Estrogen as well as insulin-like growth factor 1 (IGF-1) are potent mitogenic stimuli that share important properties in the control of cellular proliferation. However, the coupling between the signaling cascades of estrogen receptors α and β and the IGF-1 receptor (IGF-1R) is poorly understood. Therefore, we selectively transfected estrogen receptor α or β in COS7 and HEK293 cells, which contain IGF-1R. In presence of estrogen receptor α but not β, 17β-estradiol (E2) rapidly induces phosphorylation of the IGF-1R and the extracellular signal-regulated kinases 1/2. Furthermore, upon stimulation with E2, estrogen receptor α but not β bound rapidly to the IGF-1R in COS7 as well as L6 cells, which express all investigated receptors endogenously. Control experiments in the IGF-1R-deficient fibroblast cell line R- showed that after stimulation with E2 only estrogen receptor α bound to the transfected IGF-1R. Overexpression of dominant negative mitogen-activated protein kinases kinase inhibited this effect. Finally, estrogen receptor α but not β is required to induce the activation of the estrogen receptor-responsive reporter ERE-LUC in IGF-1-stimulated cells. Taken together, these data demonstrate that ligand bound estrogen receptor α is required for rapid activation of the IGF-1R signaling cascade.

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Estrogen as well as insulin-like growth factor 1 (IGF-1) are potent mitogenic stimuli that are involved in a large array of processes that control proliferation and differentiation in mammalian cells (1, 2). Both mitogens act through receptor-mediated signaling pathways. The cross-talk between these two signaling pathways is currently under investigation (3–6). Estrogen is a steroid hormone that binds to members of the nuclear receptor family and is required for rapid activation of the IGF-1R signaling cascade.

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were obtained from the American Type Culture Collection (Manassas, VA). COS7 cells were maintained in Dulbecco’s modified Eagle’s medium (Life Technologies, Inc.) supplemented with 10% charcoal-stripped, estrogen-free fetal calf serum (c.cpro, Hamburg, Germany). HEK293 were maintained in modified Eagle’s medium (Life Technologies, Inc.) supplemented with 1% charcoal-stripped, estrogen-free fetal calf serum. R-r is a fibroblast cell-line derived from a transgenic mouse that does not express the IGF-1R (29) but contains both ERα and ERβ as we confirmed by Western blotting. R-r cells were a kind gift from Dr. R. Baserga and were maintained in Dulbecco’s modified Eagle’s medium supplemented with 10% charcoal-stripped, estrogen-free fetal calf serum. The myogenic cell line L6 (30), which expresses ERα, ERβ, and the IGF-1R without transfection, was obtained from the American Type Culture Collection. L6 skeletal myoblasts were cultured as described before (31). All media contained 25 μg/ml Gentamycin (Life Technologies, Inc.). Phenol red-free medium was used throughout all experiments because phenol red acts as a weak estrogen (32).

Immunoblotting—Cellular lysates (40 μg of protein/lane) were analyzed by SDS gel electrophoresis in a 7.5% polyacrylamide gel (for detection of IGF-1R, ERα, and ERβ) or a 12% polyacrylamide gel (for detection of phospho-ERK1/2) and transferred to nitrocellulose membranes as described (33). Protein content was measured with a standard Bradford assay. Immunoblotting was performed with antibodies specific against phospho-ERK1/2 (mouse anti-Eng/kinase, Biologs, Schwalbach, Germany), ERα (mouse monoclonal, SRA-1000, Biomol, Hamburg, Germany), ERβ (rabbit polyclonal, PA1–310, Di-anova, Hamburg, Germany), p-Tyrosine (mouse monoclonal, SC-508, Santa Cruz Biotechnology, Santa Cruz, CA) and the C terminus of the IGF-1 receptor β-subunit (rabbit polyclonal, SC 713) followed by detection with ECL (Amersham Pharmacia Biotech). All experiments were performed at least in triplicate.

Immunoprecipitation—Cellular lysates (400 μg of protein) were incubated with the respective antibody (described above) against ERα, ERβ, and the IGF-1R. Cellular extracts were incubated with the primary antibody for 24 h at 4 °C. Depending on the antibody used, 40 μl of protein A or protein G-Sepharose were added to the lysate followed by incubation for 3 h at 4 °C. Samples were centrifuged in a cooled micro-centrifuge (4 °C) for 2 min at 12,000 × g. Pellets were washed twice with RIPA buffer (50 mM NaCl, 20 mM Tris, pH 7.4, 50 mM NaF, 50 mM EDTA, 20 μM Na3P2O7, 1 mM Na3VO4, 1% Triton X-100, 1 mM phenylmethylsulfonyl fluoride, 0.6 mg/ml leupeptin, 10 μg/ml aprotinin) and resuspended in 50 μl of total volume. SDS loading buffer was added, and samples were heated for 5 min at 95 °C. Sepharose beads were pelleted by centrifugation in a micro-centrifuge (4 °C) for 1 min at 4 °C. The supernatants were then analyzed by SDS-polyacrylamide gel electrophoresis and subsequent immunoblotting as described above.

Transfections—Cells were grown to an approximate confluence of 70% and transfected using a liposome-conjugated transfection technique according to the manufacturer’s instructions (DOTAP; Roche Diagnostics, Mannheim, Germany). Cells were transfected with expression plasmids for human ERα and ERβ (kind gifts from Dr. Pierre Chambon). In this study were obtained with the expression plasmid HE0 (34). This plasmid contains the human wild-type ERα cDNA-clone λO85 as described in Ref. 8, which is known to contain a point mutation in its hormone-binding domain (Gly400 → Val400), which alters its ligand binding properties (16, 35). Human ERα expressed by HE0 has a slightly reduced transactivation response compared with the human wild-type ERα. All experimental data shown are based on experiments performed with HE0 and were reproduced at least once with the expression plasmid for the human wild-type ERα (HEG0). The results of transfection and immunoprecipitation studies were found to be the same with both constructs with the only difference that transactivation responses of HEG0 were slightly higher than the data obtained with HE0 (HE0 and HEG0 were kind gifts from Dr. Pierre Chambon). In experiments that included ERβ, pCMV29 (9) (kind gift from Dr. G. Kuiper) was transfected that expresses the rat ERβ cDNA. To confirm the dependence of the observed effect on the presence of IGF-1R protein, R-r cells were transfected with a plasmid containing the IGF-1R precursor cDNA under the control of the SV40 early promoter (29) (kind gift from Dr. D. Rapraeger). Plasmids expressing dominant-negative ERK (K97S-MAPKK) and constitutively active MAPKK (S222A-MAPKK) of Xenopus MAPKK (36) were utilized to determine the influence of the activity of MAPKK on interactions between estrogen receptor and IGF-1 signaling pathways.

Transfection Assay—Cells were transfected with ERE-LUC (containing three copies of an estrogen-responsive element from the Xenopus vitellogenin promoter, driving expression of the luciferase gene, kindly provided by Dr. C. Glass) and the respective estrogen receptor expression vectors. Cells were transfected 24 h after transfection and luciferase activity was determined by staining of a subset of the transfected cells. Cells were washed with phosphate-buffered saline and then fixed in 0.5% glutaraldehyde for 10 min followed by three more washes. Then they were incubated overnight at 37 °C in a staining solution containing 15 μg K3Fe(CN)6, 15 μg K4Fe(CN)6·3H2O, 0.15 μg MgCl2, 1% MeSO, and 1 mg/ml 5-bromo-4-chloro-3-indolyl β-D-galactopyranoside (X-gal). Nuclei of cells stained for β-galactosidase activity were counted, and the results of each luciferase determination were normalized for the transfection efficiency.

Inhibitory Substances—The IGF-1R antagonist H 1356 is an IGF-1 peptide analogue with the amino acid sequence CYAAPLKPARKSC (38) (Bachem, Heidelberg, Germany) and was added in a subset of transfection studies to investigate the effect of IGF-1R inhibition on the experimental results. The estrogen receptor antagonist ICI 182,780 (39) (kind gift from Dr. A. Wakeling), which completely antagonizes ERα as well as ERβ, was used to study inhibition of the estrogen receptors. An equal volume of vehicle alone (0.1% ethanol) was added to control cells. The MAPKK inhibitor PD 98059 (40) (Calbiochem, Bad Soden, Germany) was utilized to investigate the influence of MAPKK inhibition.

Statistical Analysis—All reported values are the means ± S.D. Statistical comparisons were made by Student’s t test, two-sided with adjustment for multiple comparisons. Statistical significance was assumed if a null hypothesis could be rejected at the p < 0.01 level. All materials were obtained from Merck if not otherwise specified.

**RESULTS**

IGF-1R Autophosphorylation by E2 Requires ERα but Not ERβ—In a first step we elucidate the role of ERα and ERβ in E2-mediated activation of IGF-1R signaling. We investigated whether the phosphorylation of IGF-1R by E2 (4) depends on the presence of estrogen receptors. To distinguish between the role of ERα and ERβ in the E2-dependent activation of IGF-1R phosphorylation we used the cell line COS7, which expresses the IGF-1R but is devoid of estrogen receptors. These cells were transfected with expression plasmids for either ERα or ERβ and were subsequently stimulated with 10−7 M E2 for 0–60 min. In a series of immunoprecipitation experiments with an IGF-1R antibody and subsequent immunoblotting against phosphoryrosine residues, phosphorylation of IGF-1R was determined (Fig. 1). In the presence of ERα, stimulation with E2 led to a time-dependent induction of IGF-1R phosphorylation in COS7. In contrast, E2 did not stimulate receptor phosphorylation in the presence of Erβ. No induction of tyrosine phosphorylation after stimulation with E2 was observed in cells that had not been transfected. The ERα-dependent induction of tyrosine phosphorylation after E2 treatment was inhibited by cotreatment with the IGF-1 peptide analogue H 1356, an antagonist of the IGF-1R (38), and by ICI 182,780, an antagonist of both estrogen receptor subtypes (39). Identical results were obtained when the same experimental procedure was performed in the cell line HEK293 (data not shown).

**E2 Stimulates Binding of ERα but Not ERβ to the IGF-1R—**Because
the E2-dependent induction of IGF-1R phosphorylation was sensitive to inhibition of both the IGF-1R and the estrogen receptor, we performed a series of communoprecipitation experiments of these receptors to elucidate the underlying mechanisms. Three groups of cells were employed in these experiments: 1) COS7 cells served as models for control expression of either ERα or ERβ. As a model for controlled IGF-1R expression we used R- cells, an embryonic fibroblast cell line derived from a transgenic animal that does not express IGF-1R but does express ERα and ERβ (29). One subset of these cells was transfected with an expression plasmid for the IGF-1R. 3) The myogenic cell line L6 (30) was utilized as an example for a cell line expressing all receptors endogenously (31, 41, 42). Stimulations were performed with 10−8 M E2 for 0–60 min. Total cellular protein was harvested and subjected to immunoprecipitation with antibodies against ERα or ERβ. The precipitated fraction was used for subsequent immunoblotting with an IGF-1R antibody as shown in Fig. 2. Communoprecipitation of IGF-1R with the ERα was detected 5 min after stimulation with 10−8 M E2 in COS7 (Fig. 2A) cells transfected with ERα and in R- cells (Fig. 2B) transfected with the IGF-1R. In L6 cells (Fig. 2C) this signal was detectable after 30 min. L6 cells express all investigated receptors under the control of endogenous promoters. We therefore assume that the onset of this interaction may take considerably longer. No interaction between ERβ and the IGF-1R was observed in any experiments (Fig. 2, upper panels). In R- cells, in the absence of the IGF-1R, no interaction of ERα with ERβ was detected (Fig. 2B, upper panel). The sequence of antibodies used for precipitation and immunoblotting was reversed to exclude the possibility of false positive results caused by nonspecific cross-reactions of the antibodies. The results from both experimental approaches were in correspondence (Fig. 2, lower panels). The observed communoprecipitation was sensitive to coinubcation with the estrogen receptor antagonist ICI 182,780, the IGF-1R antagonists H1356, and the MAPKK inhibitor PD 98059 (40).

Phosphorylation of ERK1/2 Is Required for Binding of ERα to the IGF-1R—To assess the physiological relevance of E2-induced IGF-1R phosphorylation, we analyzed signaling events downstream of the IGF-1R. Phosphorylation of ERK1/2 is part of the signaling cascade downstream of the IGF-1R. Phosphorylation of ERK1/2 by E2 was detected by immunoblotting with a phospho-specific antibody against tyrosine/ threonine phosphorylated ERK1/2. COS7 cells were transfected with expression plasmids for either ERα or ERβ. ERK1/2 phosphorylation was determined after 0–60 min stimulation with 10−8 M E2. In the presence of ERα E2 rapidly induced ERK1/2 phosphorylation (Fig. 3), which reached its maximum after 15 min. In cells expressing only ERβ E2 failed to induce this reaction. ERK1/2 phosphorylation in the presence of E2 was blocked by cotreatment with the IGF-1R antagonist H1356 (29). Control experiments using E2 and PD 98059 revealed that MAPKK is involved in the process. Identical results were obtained when the same experimental procedure was performed in HEK293 cells (data not shown).

The estrogen receptor signaling pathway has been shown to be activated by binding of E2 to its receptor as well as by phosphorylation of ERα and ERβ. Thus, we were interested to understand the mechanism of these processes. We therefore performed experiments to test the hypothesis that a construct containing an estrogen-responsive enhancer element driving a luciferase cDNA (ERE-LUC) (44) was employed.

In a first step we investigated whether the expression of an estrogen-inducible reporter after incubation with E2 or IGF-1 depends on the integrity of the IGF-1 signaling pathway. R- cells were transfected with an expression plasmid for the IGF-1R and cotransfected with the reporter plasmid ERE-LUC (Fig. 5, A). Stimulation with E2 (10−8 M) resulted in a 6.3 ± 0.06-fold induction of reporter expression in the presence of IGF-1 compared with a 5.6 ± 0.03-fold induction in the absence of the IGF-1R. Furthermore, we observed that in R- cells transfected with the IGF-1R plasmid ERE-LUC expression was induced 5.0 ± 0.06-fold after incubation with IGF-1 (10−8 M), whereas in cells lacking the IGF-1R IGF-1 did not influence reporter expression. Expression of the same reporter plasmid lacking estrogen-responsive elements (TK-LUC) was neither influenced by incubation with E2 nor by incubation with IGF-1.

To dissect the role of ERα and ERβ in ERE-LUC induction by IGF-1, cells were transfected with an expression plasmid for ERα and incubated with IGF-1 (10−8 M). IGF-1 markedly induced luciferase expression, whereas no induction of reporter expression by IGF-1 was observed in cells transfected with ERβ. The IGF-1R antagonist H1356 as well as the MAPKK inhibitor PD 98059 inhibited the IGF-1-dependent induction.

Finally, we compared the transcriptional activation of ERα and ERβ by E2 and by IGF-1. Therefore, COS7 and HEK293 cells were transfected with expression plasmids for either ERα or ERβ and the reporter plasmid ERE-LUC. In the presence of E2, stimulation with 10−8 M E2 for 24 h resulted in 10.7 ± 0.05-fold induction of ERE-LUC expression in COS7 cells (Fig. 5, COST) and 13.5 ± 0.12-fold in HEK293 cells (Fig. 5, HEK293). After cotransfection with ERβ instead of E2, stimulation with 10−8 M E2 induced reporter expression 7.2 ± 0.03-fold (COST) and 7.8 ± 0.03-fold (HEK293), respectively. ICI 182,780 (10−8 M) inhibited the transactivation of reporter expression by both ERα and ERβ. To investigate the influence of MAPKK activity on E2-dependent LUC induction, cells were coinfected with the MAPKK inhibitor (PD 98059). In E2-transfected cells inhibition of ERK1/2 phosphorylation by PD 98059 (10−8 M) had a marked effect on E2-induced reporter expression (COST, −57.9 ± 3.1%; HEK293, −62.6 ± 5.9%). ERβ-dependent induction of ERE-LUC, however, was insensitive to PD 98059.

DISCUSSION

The interaction of ERα and ERβ with membrane-associated signaling pathways is currently under investigation but is still poorly understood (3, 4, 6, 26, 27). In our understanding of the role and function of estrogen receptors on the cell membrane level two major points deserve further attention: the interaction between estrogen receptors and tyrosine kinase receptor signaling pathways as well as the differences of ERα and ERβ in coupling to the cell membrane.

The data presented here contribute new observations to these points by demonstrating that: 1) E2 activates the IGF-1R signaling cascade exclusively via ERα, 2) binding of E2 to the IGF-1R is a potential mechanism for estrogen to activate the IGF-1R, 3) phosphorylation of ERK1/2 is required for binding of ERα to the IGF-1R, and 4) E2 but not ERβ is the target of ligand-independent activation by IGF-1 signal transduction via the MAPK. Rapid, so called nongenomic effects of estrogen, which occur within seconds to minutes, are part of a variety of cellular responses to estrogen. In particular, rapid effects of estrogen on NO release (45, 46), on E2- or ERα-induced NO formation (47), on calcium homeostasis (48–50), and on cAMP accumulation (51) have been described up to now, but the exact mechanisms of these processes are incompletely understood. Therefore, the observation that 1) ligand-induced ERα binds to a transmembrane receptor and that 2) E2 rapidly activates phosphorylation of the IGF-1R in the presence of ERα

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FIG. 2. E2 stimulates binding of IGF-1R to ERα but not ERβ. COS7 (A), R² (B), and L6 cells (C) were stimulated with 10⁻¹⁰ M E2 for 0–60 min. COS7 cells were transfected with expression plasmids for ERα (ERα⁺) or ERβ (ERβ⁺). R² cells were additionally transfected with an expression plasmid for the IGF-1R (IGF-1R⁺) because these cells do not contain the respective receptors. Protein lysates were subjected to immunoprecipitation with ERα or ERβ antibodies with subsequent immunoblotting of the precipitated fraction with an IGF-1R antibody (upper panels) or vice versa immunoprecipitation of the IGF-1R with subsequent immunoblotting with an ERα antibody (lower panels). In cells expressing endogenous estrogen receptors (L6, R²), immunoprecipitation (IP) of ERα or ERβ was performed previous to immunoblotting with an antibody against the IGF-1R. A subset of the cell cultures was cotreated with antagonists of the IGF-1R (H, H 1356, 10⁻⁷ M) and of estrogen receptors (ICI, ICI 182,780, 10⁻⁸ M) and with an inhibitor of MAPKK (PD, PD 98059, 10⁻⁵ M). These results are representative of at least three experiments.
may offer a potential mechanism to gain further insight into the previous findings. Our data provide a model for how ligand-bound ER\textsubscript{a} activates growth factor signaling cascades in a rapid nongenomic fashion: by binding to the IGF-1R followed by its phosphorylation. Recently, it was reported that estrogen stimulates the phosphorylation of the membrane bound IGF-1R in the uterus after 6 h and involves the phosphatidylinositol 3-kinase signaling pathway (4, 26). Our findings extend these observations by demonstrating a rapid effect of estrogen on IGF-1R phosphorylation within minutes. The presence of a putative membrane-bound ER (51–55) has to be discussed in the light of these data.

Previously, it was demonstrated that the estrogen-independent phosphorylation and activation of estrogen receptors can be mediated via the MAPK pathway (5, 25). MAPKs such as ERKs are important regulators in signaling pathways in response to a wide array of extracellular stimuli. This observa-
differences may be in part due to different AF-1 domains be-
regulatory functions of the two estrogen receptor subtypes. The
consequence, the binding of ERα MAPKK activity and is induced via the MAPK pathway. As a
that in turn stimulates the activity of ERα, thus establishing a positive feedback loop between estrogen receptor and receptor tyrosine kinase signaling.

In summary, we were able to demonstrate that after ligand
binding and phosphorylation by the MAPK cascade ERα is able to bind to the IGF-1R. This binding induces autophosphorylation of the IGF-1R and thus its activation. IGF-1R activation stimulates MAPKK and consequently phosphorylation of ERK1/2. Activation of ERK1/2 may, in turn, lead to phosphorylation of ERα and provides a possible mechanism for ligand-independent activation of ERα but not of ERβ (Fig. 6). Further

investigations, however, are required to understand how estrogen and the expression patterns of the two estrogen receptor subtypes as well as IGF-1R signal transduction cooperate in the regulation of growth and differentiation.

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REFERENCES
1. Katzenellenbogen, B. S. (1996) Biol. Reprod. 54, 287–293
2. Rubin, B., and Baserga, R. (1985) Lab. Invest. 53, 311–331
3. Ignatow-Trowbridge, M. C., Curtis, S. W., Washburn, T. F., McLaughlin, J. A., and Korach, K. S. (1992) Proc. Natl. Acad. Sci. U. S. A. 89, 6458–6462
4. Richards, R. G., Diaugustine, R. P., Petrusz, P., Clark, G. C., and Sebastian, J. (1996) Proc. Natl. Acad. Sci. U. S. A. 93, 12002–12007
5. Kato, S., Endoh, H., Masuhira, Y., Kitamoto, T., Uchiyama, S., Sasaki, H., Masushige, S., Gotoh, Y., Nishida, E., Kowashima, H., Metzger, D., and Chambon, P. (1995) Science 270, 1491–1494
6. Lee, A. V., Weng, C. N., Jackson, J. G., and Yee, D. (1997) J. Endocrinol. 152, 39–47
7. Evans, R. M. (1988) Science 240, 889–895
8. Walter, P., Green, S., Greene, G., Krust, A., Bornert, J.-M., Waterfield, M., and Chambon, P. (1985) Proc. Natl. Acad. Sci. U. S. A. 82, 7889–7893
9. Kuiper, G. G. J. M., Enmark, E., Pelto-Huikko, M., Nilsson, S., and Gustafsson, J. A. (1996) Proc. Natl. Acad. Sci. U. S. A. 93, 5925–5930
10. Tora, L., White, J., Brou, C., Tasset, D., Webster, N., Scheer, E., and Chambon, P. (1989) Cell 57, 477–487
11. Masselmann, S., Polman, J., and Dijkema, R. (1996) FEBS Lett. 392, 49–53
12. Tzukerman, M. T., Esty, A., Sanzio Mere, D., Danielian, P., Parker, M. G., Stein, R. B., Pike, J. W., and McDonnell, D. P. (1994) Mol. Endocrinol. 8, 21–30
13. Jones, P. S., Parrott, E., and White, I. N. H. (1999) J. Biol. Chem. 274, 32008–32014
14. Ali, S., Metzger, D., Bornert, J.-M., and Chambon, P. (1993) EMBO J. 12, 1533–1540
15. Webb, P., Nguyen, P., Valentine, C., Lopez, G. N., Kwok, G. R., Mcinerney, E., Katzenellenbogen, B. S., Enmark, E., Gustafsson, J. A., Nilsson, S., and Kushner, P. J. (1999) Mol. Endocrinol. 13, 1872–1885
16. Paeck, K., Webb, P., Kuiper, G. G. J. M., Nilsson, S., Gustafsson, J. A., Kushner, P. J., and Scanlan, T. S. (1997) Science 277, 1508–1510
17. Hall, J. M., and McDonnell, D. P. (1999) Endocrinology 140, 5566–5578
18. Cowley, S. M., Hoare, S., Masselmann, S., and Parker, M. G. (1997) J. Biol. Chem. 32, 19858–19862
19. Warner, M., Nilsson, S., and Gustafsson, J. A. (1999)Curr. Opin. Obstet. Gynecol. 11, 2494
20. Ogawa, S., Jan, C., Chester, A. E., Gustafsson, J.-A., Korach, K. S., and Paff, D. W. (1999) Proc. Natl. Acad. Sci. U. S. A. 96, 12887–12892
21. Makela, S., Savilaanen, H., Myllarniemi, M., Strauss, L., Tsuchin, E., Gustafsson, J.-A., and Hassay, P. (1999) Proc. Natl. Acad. Sci. U. S. A. 96, 7077–7082
22. Aronica, S. M., and Katzenellenbogen, B. S. (1993) Mol. Endocrinol. 7, 743–752
23. M.C. Santiago, S., Patrone, C., Pollino, V., Vegeto, F., and Maggi, A. (1994) Mol. Endocrinol. 8, 910–918
24. Smith, C. L. (1998) Biol. Reprod. 58, 627–632
25. Bunone, G., Brand, P.-A., Miusiek, R. J., and Picard, D. (1996) EMBO J. 15, 2174–2183
26. Richards, R. G., Walker, M. P., Sebastian, J., and DiAugustine, R. P. (1998) J. Biol. Chem. 273, 11929–11932
27. Kleinman, D., Karas, M., Roberts, C. T., LeRoith, D., Philip, M., Segev, Y., Levy, J., and Sharoni, Y. (1995) Endocrinology 140, 2531–2537
28. Lee, A. V., Jackson, J. G., Gooch, J. L., Hilsenbeck, S. G., Coronado-Heinsohn, E., and Yee, D. (1999) Mol. Endocrinol. 13, 787–796
29. Sell, C., Rubini, M., Rubin, R., Liu, J.-P., Efstratiadis, A., and Baserga, R. (1993) Proc. Natl. Acad. Sci. U. S. A. 90, 11217–11221
30. Yaffe, D. (1968) Proc. Natl. Acad. Sci. U. S. A. 61, 1783–1788
31. Kahlert, S., Groh, C., Karas, R. H., Lobbert, K., Reyes, L., and Vetter, H. (1997) Biophys. Biochem. Res. Commun. 232, 373–378
32. Berthois, Y., Katzenellenbogen J., A., and Katzenellenbogen, B. S. (1986) Proc. Natl. Acad. Sci. U. S. A. 83, 2560–2564
33. Nuedling, S., Kahlert, S., Lobbert, K., Meyer, R., Vetter, H., and Groh, C. (1999) FEBS Lett. 454, 271–275
34. Green, S., and Chambon, P. (1987) Nature 325, 75–78
35. Tora, L., Mulllick, A., Metzger, D., Ponglikitmongkol, M., Park, I., and Chambon, P. (1989) EMBO J. 8, 1981–1986
36. Gotof, Y., Matsuda, T., Tanaka, K., Hattori, S., Iwamatsu, A., Ishikawa, M., Kosaka, H., and Nishida, E. (1994) Oncogene 9, 1891–1898
37. DeWet, J. R., Wood, K. V., DeLuca, M., Heinski, D. R., and Subramani, S. (1987) Mol. Cell. Biol. 7, 725–737
38. Pietrzkowski, Z., Wernicke, D., Parce, P., Jameson, B. A., and Baserga, R. (1992) Cancer Res. 52, 6447–6451
39. Wakeling, A. E., and Bowler, J. (1992) J. Steroid Biochem. Mol. Biol. 43, 173–177
40. Dudley, D. T., Pang, L., Decker, S. J., Bridges, A. J., and Saltiel, A. R. (1995) Proc. Natl. Acad. Sci. U. S. A. 92, 7686–7689
41. Beguinot, F., Kahn, C. R., Moses, A. C., and Smith, R. J. (1985) J. Biol. Chem. 260, 15892–15898
42. Grohé, C., Meyer, R., and Vetter, H. (1999) in Cardiovascular Specific Gene Expression (Doevendans, P., and Reneman, R., eds) pp. 227–235, Kluiver, Dordrecht, The Netherlands
43. Sahlin, L., and Eriksson, H. (1996) J. Steroid Biochem. Mol. Biol. 58, 359–365
44. Glass, C. G., Holloway, J. M., Devary, O. V., and Rosenfeld, M. G. (1988) Cell 54, 313–323
45. Caulin-Glaser, T., Garcia-Gardena, G., Sarrel, P., Sessa, W. C., and Bender, J. R. (1997) Circ. Res. 81, 8885–8928
46. Rubanyi, G. M., Freay, A. D., Kauser, K., Sukovich, D., Burton, G., Lubahn, D. B., Couse, J. F., Curtis, S. W., and Korach, K. S. (1997) J. Clin. Invest. 99, 2429–2437
47. Chen, Z., Yuhanna, I., Galcheva-Gargova, Z., Karas, R. H., Mendelsohn, M. E., and Shaui, P. (1999) J. Clin. Invest. 103, 491–496
48. Morley, P., Whitfield, J. F., Vanderhyden, B. C., Tsang, B. K., and Schwartz, J. L. (1992) Endocrinology 131, 1305–1312
49. Jiang, C., Poole-Wilson, P. A., Sarrel, P. M., Mochizuki, S., Collins, P., and MacLeod, K. T. (1992) Br. J. Pharmacol. 106, 739–745
50. Meyer, R., Linz, K. W., Surges, R., Meinardus, S., Vees, J., Hoffmann, A., Windholz, O., and Grohé, C. (1998) Exp. Physiol. 83, 305–321
51. Nakoha, A. M., Khan, M. S., Romas, N. P., and Rosner, W. (1994) Proc. Natl. Acad. Sci. U. S. A. 91, 5402–5405
52. Pappas, T. C., Gametchu, B., and Watson, C. S. (1995) FASEB J. 9, 404–410
53. Zheng, J., and Ramirez, V. D. (1997) J. Steroid Biochem. Mol. Biol. 62, 327–336
54. Stefano, G. B., Prevot, V., Beauvillain, J. C., Fimiani, C., Welters, I., Cadet, P., Breton, C., Pestel, J., Salzet, M., and Bilfinger, T. V. (1999) J. Immunol. 163, 3755–3763
55. Razandi, M., Pedram, A., Greene, G. L., Levin, E. R. (1999) Mol. Endocrinol. 13, 307–319
56. Migliaccio, A., Di Domenico, M., Green, S., DeFalco, A., Katjaniak, E. L., Blasi, F., Chambon, P., and Auricchio, F. (1989) Mol. Endocrinol. 3, 1061–1069
57. Migliaccio, A., DiDomenico, M., Castoria, G., DeFalco, A., Bontempo, P., Nola, E., and Auricchio, F. (1996) EMBO J. 15, 1292–1300
58. Improta-Brears, T., Whorton, A. R., Codazzi, F., York, J. D., Meyer, T., and McDonnell, D. P. (1999) Proc. Natl. Acad. Sci. U. S. A. 96, 4686–4691
59. Cowley, S. M., and Parker, M. G. (1999) J. Steroid Biochem. Mol. Biol. 69, 165–175
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