The binding of urokinase plasminogen activator (uPA) to its specific receptor (uPAR) facilitates migration of vascular smooth muscle cells (VSMC). However, the signaling cascade utilized by the urokinase receptor is only incompletely understood. We investigated intracellular uPA/uPAR signaling in human aortic VSMC from the cell membrane to the nucleus. uPA binding to VSMC induced a rapid and pronounced increase in tyrosine phosphorylation of several proteins with molecular masses of 53–60, 85–90, and 130–140 kDa. By using co-immunoprecipitation techniques and in vitro kinase assays, the uPAR-associated proteins were identified as Janus (Jak) and Src non-receptor protein-tyrosine kinases (PTK) Jak1, Tyk2, and p59fgr, p53/56fgr, p53/59fgr, and p55fgr. Furthermore, uPA induced a time-dependent reversible translocation of the Stat1 (signal transducer and activator of transcription) protein to the VSMC nuclei, as shown by confocal microscopy studies. Using an electrophoretic mobility shift assay, we then demonstrated that Stat1 is rapidly activated in response to stimulation with uPA and specifically binds to the DNA regulatory elements GAS (interferon-γ activation site) and ISRE (interferon-stimulated response element). Mobility supershift experiments confirmed DNA-protein complexes containing Stat1 protein. Migration experiments with double immunofluorescence staining revealed polarization of uPAR, and colocalization with Jak1 and Tyk2 to the leading edge of the migrating cells. Under the same conditions, Jak2, Jak3, and the Src-PTKs remained randomly distributed over the entire body of the cells. Our studies therefore suggest that, in VSMC, the uPAR-signaling complex utilizes at least two different mechanisms, a direct signaling pathway utilizing the Jak/Stat cascade and a second signal transduction mechanism via Src-like protein-tyrosine kinases. uPA-induced signaling via Jak/Stat is most likely involved in the regulation of cell migration, while the functional purpose of the uPA-associated Src-PTK activation remains to be elucidated.

Vascular smooth muscle cells (VSMC)+ are the predominant cell type in the mammalian arterial wall. In response to vascular injury such as balloon angioplasty, or in chronic pathological processes such as atherosclerosis, the differentiated VSMC dedifferentiate. The associated functional changes allow medial VSMC to migrate from the media into the intima where they proliferate and contribute to neointima formation and restenosis. To date, a number of factors which contribute to the regulation of VSMC migration and/or proliferation have been identified, including numerous growth factors and cytokines (1, 2). In addition to these mechanisms, a substantial body of evidence implicates regulatory proteases, such as urokinase-type plasminogen activator (uPA), to play a decisive role in cell migration and tissue remodeling (3, 4).

uPA binding to the cell surface via uPAR is a critical step in uPA function, allowing uPA to act as a membrane-associated ectoenzyme, focusing proteolysis to the immediate pericellular environment (5, 6). In non-migrating cells, uPAR is distributed over the entire cell surface, while uPAR is polarized toward the leading edge of migrating monocytes (6, 7), endothelial cells (8), and VSMC (9, 10). Furthermore, beyond merely facilitating extracellular proteolysis, the binding of uPA to its receptor also induces an intracellular signal (7, 11). Moreover, intracellular signals were also induced by stimulation with the NH2-terminal fragment of uPA, which retains receptor binding properties, but is devoid of enzymatic activity (12). However, because of the receptor’s special topology in the cell membrane implying the extracellular localization of uPAR and its membrane attachment via a glycosyl phosphatidylinositol (GPI) anchor, the mechanisms responsible for extra/intracellular signaling via uPAR still remain unclear (13, 14). The finding that cytoplasmic protein-tyrosine kinases (PTK) are noncovalently associated with GPI-anchored proteins (15) including uPAR (12, 16) has encouraged a search for probable signal transduction mechanisms by which this class of molecules induces intracellular signals.

Since uPA-induced serine phosphorylation of two cyclotransfins has been observed in migrating human epithelial cells (17), Src-PTKs are not the only kinases that may be utilized in uPAR-mediated signaling. Furthermore, uPAR-related changes in diacylglycerol formation (18) and the activation of the c-fos gene (19) via an unknown signaling pathway have also been demonstrated. The important question as to whether the different functions of uPAR are mediated through different signaling mechanisms and/or by kinases in addition to Src, has not yet been addressed. One potential candidate for alternative transducers and activators of transcription; uPA, urokinase-type plasminogen activator; uPAR, urokinase-type plasminogen activator receptor; PAGE, polyacrylamide gel electrophoresis; DTT, dithiothreitol; mAb, monoclonal antibody; GAS, interferon-γ activation site; ISRE, interferon-stimulated response element.
Jak/Stat Signaling and the Urokinase Receptor

uPAR-related signaling is the Jak/Stat pathway, a system that has recently been demonstrated to be involved in the signaling induced by a variety of growth factors, cytokines, and interferons (20–22). An important functional role for certain Stat proteins has been demonstrated in VSMC (23) after injury. We here report data which suggest that, in human aortic VSMC, the uPAR-signaling complex in addition to its close association with Src-PTK directly activates the Jak/Stat signaling cascade. uPA induces Jak1 and Tyk2 activation and causes a rapid translocation of Stat1 to the nucleus, where Stat1 selectively binds to the interferon-γ activation site/interferon-stimulated response element (GAS/ISRE) DNA transcription elements. In addition, we demonstrate that in migrating VSMC uPAR is localized to the leading edge of the cells where it is colocalized with the Jak, but not with the Src kinases. These observations suggest the involvement of Jak1 and Tyk2 in the regulation of cell migration.

EXPERIMENTAL PROCEDURES

Materials—Chemicals were purchased from Sigma, Pharmacia LKB Biotechnology (Uppsala, Sweden), Merck (Darmstadt, Germany), or Serva (Heidelberg, Germany). Radiochemicals were obtained from NEN Life Science Products, chemiluminescent signal enhancers were from Tropix, Inc. (Bedford, Massachusetts), and the protein-tyrosine kinase inhibitors genistin and herbimycin A (Streptomyces spp.) were obtained from Calbiochem-Novabiochem (La Jolla, CA) and San Diego, CA). Aqua-PolyMount mounting medium was purchased from Polysciences, Inc. (Warrington, PA).

Antibodies—Anti-uPAR (CD 87) polyclonal (products 399B and 399G) and monoclonal antibodies (products 3996 (IgG2a) and 3937 (IgGl1)) were purchased from American Diagnostica, Inc. (Greenwich, CT). Monoclonal anti-phosphotyrosine antibodies (IgGl1 and PY20, IgG2a) were from Boehhringer Mannheim (Heidelberg, Germany) and Santa Cruz Biotechnology, Inc. (Santa Cruz, CA); monoclonal anti-Statlα/β antibodies (STAT 91/84, IgG2b and IgG1 as gel supershift reagent) were from Dianova (Hamburg, Germany) and Santa Cruz Biotechnology, Inc. Polyclonal antibodies for Jak and Src-PTK were purchased from Santa Cruz Biotechnology, Inc. Cy5- and Cy3-conjugated donkey anti-rabbit and anti-mouse IgG (H + L) were obtained from Dianova. Fluorescein-conjugated goat anti-mouse IgG (H + L) was from Pierce and from Dianova.

Cell Culture—Human aortic VSMC were obtained from Clonetics (San Diego, CA). The cells were grown in SmGM2 medium (Clonetics) supplemented with 5% fetal bovine serum and were used between passages 3 and 6. For uPA stimulation experiments, the cells were cultured for 48 h in serum-free SmGM2 medium and were then treated with uPA as described below.

Wound Assay—The wound assay was performed as described elsewhere (24, 25). The images were acquired with NORTAN Instrument Odyssey XL supported with Intervision 1.4.1 software, and with a Bio-Rad MRC 600 confocal imaging system (Bio-Rad Laboratories, Freiburg, Germany) with an argon-krypton laser. At least 20–40 cells from at least seven separate experiments were examined under each experimental condition. The observers were unaware of the experimental design and antibodies used.

Tyrosine Phosphorylation and Western Blotting—Subconfluent VSMC were cultured in serum-free medium for 48 h, washed twice with HEPES/StaCel buffer (20 mM HEPES, pH 7.3, 130 mM NaCl), and treated with 10 nM uPA at 37 °C for 1–30 min in HEPES/StaCel buffer containing 0.2 mM sodium orthovanadate, 1 mM phenylethylsulfonyl fluoride, 10 µM l-phenylalanine, and 10 µg/ml leupeptin, 0.1 µg/ml pepstatin, 0.1 µg/ml trypsin, 0.1 µg/ml chymotrypsin, and 0.1 µg/ml aprotinin. The cell suspension was then centrifuged, and the pellets were then lysed in buffer (20 mM Tris-HCl, pH 8.0, 138 mM NaCl, 10 mM MgCl2, 2 mM EDTA, 1% Nonidet P-40 or 1% Triton X-100, and protease inhibitors as indicated above), for 5 min on ice. Supernatant proteins were subjected to SDS-PAGE and Western blotting, as described elsewhere (26).

Immunoprecipitation and Immune Complex Kinase Assay—For the immunoprecipitation, cell lysates containing 400–800 µg of protein were preclarified for 90 min at 4 °C with Gamma-Stop (Pharma-}

Molecular masses of

5

9

3

8

6

4

2

1

0

80 °C.

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1

l, con-

results of these experiments are shown in Fig. 1a. After 5 min of uPA application, a pronounced increase in tyrosine phosphorylation of several proteins with molecular masses of –38–42, 53–60, 85–90, and 130–140 kDa was observed (Fig. 1a, lanes 3–6). The increase in phosphorylation was rapid, peaked between 5 and 15 min, and decreased after 30 min. The control VSMC medium did not increase tyrosine phosphorylation. To exclude a potential contribution of proteolytic activity to the mechanism of tyrosine phosphorylation, disopropyl fluorophosphate-inactivated uPA was used for cells stimulation. This material provided the same effect (data not shown), confirming the involvement of proteolytically inactive uPA and amino-terminal fragments of uPA devoid of proteolytic activity in signaling events. VSMC pretreatment for 15 min with the tyrosine kinase inhibitor genistin abolished the uPA-induced phosphorylation completely (Fig. 1a, lane 2). The 38–42-kDa phosphorylated doublet in the VSMC lysates (Fig. 1a) may contain members of the mitogen-activated protein kinase family and the presence of 53–60-kDa phosphorylated proteins after uPA treatment suggested identity with the pre-
vously described Src-PTK. Of interest were the non-identified bands of phosphorylated proteins with molecular masses 85–90 and 130–140 kDa.

To determine whether the phosphorylated 85–90-kDa and/or 130–140-kDa proteins were associated with uPAR, cells were lysed under mild conditions (see “Experimental Procedures”), and immunoprecipitation was performed using anti-uPAR polyclonal antibodies. SDS-PAGE-separated immunoprecipitates were immunoblotted with anti-phosphotyrosine monoclonal antibodies. A similar pattern of phosphorylated 130–140-kDa proteins and a weak band of 85–90-kDa proteins were visualized by chemiluminescence after immunoblotting with monoclonal anti-Tyr(P) antibody.

**uPAR-induced Nuclear Translocation of Stat1 in VSMC**—To determine whether or not the activation of Jak proteins upon uPA treatment induced the activation of transcription factors, Stat1 nuclear translocation experiments were performed. Stat1 was chosen because of its recently demonstrated role in VSMC signaling and transcriptional regulation (23). For the induction and activation of Stat1 (p91/84), VSMC were treated with 1 nM uPA. The VSMC were washed, fixed, and stained before and after the uPA stimulation. Immunochemical staining with anti-Stat1 mAb revealed that Stat1 protein was localized diffusely within the cytoplasm and to a lesser extent in the nucleus of untreated VSMC (Fig. 3a). After 5 min of treatment with 1 nM uPA, anti-Stat1 staining was intensively increased in the perinuclear space. Furthermore, some Stat1 protein was also found in the nucleus (Fig. 3b). Ten and 15 min of VSMC activation resulted in predominantly nuclear staining (Fig. 3, c and d). After 20 min of uPA treatment, VSMC immunoreactivity decreased (Fig. 3e). These experiments demonstrate that uPA activation promotes Stat1 translocation in the nucleus.

**uPA Induces a Specific GAS/ISRE Binding Activity in VSMC**—An adequate test for Stat activation is a DNA binding assay (EMSA) analyzing the mobility of the oligonucleotides to which activated Stat proteins bind. In our EMSA, 32P-labeled GAS/ISRE oligonucleotide containing a consensus binding site was chosen because of its recently demonstrated role in VSMC signaling and transcriptional regulation (23). For the induction and activation of Stat1 (p91/84), VSMC were treated with 1 nM uPA. The VSMC were washed, fixed, and stained before and after the uPA stimulation. Immunochemical staining with anti-Stat1 mAb revealed that Stat1 protein was localized diffusely within the cytoplasm and to a lesser extent in the nucleus of untreated VSMC (Fig. 3a). After 5 min of treatment with 1 nM uPA, anti-Stat1 staining was intensively increased in the perinuclear space. Furthermore, some Stat1 protein was also found in the nucleus (Fig. 3b). Ten and 15 min of VSMC activation resulted in predominantly nuclear staining (Fig. 3, c and d). After 20 min of uPA treatment, VSMC immunoreactivity decreased (Fig. 3e). These experiments demonstrate that uPA activation promotes Stat1 translocation in the nucleus.

**Identification of uPAR-associated PTK**. uPAR-signaling complex was immunoprecipitated from the cell lysates using monoclonal anti-uPAR antibody and analyzed by immunoblotting with the indicated individual anti-Jak (a and b) and anti-Src (c) polyclonal antibodies (0.5 μg/ml), followed by chemiluminescent staining. b, lysates from the same cells were immunoprecipitated (IP) as above with anti-uPAR antibody, subjected to the in vitro kinase assay, and subjected to the second round of immunoprecipitation followed by 7.5% SDS-PAGE and autoradiography. The material after the first immunoprecipitation was reimmunoprecipitated (re-IP) with anti-Jak1 (lane 1), anti-Tyk2 (lane 2), anti-p59fyn, anti-p53/56fyn, anti-p55gar, and anti-p55/59hck (lanes 3–6).

**Jak/Stat Signaling and the Urokinase Receptor**

**FIG. 1. uPA-induced tyrosine phosphorylation in VSMC.** a, VSMC were incubated with medium alone (lane 1) or treated with 10 nM uPA at 37°C for 5 min (lane 3), 10 min (lane 4), 15 min (lane 5), and 30 min (lane 6). Lane 2 shows uPA treatment (10 nM, 10 min) after the preincubation of cells for 15 min with 100 μg genistein. The cell lysates were fractionated on 7.5% SDS-PAGE and immunoblotted with monoclonal anti-Tyr(P) antibody. b, VSMC were treated for 10 min with 10 nM uPA, lysed, and immunoprecipitated (IP) with anti-uPAR polyclonal antibody (lane 1), or the corresponding control IgG (lane 2). Tyrosine-phosphorylated proteins in the immunoprecipitates were visualized by chemiluminescence after immuno blotting with monoclonal anti-Tyr(P) (anti-(P)Tyr) antibody.

**FIG. 2. Identification of uPAR-associated PTK.** a, VSMC—uPAR signaling complex was immunoprecipitated from the cell lysates using monoclonal anti-uPAR antibody and analyzed by immunoblotting with the indicated individual anti-Jak (a and b) and anti-Src (c) polyclonal antibodies (0.5 μg/ml), followed by chemiluminescent staining. d, lysates from the same cells were immunoprecipitated (IP) as above with anti-uPAR antibody, subjected to the in vitro kinase assay, and subjected to the second round of immunoprecipitation followed by 7.5% SDS-PAGE and autoradiography. The material after the first immunoprecipitation was reimmunoprecipitated (re-IP) with anti-Jak1 (lane 1), anti-Tyk2 (lane 2), anti-p59fyn, anti-p53/56fyn, anti-p55gar, and anti-p55/59hck (lanes 3–6).
Stat1 in the observed complexes was tested by using anti-Stat1 antibody in gel retardation assays. Addition of antibody abolished the corresponding band (Fig. 4, lane 10); the effect was consistent with the characteristic of anti-Stat1 antibody used in these experiments (Santa Cruz Biotechnology commercial recommendations). The kinetics of DNA binding activity (Fig. 4, lanes 2–4) correlated very well with Stat1 nucleus translocation experiments done by confocal microscopy (Fig. 3). In both cases the effects were rather transient; the maximum of uPA-induced activation was observed within 10–15 min and declined significantly after 20–30 min.

Jak1 and Tyk2 Are Polarized with uPAR to the Leading Edge of Migrating VSMC—One of the most established uPAR functions is cell migration. The association between uPAR and cell migration is presumably independent of extracellular matrix proteolysis; however, the process may also involve signal transduction (10–12). To explore the possible role of uPAR signaling on cell migration, we used a migration wound assay. VSMC migration in a wounded monolayer is shown on Fig. 5. VSMC migration in one general direction following wounding was observed by 4 h after injury and was pronounced at 24 h (Fig.
In confluent VSMC, uPAR was distributed evenly over the body of the cell in a punctate pattern, with some increased staining at the periphery. However, the staining was not restricted to a specific site on the cell membrane (Fig. 6a). In response to injury, about 25% of migrating cells demonstrated a highly asymmetric distribution of uPAR along the leading edge of the cell membrane in a polarized fashion (Fig. 6b).

To obtain evidence that Jak proteins and Src-PTK exist in the same physical complex as uPAR upon cell migration, double immunolabeling experiments were performed using anti-uPAR mAb and pAb to individual kinases. Pronounced polarization and colocalization with uPAR at the leading edge of the migrating cells was found for Jak1 (Fig. 7, a–c) and Tyk2 (Fig. 7, a′–c′). Antibodies to Jak2 and Jak3 demonstrated a homogeneous punctate staining pattern, with increased staining at the sites of cell-cell contacts. However, the staining was not restricted to the leading edge of the cells either in wounded and nonwounded cultures (Fig. 8c, shown for Jak3). Strongly pronounced polarization of Jak1 and Tyk2 to the leading edge of migrating cells and colocalization with uPAR could be seen already 6 h after wounding. Control antibodies showed no staining above background autofluorescence (Fig. 7, d and e).

Finally, we performed double staining for uPAR and p59^{fyn}, p53/56^{lyn}, p55^{fgr}, and p55/59^{hck}, four Src family PTK found to be coimmunoprecipitated in our experiments with uPAR. This staining demonstrated a uniform patch-like pattern over the body of the cell, with some mildly increased staining at the periphery for all four kinases in both subconfluent and wounded confluent cultures (Fig. 8, a and a′, shown for p55^{fgr} and p55/59^{hck}). uPAR displayed high polarization to the leading edge of migrating cells (Fig. 8, b and b′).

DISCUSSION

We here demonstrate that uPAR can directly activate the Jak/Stat signaling pathway in human aortic VSMC. Coimmunoprecipitation experiments showed the association of uPAR with two Janus kinases: Jak1 and Tyk2, and uPA-dependent activation of these two Jak kinases was demonstrated by in
proteins, and an

for the characterization of molecular interactions with GPI

VSMC. Using co-immunoprecipitation, a standard technique

these PTK. These earlier findings are confirmed by our study in

research on uPA/uPAR signal transduction was focused on

(12), the PTK of the Src family coprecipitate with uPAR, recent

machinery.

dence that uPA activates a definite chain of signal transduction

ments. To our knowledge, these findings provide the first evi-

selectively binds to the GAS/ISRE DNA transcriptional ele-

duces rapid translocation of Stat1 to the nucleus, where it

kinase assay. In addition, we demonstrate that uPA in-

vitro

ings.

wounded culture 18 h after wound-

Jak3 in VSMC migrating from

are known to be substrates for Jak kinases in a number of

cytokine receptor systems (21). Actually, immunoprecipitation

experiments, combined with in vitro kinase assays, allowed us
to identify two members of Janus kinases, namely Jak1 and

Tyk2, to be associated with uPAR in one signal transducing

complex.

The activation of Jak by cytokines or growth factors leads to

the rapid phosphorylation of Stat proteins on tyrosine residues.
The phosphorylated Stat proteins translocate immediately to

the nucleus and bind to specific DNA sequences such as GAS,

ISRE, or Sis-inducible element, and hence activate specific

gene expression (20–23). To confirm that uPA via uPAR does

induce Jak/Stat signaling, we further examined uPA-induced

translocation of Stat1 to the nuclei of VSMC and its binding to

dNA sequences GAS/ISRE. Stat1 was selected because of

its previously shown functional importance for VSMC (23).

These studies allowed us to demonstrate that uPA activation

actually leads to the rapid reversible translocation of Stat1 to

the nucleus. Gel shifts of VSMC nuclear fractions were per-

formed using the GAS/ISRE consensus binding sequence for

interferon-γ activation factor. They showed the specific forma-

tion of protein-DNA complexes in response to stimulation with

uPA. In addition, the kinetics of uPA-induced DNA binding

activity in the cell nuclear extracts was rapid and time-depend-

ent and had a rather transient character correlating with the

kinetics of uPA-dependent Stat1 translocation into the nucleus.

In electrophoretic mobility supershift experiments, anti-Stat1

antibody abolished the protein-DNA complex, thus demon-

strating that these complexes did indeed contain Stat1 protein.

These results suggest a novel mechanism for uPAR-dependent

signal transduction and provide further evidence that links

uPA to a dynamic intracellular event. These findings are in

agreement with other studies showing that the signaling ma-

chinery induced by cytokines and growth factors may involve

two or more interacting pathways, the activation of Jak/Stat

system and the tyrosine phosphorylation of Src-PTK (29–31).

To further explore the probable functions of both these sig-

naling pathways, VSMC migration experiments were per-

formed using a wound assay. In this assay, a highly asymmet-

ric distribution of uPAR was found in response to wounding,

localizing uPAR to the leading edge of the cells. This finding is

in agreement with the observation that uPAR polarization

Fig. 8. Immunofluorescence localization of uPAR, p55fos, p55/59hck and

Jak3 in VSMC migrating from wounded culture 18 h after wound-

ning. Polarized distribution of uPAR (b, b′, d) and diffused localization of p55fos (a),
p55fos, and p55/59hck (a′), and Jak3 (c) are shown. The direction of the wound edge is indi-
cated by arrows. Bar = 10 μm.
occurs upon injury in human umbilical vein VSMC (9, 10) and in endothelial cells (8). In addition, similar polarization of uPAR has been observed in human monocytes in response to chemotactic gradients (6, 7). Our experiments also demonstrated pronounced redistribution of both uPAR-associated Janus kinases, Jak1 and Tyk2, to the leading edge of migrating cells, where they colocalized with uPAR. Under the same experimental conditions, Jak2, Jak3, and the members of the Src family remained randomly distributed over the entire body of the cell.

Redistribution of the molecules participating in the regulation of cell migration to the leading edge, as compared with a random distribution, is of advantage for the migrating cell. Focal concentration of the molecules potentially increases the information content of the signal and thus accelerates its transduction. Induced proximity therefore may be regarded as a very important event in intracellular signaling (32). Redistribution of the molecules responsible for cell migration may thus be a highly conserved mechanism for maximizing signal transduction. Our data on the redistribution and colocalization of Jak1 and Tyk2 with uPAR to the leading edge of migrating cells indicate that the Jak/Stat pathway does play an important role in the uPAR-related regulation of cell migration. This notion is well in agreement with recent findings on the requirement of Jak1 kinase for cell migration and anterior specification in zebra fish embryos (33). This work also implies that, in addition to its role in signal transduction of cytokines in adult tissues, Jak1 has a role in early embryonic development and tissue remodeling. The involvement of the Jak/Stat signaling pathway in uPAR signaling thus strongly suggests a mechanism that optimizes gene induction during cell migration. Further research that targets to the identification of Stat1 transcriptionally regulated genes should therefore be able to define their potential roles in VSMC functional responses to uPA. The functional role of the Src kinases in uPAR-related signaling as well as the nature of the mechanism providing extra/intracellular conduction of the uPAR-related signal also remains to be established. The latter may include adapter molecules, co-receptor functions, and other more indirect interactions (34).

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REFERENCES
1. Casscells, W. (1992) Circulation 86, 723–729
2. Ross, R. (1993) Nature 362, 801–809
3. Blasi, F. (1993) BioEssays 15, 105–110
4. Van Leeuwen, R. T. J., and Orci, L. (1996) Fibrinolysis 10, 59–74
5. Dano, K., Andreeasen, P. A., Grondaai-Hansen, J., Kristensien, P., Nielsen, L. S., and Skriver, L. (1985) Adv. Cancer Res. 44, 139–266
6. Estreecher, A., Mulhauzer, J., Carr, N., M., Ori, L., and Vassalli, J.-D. (1990) J. Cell Biol. 111, 783–792
7. Gyerek, M. R., Todd, R. F., III, Wilkinson, C. C., and Sitrin, R. G. (1994) J. Clin. Invest. 93, 1380–1387
8. Pepper, M. S., Sappino, A.-P., Stocklin, R., Montesano, R., Ori, L., and Vassalli, J.-D. (1993) J. Cell Biol. 122, 673–684
9. Okada, S. S., Tomaszewski, J. E., and Barnathan, E. S. (1995) Exp. Cell Res. 217, 180–187
10. Okada, S. S., Grobmyer, S. R., and Barnathan, E. S. (1996) Arterioscler. Thromb. Vasc. Biol. 16, 1269–1276
11. Stahl, A., and Mueller, B. (1994) Cancer Res. 54, 3066–3071
12. Resnati, M., Guttering, M., Valecamonica, S., Sidenius, N., Blasi, F., and Fazioli, F. (1996) EMBO J. 15, 1572–1582
13. Roldan, A. L., Cubella, M. V., Masucci, M. T., Behrendt, N., Lund, L. R., Dans, K., Appella, E., and Blasi, F. (1996) EMBO J. 15, 467–474
14. Flou, M., Ronne, K., Behrendt, N., Jensen, L., Blasi, F., and Dans, K. (1991) J. Biol. Chem. 266, 1926–1933
15. Stefanova, I., Herejvi, V., Ansotegui, I. J., Knapp, W., and Stockinger, H. (1991) Science 254, 1016–1019
16. Bukoslav, J., Herejvi, V., Hansmann, C., Stochl, J., Weidle, U. H., Majdic, O., Bartke, I., Knapp, W., and Stockinger, H. (1995) J. Exp. Med. 181, 1381–1390
17. Busso, N., Masur, S. K., Lazega, D., Wuxan, S., and Ossowski, L. (1994) J. Cell Biol. 126, 259–270
18. Del Russo, M., Anichini, E., Ledersen, N., Blasi, F., Fibbi, G., Piret, M., and Ruggiero, M. (1995) Biochem. Biophys. Res. Commun. 190, 347–352
19. Dumerle, I., Petri, T., and Schletten, W.-D. (1994) FEBS Lett. 343, 103–106
20. Briscoe, J., Gueschin, D., and Muller, M. (1994) Curr. Biol. 4, 1023–1025
21. Ziemiecki, A., Harpur, A. G., and Wilks, A. F. (1994) Trends Cell Biol. 4, 207–212
22. Briscoe, J., Kuhlhuber, F., and Muller, M. (1996) Trends Cell Biol. 6, 336–340
23. Yamasato, H., Crow, M., Cheung, L., Lakatta, E., and Kinseela, d. (1990) Exp. Cell Res. 222, 125–130
24. Haller, H., Lindschau, C., Quass, P., and Dittmier, A. (1995) Circ. Res. 76, 21–29
25. Haller, H., Bauer, E., Quass, P., Behrendt, M., Lindschau, C., Dittmier, A., and Lufi, F. C. (1995) Kidney Int. 47, 1057–1067
26. Tobin, H., Staeelin, T., and Gordon, J. (1979) Proc. Natl. Acad. Sci. U. S. A. 76, 4530–4537
27. Dumerle, I., Petri, T., and Schletten, W.-D. (1993) FEBS Lett. 327, 37–40
28. Schney-Scaria, A. M., Kwong, J., Fujita, T., Oszyw, M. W., Shaw, S. A., and Luftl, D. M. (1992) J. Immunol. 149, 3535–3541
29. Cao, X., Toy, A., Guy, G. R., and Tan, Y. H. (1996) Mol. Cell. Biol. 16, 1595–1603
30. Marrero, M. B., Paxton, W. G., Schieffer, B., Ling, B. N., and Bernstein, K. E. (1996) Cell. Signalling 8, 21–26
31. Zeng, C., Yan, R., August, A., Darnell, E. J., Jr., and Hanafusa, H. (1996) EMBO J. 15, 4515–4525
32. Crabtree, G. R., and Schreiber, S. L. (1996) Trends Biochem. Sci. 21, 418–422
33. Conway, G., Margoliath, A., Wong-Madden, S., Roberts, R. J., and Gilbert, W. (1997) Proc. Natl. Acad. Sci. U. S. A. 94, 3082–3087
34. Dumerle, I., Huclo, F., and Gulba, D. C. (1997) Fibrinolysis & Proteolysis 11, Suppl. 2, 165–170