889
17. Heldin, C. H. and Westmark, E. (1999) Physiol. Rev. 79, 1283–1316
18. Finkel, T. (1998) Curr. Opin. Cell Biol. 10, 248–253
19. Heldin, C. H. (1997) FEBS Lett. 410, 17–21
20. Carpenter, G., and Ji, Q. (1999) Exp. Cell Res. 253, 15–24
21. Eguchi, S., Matsumoto, T., Motley, E. D., Utsunomiya, H., and Inagami, T. (1996) J. Biol. Chem. 271, 14169–14175
22. Ohba, M., Ishino, K., Kashiwagi, M., Kawabe, S., Chida, K., Huh, N., and Kuraki, T. (1998) Mol. Cell. Biol. 18, 5199–5207
23. Eguchi, S., Numaguchi, K., Iwasaki, H., Matsumoto, T., Yamakawa, T., Utsunomiya, H., Kawakatsu, H., Orwada, K. M., Hisata, Y., Marumo, F., and Inagami, T. (1999) J. Biol. Chem. 274, 8860–8866
24. Preznel, N., Zwick, E., Daub, H., Sauerer, M., Abraham, R., Wallasch, C., and Ulrich, A. (1999) Nature 402, 884–888
25. Kalmes, A., Vesi, B. R., Daum, G., Abraham, J. A., and Clowes, A. W. (2000) Circ. Res. 87, 92–98
26. Eguchi, S., Dempsey, P. J., Frank, G. D., Motley, E. D., and Inagami, T. (2001) J. Biol. Chem. 276, 7857–7862
27. Pierce, K. L., Tohgo, A., Ahn, S., Field, M. E., Luttrell, L. M., and Leikowitz, R. J. (2001) J. Biol. Chem. 276, 23155–23160
28. Levitzki, A., and Gazit, A. (1995) Science 267, 1782–1788
29. Konishi, H., Tanaka, M., Takekura, Y., Matsuzaki, H., Ono, Y., Kikkawa, U., and Nishinaka, Y. (1997) Proc. Natl. Acad. Sci. U.S.A. 94, 11233–11237
30. Ponomareva, S., Nishimura, Y., Hase, M., Koyama, H., Yamanaka, H., Ohno, S., and Mori, H. (1997) J. Biol. Chem. 272, 13816–13822
31. Gescheidt, M., Muller, H. J., Keibass, K., Zang, R., Kiststein, W., Rincke, G., and Marks, B. (1984) Biochem. Biophys. Res. Commun. 199, 83–88
32. Bowler, S., Mortad, K., Jr., Carr, D., and Nussenzweig, A. M. (2000) Biochem. J. 349, 655–610
33. Sanna, P. P., Berton, F., Cammalleri, M., Tallent, M. J., Siggins, G. R., Bloom,
F. E., and Francesconi, W. (2000) Proc. Natl. Acad. Sci. U.S.A. 97, 8653–8657
34. Joseloff, E., Cataisson, C., Aamodt, H., Ocheni, H., Blumberg, P., Kraker, A. J., and Yuspa, S. H. (2002) J. Biol. Chem. 277, 12318–12323
35. Benes, C., and Soltoff, S. P. (2001) Am. J. Physiol. 280, C1498–C1510
36. Song, J. S., Swann, P. G., Szallasi, Z., Blank, U., Blumberg, P. M., and Rivera, J. (1998) Oncogene 16, 3357–3366
37. Pawson, T. (1997) Nature 385, 592–595
38. Escargueil-Blanc, I., Salvayre, R., Vacaresse, N., Jurgens, G., Darblade, B., Arnal, J. F., Parthasarathy, S., and Negre-Salvayre, A. (2001) Circulation 104, 1814–1821
39. Heldin, C. H., Eriksson, U., and Ostman, A. (2002) Arch. Biochem. Biophys. 398, 284–290
40. Min, D. S., Kim, E.-G., and Exton, J. H. (1998) J. Biol. Chem. 273, 29886–29994
41. Motley, E. D., Kabir, S. M., Gardner, C. D., Eguchi, K., Frank, G. D., Kuroki, T., Ohba, M., Yamakawa, T., and Eguchi, S. (2002) Hypertension 39, 508–512
Ligand-independent trans-Activation of the Platelet-derived Growth Factor Receptor by Reactive Oxygen Species Requires Protein Kinase C-δ and c-Src
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J. Biol. Chem. 2002, 277:44695-44700.
doi: 10.1074/jbc.M208332200 originally published online September 10, 2002

Access the most updated version of this article at doi: 10.1074/jbc.M208332200

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