Stromal Cell-derived Factor-1α Induces Tube-like Structure Formation of Endothelial Cells through Phosphoinositide 3-Kinase*

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Stromal cell-derived factor-1α (SDF-1α) is a CXC chemokine, which induces tube formation of endothelial cells. Although SDF-1α transduces signals via CXC receptor 4 (CXCR4), resulting in activating a panel of downstream signaling molecules, such as phosphoinositide 3-kinase (PI3-kinase), little is known about the SDF-1α-mediated signaling pathways leading to tube formation. Here we examined the signal transduction pathway involved in SDF-1α-mediated tube formation by primary human umbilical endothelial cells and murine brain capillary endothelial cell line (IBE (immortalized murine brain capillary endothelial) cells). SDF-1α stimulated tube formation by IBE cells, which was blocked by LY294002 and pertussis toxin, suggesting that PI3-kinase and Gαi protein were involved in this process. SDF-1 also stimulated tube formation of human umbilical endothelial cells, and the response was LY294002-sensitive. SDF-1α activated PI3-kinase in IBE cells. In stable IBE cell lines expressing either the mutant p85 subunit of PI3-kinase (denoted p85-8 cells), which lacks association with the p110 subunit, or kinase-inactive c-Fes (denoted KEFes 5-15 cells), SDF-1α failed to activate PI3-kinase and to stimulate tube formation. SDF-1α-induced tube formation was inhibited by an antibody against murine vascular endothelial cadherin. The antibody as well as LY294002 attenuated SDF-1α-mediated compact cell-cell contact, which proceeded to tube formation. Taken together, SDF-1α induces compact cell-cell contact through PI3-kinase, resulting in tube formation of endothelial cells.

CXC chemokines are involved in angiogenesis (1–4). They are divided into two groups, angiogenic stimulators, which share a consensus Glu-Leu-Arg-motif preceding the first cysteine residue, and inhibitors that lack this motif in their sequence. Among angiogenic CXC chemokines, stromal cell-derived factor-1α (SDF-1α) plays pivotal roles in inflamed immune responses and angiogenesis. Targeted disruption of a gene encoding SDF-1α in mouse resulted in impaired hematopoiesis and lymphopoiesis (5). SDF-1α transduces signals via its receptor CXCR4. CXCR4 knockout in mice demonstrated impaired vasculogenesis in intestine, suggesting that signals via CXCR4 may contribute to vasculogenesis and angiogenesis. In fact, CXCR4 is expressed in vascular endothelial cells (6, 7), and its expression is up-regulated by angiogenic growth factors, fibroblast growth factor-2, and vascular endothelial growth factor (8, 9). Furthermore, treatment of endothelial cells by SDF-1α induces tube-like structure formation and migration (10, 11).

Activation of CXCR4 in lymphatic cells resulted in activation of Gαq protein, the Ras/mitogen-activated protein kinase (MAPK) pathway, phosphoinositide 3-kinase (PI3-kinase), focal adhesion kinase, SHP2, c-Fyn, c-Lyn, and Pyk2 (12–16). SDF-1α activated PI3-kinase and SHP2 have been implicated in migration of lymphocytes and leukemia cells (14, 15). However, little is known about the roles of these signaling molecules in SDF-1α-mediated angiogenic responses of endothelial cells to date.

Previously, we have established a murine brain capillary endothelial cell line from ts-A58-H-2Kb transgenic mice, denoted IBE (Immortomouse Brain Endothelial) cells. IBE cells can form lumen-containing tube-like structures in response to fibroblast growth factor 2 (FGF-2) and angiopoietin 2 (Ang2) treatment (17–19). Using this culture model, we have shown previously that expression of dominant negative c-Fes caused impaired chemotaxis toward FGF-2 and Ang2 (19, 20). It has also been shown that Ang2-induced PI3-kinase activation depended on c-Fes (19). Furthermore, expression of dominant negative c-Fyn inhibited FGF-2- and Ang2-mediated tube formation (19, 21).

In the present study, we examined the signal transduction pathways leading to SDF-1α-mediated tube-like structure formation of IBE cells and human umbilical cord vein endothelial cells (HUVECs). SDF-1α stimulated tube formation of both cells, and PI3-kinase inhibitor LY294002 blocked tube formation, suggesting that PI3-kinase might be involved in this process by these cells. PI3-kinase was activated by SDF-1α-treatment in IBE cells, and the activation was dependent on c-Fes kinase activity. These results suggest that PI3-kinase is an important signaling molecule of SDF-1α-induced tube-like structure formation of endothelial cells.

**EXPERIMENTAL PROCEDURES**

Reagents—Anti-phosphotyrosine (PY99) antibody was purchased from Santa Cruz Biotechnology (Santa Cruz, CA). Rat monoclonal antibody against mouse vascular endothelial cadherin (VE-cadherin) was from Pharmingen. Mouse recombinant SDF-1α was obtained from R&D Systems (Minneapolis, MN). LY294002, PP2, PD98059, and pertussis toxin were from Calbiochem-Novabiochem and dissolved in dimethyl sulfoxide (Me2SO) as a stock solution, except pertussis toxin.
and stored at −30 °C until use. Stock solutions were further diluted with Me₂SO and dissolved in culture medium. Final concentration of Me₂SO was 0.1% in all cases. Pertussis toxin was suspended in Tris-buffered saline and was kept at 4 °C until use.

Cell Culture—HUVECs and their culture medium were purchased from BioWhittaker, Inc. (Walkersville, MD) and cultured in endothelial cell basal medium supplemented with endothelial cell growth supplement, dexamethasone, fetal bovine serum, insulin, and epidermal growth factor as described in the protocol provided by the manufacturer. Parental IBE cells obtained from temperature-sensitive mutant SV40 large T transgenic mouse brain capillaries were cultured in Ham's F-12 medium containing fetal bovine serum, endothelial cell growth supplement, insulin, interferon-γ, and epidermal growth factor as has been described previously (17). Stable IBE cell lines expressing kinase-inactive (dominant negative) c-Fes (denoted KEFes5-15 cells) were described elsewhere (20). A stable cell line expressing deleted mutant p85 PI3-kinase subunit, which does not interact with p110 catalytic subunit (22) (denoted Ap85-S cells), was established, which demonstrated the dominant negative effect on epidermal growth factor-mediated PI3-kinase activation (23). Experiments using IBE cell lines were performed at 33 °C rather than at 39 °C because at the latter temperature, cells became senescent and lost responsiveness to extracellular stimuli (17).

Tube Formation Assay—For IBE cells, cells were cultured between two layers of collagen gels in Ham's F-12 medium containing 0.25% bovine serum albumin with or without indicated samples as described previously (17). Stable IBE cell lines expressing kinase-inactive (dominant negative) c-Fes (denoted KEFes5-15 cells) were described elsewhere (20). A stable cell line expressing deleted mutant p85 PI3-kinase subunit, which does not interact with p110 catalytic subunit (22) (denoted Ap85-S cells), was established, which demonstrated the dominant negative effect on epidermal growth factor-mediated PI3-kinase activation (23). Experiments using IBE cell lines were performed at 33 °C rather than at 39 °C because at the latter temperature, cells became senescent and lost responsiveness to extracellular stimuli (17).
Immunocomplex PI3-Kinase Assay—The method used for determination of PI3-kinase activity in immunoprecipitates of anti-phosphotyrosine was described previously (25). In brief, serum-starved cells were lysed in Nonidet P-40 lysis buffer and incubated with anti-phosphotyrosine antibody followed by absorption with protein A-agarose beads. After extensive washing, immunoprecipitates were incubated with phosphatidylinositol and $[^{32}P]ATP$, and reaction products were separated by thin layer chromatography on silica gel 60 plates. Incorporation of $[^{32}P]ATP$ into phosphatidylinositol was measured by Image Analyzer BAS 5000 (Fuji) followed by exposure on x-ray films (Amerham Biosciences).

Immunoprecipitation and Immunoblotting—Serum- and growth factor-starved IBE cells were either stimulated or left unstimulated with 500 ng/ml SDF-1α in the presence of orthovanadate (50 μM) for 10 min. c-Akt was immunoprecipitated with anti-Akt antibody followed by immunoblotting with either anti-phospho-Akt or anti-Akt antibodies.

**RESULTS AND DISCUSSION**

SDF-1α induces tube-like structure formation of primary human endothelial cells (10, 11). To examine whether SDF-1α also stimulates tube formation of IBE cells, we tested the effect of SDF-1α on morphological changes of the cells. IBE cells respond to FGF-2 and angiopoietin 2 (Ang2) to form lumen-containing tube-like structures (18, 19). As shown in Fig. 1A, FGF-2 induced multicellular aggregates of IBE cells followed by sprouting and fusion of aggregates, resulting in branching tube-like structures (26). SDF-1α induced the formation of the tube-like structures of IBE cells, which was similar to the effect of FGF-2. CXCR4 is a G protein-coupled receptor. We then examined the effect of pertussis toxin on SDF-1α-induced tube formation. As shown in Fig. 1B, pertussis toxin at 50 ng/ml inhibited SDF-1α-induced tube formation.

**FIG. 2.** As shown in A, SDF-1α induces tube-like structure formation of HUVECs. HUVECs were cultured on the surface of Matrigel in the presence or absence of indicated growth factors. Tube length obtained from FGF-2-stimulated cells was set to 100. As shown in B, the SDF-1α-induced tube-like structure formation of HUVECs is LY294002-sensitive. HUVECs were seeded onto the surface of Matrigel in the presence of either 0.1% Me2SO (DMSO) or 10 μM LY294002 and cultured for 24 h. Tube length obtained from SDF-1α-stimulated cells was set to 100. Data shown are reproduced from two experiments. Bar, 100 μm.

**FIG. 3.** As shown in A, SDF-1α increases PI3-kinase activity in immunoprecipitates (IP) of anti-phosphotyrosine antibody. Serum-starved IBE cells were treated with 10 μM LY294002 or 0.1% Me2SO (DMSO) for 30 min and were either stimulated with SDF-1α or left unstimulated for 5 min. HUVECs were serum-starved for 1 h and then stimulated with SDF-1α for 5 min. Particular proteins were immunoprecipitated with anti-phosphotyrosine antibody. PI3-kinase activity in the immunoprecipitated proteins was measured as described under “Experimental Procedures.” Relative phosphorylation was measured by the use of the BAS5000 BioImager (Fuji), and phosphorylation of phosphatidylinositol in untreated cells was set to 1.00. ori, start point; PIP, phosphatidylinositol 3-phosphate. As shown in B, SDF-1α mediated PI3-kinase activation depends on the c-Fes kinase activity and association with tyrosine phosphorylated proteins. KEFes 5-15 cells or Δp65-8 cells were serum-starved overnight. Cells were then either stimulated or left unstimulated with SDF-1α, and PI3-kinase activity was measured. As shown in C, SDF-1α phosphorylates c-Akt at serine 473 in IBE cells but not in KEFes 5-15 cells. Cells were serum-starved for overnight and then either stimulated or left unstimulated with SDF-1α for 10 min. c-Akt was immunoprecipitated with anti-Akt antibody, and phosphorylated c-Akt was detected by anti-phospho-Akt antibody. Data shown are representative of two experiments. IB, immunoblots.
blocked SDF-1α-induced tube formation, suggesting that G protein was involved in this process. We then tested the effects of pharmacological inhibitors on SDF-1α-induced tube formation. Neither Src family inhibitor PP2 nor mitogen-activated protein kinase/extracellular signal regulated kinase inhibitor PD98059 inhibited SDF-1α-induced tube formation of IBE cells (data not shown). Treatment of cells with PI3-kinase inhibitor LY294002 blocked SDF-1α-induced tube formation (Fig. 1C). PI3-kinase inhibitor could not block FGF-2- and Ang2-mediated tube formation (19, 25). FGF-2- and Ang2-mediated tube formation was dependent on c-Fyn kinase activity (19, 21). Ang2 could not further stimulate FGF-2-induced tube formation (19), suggesting that Ang2 and FGF-2 utilized a common signaling pathway leading to tube formation, such as c-Fyn. To test whether SDF-1α-induced tube formation requires different signaling pathways activated by FGF-2 and Ang2, we examined the additive effect of SDF-1α on FGF-2- and Ang2-induced tube formation. As shown in Fig. 1D, SDF-1α further stimulated FGF-2- and Ang2-induced tube formation. These results suggest that SDF-1α-induced tube formation of IBE cells may be dependent on PI3-kinase, which is not involved in FGF-2- and Ang2-mediated tube formation. We also examined the formation of tube-like structures by primary HUVECs on Matrigel. Fig. 2A shows that FGF-2 as well as SDF-1α induced the formation of tube-like structures. In addition, LY294002 markedly inhibited SDF-1α-mediated formation of tube-like structures of HUVECs (Fig. 2B). LY294002 showed little effect on FGF-2-induced formation of tube-like structures of HUVECs. 2 Considered collectively, PI3-kinase may be involved commonly in SDF-1α-mediated tube formation by endothelial cells from different origins.

We next examined the effect of SDF-1α on PI3-kinase activity. IBE cells were treated with either MeSO (vehicle) or LY294002 for 30 min and then stimulated with SDF-1α. Cells were lysed, and PI3-kinase activity in immunoprecipitates was examined by thin layer chromatography. As shown in Fig. 3A, PI3-kinase activity in immunoprecipitates of anti-phosphotyrosine antibody from IBE cells was increased by SDF-1α treatment, suggesting that SDF-1α induced tyrosine phosphorylation of particular proteins followed by guest on July 25, 2018http://www.jbc.org/Downloaded from 2 S. Kanda, unpublished observations.

**Fig. 4.** SDF-1α cannot induce tube-like structure formation by KEFes 5-15 cells (A) or Δp85-8 cells (B). Indicated IBE cell lines were treated or untreated with 500 ng/ml of SDF-1α or FGF-2 (as a positive control) and cultured between two layers of collagen gels. Tube length obtained from FGF-2-stimulated cells was set to 100. Bar, 100 μm. Data shown are representative of two experiments.

**Fig. 5.** As shown in A, SDF-1α stimulates tight cell-cell contact (compaction) by IBE cells. Cells either treated with 500 ng/ml SDF-1α or left untreated were covered with the second layers of collagen gels. After 2 or 8 h, photographs were taken under a phase contrast microscope. Observation. As shown in B, SDF-1α-mediated tight cell-cell contact is not observed in cells treated with anti-VE-cadherin antibody. Cells were seeded on the first layer of collagen gels with either normal rat IgG or anti-VE cadherin antibody. One h later, cells were treated with SDF-1α at 500 ng/ml and cultured for 3 h. Culture medium was removed, and the cells were covered by the second layer of collagen gels. Photographs were taken after 8 h. As shown in C, SDF-1α-induced tube formation is blocked by anti-VE-cadherin monoclonal antibody. IBE cells were seeded onto the first layer of collagen gels in the presence of either normal rat IgG or rat monoclonal antibody against mouse VE-cadherin at 100 μg/ml. One h later, SDF-1α was added, and after 3 h, cells were covered with the second layer of collagen gels. Tube length obtained from FGF-2-stimulated cells was set to 100.

**Fig. 6.** Treatment of cells with LY294002 or cells expressing kinase-inactive c-Fes and mutant p85 subunit of PI3-kinase reduces tight cell-cell contact mediated by 500 ng/ml SDF-1α. Parental IBE cells were incubated with 0.1% MeSO (DMSO) or 10 μM LY294002. One h later, SDF-1α was added, and after 3 h, cells were covered with the second layer of collagen gels. KEFes 5-15 cells or Δp85-8 cells were either stimulated with 500 ng/ml SDF-1α or left unstimulated for 4 h. Cells were covered with collagen gels, and 8 h later, photographs were taken.
by association with PI3-kinase. SDF-1 increased the PI3-kinase activity in cultured H9251 endothelial cells. c-Fes tyrosine kinase is exclusively expressed in endothelial cells and hematopoietic cells. Activation of c-Fes by extracellular stimuli requires oligomerization by its coiled-coil domain followed by autophosphorylation (27). c-Fes tyrosine kinase is expressed in both HUVECs and IBE cells (20). In a recent study, we showed that Ang2-mediated activation of PI3-kinase was dependent on c-Fes (19). We then examined the effect of SDF-1α on PI3-kinase in KEFes 5-15 cells. As shown in Fig. 3B, SDF-1α could not elevate the PI3-kinase activity in anti-phosphotyrosine immunoprecipitates of KEFes 5-15 cells. This result suggests that SDF-1α-mediated tyrosine phosphorylation of particular proteins, which subsequently associate with PI3-kinase, may be c-Fes-dependent. SDF-1α also failed to increase the PI3-kinase activity in Δp85-8 cells, suggesting that the association of the p110 catalytic subunit of PI3-kinase with tyrosine phosphorylated proteins was required in this reaction. c-Akt/protein kinase B is one of the important downstream targets of PI3-kinase and is involved in cell survival. We examined the activation of c-Akt by SDF-1α. As shown in Fig. 3C, phosphorylation of c-Akt was increased by SDF-1α-treatment in IBE cells, and the increase was not observed in KEFes 5-15 cells. Considered collectively, these data suggest that SDF-1α utilized c-Fes, resulting in activation of PI3-kinase and c-Akt in IBE cells. We also examined the SDF-1α-mediated tube formation in KEFes 5-15 and Δp85-8 cells. As shown in Fig. 4, SDF-1α failed to stimulate tube formation in KEFes 5-15 cells as well as Δp85-8 cells. These results strongly suggest that SDF-1α-mediated tube-like structure formation by endothelial cells requires PI3-kinase activation, possibly through c-Fes.

Although distinct methods are employed to assess the ability of cultured endothelial cells to form tube-like structures, common behavior involved in this process includes cell-cell contact. Endothelial cells contact each other to form cellular aggregates followed by lumen formation between aggregated cells (26, 28–30). We then examined the effect of SDF-1α on endothelial cell-cell contact. When treated with SDF-1α, IBE cells adhered to neighboring cells and formed compact aggregation at 8 h, which is characterized by the disappearance of borders between aggregated cells (Fig. 5A). This tight cell-cell contact, denoted cell compaction, is observed in cadherin-dependent cell-cell aggregation (31, 32). Tight cell-cell contact was not observed in untreated IBE cells (Fig. 5A). As shown in Fig. 5B, cell compaction was inhibited by anti-VE-cadherin antibody, suggesting that VE-cadherin was required for cell compaction. Consequently, anti-mouse VE-cadherin antibody inhibited SDF-1α-induced tube formation (Fig. 5C), suggesting that VE-cadherin-mediated cell-cell contact may be involved in this process. As shown in Fig. 6, compaction was hardly observed in SDF-1α–treated IBE cells in the presence of LY294002. Only loose cell-cell contact was observed in SDF-1α–treated KEFes 5-15 and in Δp85-8 cells as well. These results suggest that SDF-1α-induced tube formation may be regulated by PI3-kinase-dependent tight cell-cell contact. Considered collectively, PI3-kinase and its downstream target molecules, such as c-Akt, seem to be required for SDF-1α-induced tube formation. In fact, recent reports have demonstrated that c-Akt was involved in tube formation of endothelial cells (33–35). Although FGF-2 induced cell compaction of IBE cells as well, PI3-kinase inhibitor did not inhibit the cell compaction (data not shown). FGF-2 sufficiently promoted tube formation by KEFes 5-15 cells and Δp85-8 cells. FGF-2 activates PI3-kinase through activated Ras but not through binding to tyrosine phosphorylated proteins (23). Ang2 activated PI3-kinase through binding to tyrosine phosphorylated proteins, and the activation was dependent on c-Fes kinase activity (19). Ang2-induced PI3-kinase activity was involved in chemotaxis of IBE cells. Treatment of cells with LY294002 did not inhibit Ang2-induced tube formation (19), suggesting that PI3-kinase does not seem to be involved in this response. On the other hand, FGF-2 and Ang2 activated c-Fyn in IBE cells (19, 21). Treatment of cells with PP2 failed to inhibit Ang2-induced tube formation, suggesting that signals through receptor tyrosine kinases leading to tube formation seem to require c-Fyn but not PI3-kinase (19, 21). A previous study has shown that c-Fyn was activated by SDF-1α treatment in Jurkat T cells (15). However, we could not detect SDF-1α-induced c-Fyn activation in IBE cells (data not shown). Additionally, PP2 failed to inhibit SDF-1α-induced tube formation. Since induction of chemotaxis involves dissociation of cells, Ang2-mediated PI3-kinase activation would not be involved in cell compaction. Conversely, SDF-1α-induced PI3-kinase activation was required for cell compaction. A number of protein kinases are activated by lipid products of PI3-kinase (36, 37). Depending on the culture condition (i.e. two dimensional culture for migration assay and three-dimensional culture for tube formation), qualitatively different signaling molecules may be accumulated into focal adhesion complexes or cell-cell contacts, where cross-talk between growth factor signaling and cell adhesion signaling exist. Therefore, PI3-kinase activated by Ang2 or SDF-1α may regulate distinct sets of downstream signaling molecules. In conclusion, we have shown in the present study that SDF-1α-induced tube formation of endothelial cells through c-Fes-dependent activation of PI3-kinase, and formation of cadherin-dependent tight cell-cell contact seemed to be involved in this process.

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REFERENCES

1. Strieter, R. M., Polverini, P. J., Kunkel, S. L., Arenberg, D. A., Burdick, M. D., Kasper, J., Drulba, J., Van Damme, J., Walz, A., Marriett, D., Chan, S.-Y., Roceznai, S., and Shanafelt, B. (1995) J. Biol. Chem. 270, 73738–73757
2. Moore, B. R., Arenberg, D. A., Addison, C. L., Keane, P. M., and Strieter, R. M. (1998) J. Lab. Clin. Med. 132, 97–103
3. Horuk, R. (2001) Cytokine Growth Factor Rev. 12, 313–335
4. Dias, S., Choy, M., and Razi, S. (2001) Cancer Invest. 19, 722–738
5. Naganawa, T., HirotA, S., Tachibana, K., Takakura, N., Nishikawa, S., Kitamura, Y., Yoshida, N., Kikutani, H., and Kishimoto, T. (1996) Nature 382, 635–638
6. Gupta, S. K., Lysko, P. G., Pillarsetti, K., Ohlstein, E., and Stadel, J. M. (1998) J. Biol. Chem. 273, 4282–4287
7. Violin, M. V., Joseph, L., Shockley, M. S., and Davies, P. F. (1998) Biochem. Biophys. Res. Commun. 245, 46–53
8. Feil, Ç., and Augustin, H. G. (1998) Biochem. Biophys. Res. Commun. 24/7, 39–45
9. Salesse, R., Wasserman, K., Young, H. A., Grimm, M. C., Howard, O. M., Anver, M. R., Kleinman, H. K., Murphy, W. J., and Oppenheim, J. J. (1999) Am. J. Pathol. 154, 1125–1135
10. Mirshahi, F., Pourtou, J., Li, H., Muraine, M., Trehon, V., legrand, E., Vannier, J.-P., Soria, J., Vasae, M., and Soria, C. (2000) Thromb. Res. 99, 587–594
11. More, M., Wolkails, M. J., Prevust, N., Pratixo, D., Barnathan, E. S., Taraboletti, G., Haggerty, B. S., Hesse1gess1er, J., Horuk, R., Hoxie, J. A., and Brasl, J. F. (2000) Biochem. Biophys. Acta 1500, 227–240
12. Davis, C. B., Dike, I., Un1mat, D., Hill, C. M., Arthos, J., Siani, M., Thompson, D. A., Schles1nger, J., and Littman, D. R. (1997) J. Exp. Med. 186, 1793–1798
13. Chen, W. J., Jayawickreme, C., Wat1on, C., Wells, H., Ferris, R., Ar1mour, S., Dallas, W., Chen, G., Bone, L., Luther, M., and Renakian, T. (1998) Mol. Pharmacol. 53, 171–177
14. Ganjo, R. K., Brubaker, S. A., meyer, J., Dutt, P., Yang, Y., Qin, S., Newman, V., and Groppman, J. E. (1998) J. Biol. Chem. 273, 31699–31735
15. Chemok. R. D., Cherka, R., and Ganjo, R. K. (2001) Blood 97, 608–615
16. Weber, K. S. C., Ostermann, G., Zernecke, A., Schroder, A., Krickstein, L. B., and Weber, C. (2001) J. Biol. Chem. 276, 8074–8086
17. Randa, S., Landgren, E., Ljungstrom, M., and Claesson-Welsch, L. (1996) Cell Growth & Differ. 7, 383–395
18. Rahmanian, M., Pertoft, H., Kanda, S., Christofferson, R., Claesson-Welsch, L., and Heldin, P. (1997) Exp. Cell Res. 237, 223–230
19. Mochizuki, Y., Nakamura, T., Kanetake, H., and Kanda, S. (2002) J. Cell Sci. 115, 175–183
20. Kanda, S., Lerner, E. C., Tsuda, S., Shono, T., Kanetake, H., and Smithgall, T. E. (2000) J. Biol. Chem. 275, 10105–10111
21. Tsuda, S., Ohtsuru, A., Yamashita, S., Kanetake, H., and Kanda, S. (2002) Biochem. Biophys. Res. Commun. 290, 1354–1360
22. Kotani, K., Yonezawa, K., Hara, K., Ueda, H., Kitamura, Y., Sakaue, H., Ando, A., Chavanieu, A., Calas, B., Grigorescu, F., Nishiyama, M., Waterfield, M. D., and Kasuga, M. (1994) EMBO J. 13, 2313–2321
23. Mochizuki, Y., Tsuda, S., Kanetake, H., and Kanda, S. (2002) Oncogene 21, 7027–7033
24. Dawson, D. W., Pearce, S. F., Zhong, R., Silverstein, R. L., Frazier, W. A., and Bouck, N. P. (1997) J. Cell Biol. 138, 707–717
25. Matsumoto, T., Turesson, I., Book, M., Gerwins, P., and Claesson-Welsh, L. (2002) J. Cell Biol. 156, 149–160
26. Kanda, S., Tomasini-Johansson, B., Rubin, K., and Claesson-Welsh, L. (1999) Exp. Cell Res. 248, 203–213
27. Smithgall, T. E., Rogers, J. A., Peters, K. L., Li, J., Briggs, S. D., Lionberger, J. M., Cheng, H., Shibata, A., Scholtz, B., Schreiner, S., and Dunham, N. (1998) Crit. Rev. Oncog. 9, 43–62
28. Montesano, R., Orci, L., and Vassalli, P. (1983) J. Cell Biol. 97, 1648–1652
29. Ingber, D. E., and Folkman, J. (1989) J. Cell Biol. 109, 317–330
30. Matsumoto, T., Turesson, I., Book, M., Gerwins, P., and Claesson-Welsh, L. (2002) J. Cell Biol. 156, 149–160
31. Vestweber, D., and Kemler, R. EMBO J. 4, 3393–3398
32. Matsubara, S., and Ozawa, M. J. Cell Biol. 154, 573–584
33. Lee, M. J., Thangada, S., Claffey, K. P., Ancelin, N., Liu, C. H., Kluk, M., Volpi, M., Sha'afi, R. I., and Hla, T. (1999) Cell 99, 301–312
34. Kuwabata, Y., Luo, Z., Shigematsu, I., Bialik, A., Fulton, D., Lefer, D. J., Sessa, W. C., and Walsh, R. (2000) Nat. Med. 6, 1004–1010
35. Lee, M. J., Thangada, S., Paik, J. H., Sapkota, G. P., Ancelin, N., Chae, S. S., Wu, M., Morales-Ruiz, M., Sessa, W. C., Alessi, D. R., and Hla, T. (2001) Mol. Cell 8, 693–704
36. Fruman, D. A., Meyers, R. E., and Cantley, L. C. (1998) Annu. Rev. Biochem. 67, 481–507
37. Chan, T. O., Rittenhouse, S. E., and Tsichlis, P. N. (1999) Annu. Rev. Biochem. 68, 965–1014
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