FEBS Letters 459 (1999) 272–276 FEBS 22697

Hormone-activated nuclear receptors inhibit the stimulation of the JNK and ERK signalling pathways in endothelial cells

María Victoria González[a], José Manuel González-Sancho[a], Carme Caelles[b], Alberto Munoz[a,*], Benilde Jiménez[a]

[a]*Instituto de Investigaciones Biomédicas 'Alberto Sols', Consejo Superior de Investigaciones Científicas, Universidad Autónoma de Madrid, Arturo Duperier 4, E-28029 Madrid, Spain*
[b]*Facultad de Farmacia, Universidad de Barcelona, E-08028 Barcelona, Spain*

Received 3 September 1999

Abstract Glucocorticoid hormones, retinoids, and vitamin D3 display anti-angiogenic activity in tumor-bearing animals. However, despite their in vivo effect on the tumor vasculature little is known about their mechanism of action. Here we show that the synthetic glucocorticoid dexamethasone (Dex) and retinoic acid (RA) inhibit the activation of c-Jun N-terminal kinase (JNK) and extracellular-regulated kinase (ERK) signalling pathways by the pro-angiogenic agents tumor necrosis factor and vascular endothelial growth factor in endothelial cells. In contrast, Dex and RA failed to inhibit the activation of the p38 mitogen-activated protein kinase cascade. As a number of pro-angiogenic factors activate AP-1 transcription factor via the JNK and ERK pathways, our results suggest that the antagonism with AP-1 may underlie at least partially the anti-angiogenic effect of glucocorticoids and retinoids.

Key words: Glucocorticoid; Retinoid; JNK signalling; ERK signalling; Angiogenesis; AP-1 antagonism

1. Introduction

Angiogenesis, the formation of new blood vessels from pre-existing ones, is a tightly regulated process whose contribution to the development of a number of pathologies has been extensively documented [1,2]. The angiogenic process involves several steps: degradation of the basal membrane, endothelial cell chemotaxis towards inducers of angiogenesis and endothelial cell proliferation [1]. This complex process is regulated by an array of pro-angiogenic factors that stimulate angiogenesis and of anti-angiogenic factors that halt angiogenesis [1]. Interest in both types of factors arises from their potential application as therapeutic agents for angiogenesis-dependent diseases. In particular, much attention has focused on anti-angiogenic factors as potential anti-tumor agents [3–5]. Both anti-angiogenic and anti-tumor effects have been described for hormones acting through nuclear receptors such as glucocorticoids [6–9], retinoic acid (RA) [10,11] and vitamin D3 (vitD3) [12,13]. These hormones exert their action through binding to receptors that are hormone-regulated transcription factors that may activate or repress gene expression [14]. A large number of agents relevant for the angiogenic process have been described to be regulated by nuclear hormones. Among them are potent inducers of angiogenesis like vascular endothelial growth factor (VEGF) [15,16] or moderate inducers like transforming growth factor-β [17,18] or prostaglandin E2 [19]. Enzymes with a regulatory role in angiogenesis such as cyclooxygenases [20,21] or the inducible nitric oxide synthase are regulated by glucocorticoids [22]. The tissue- and urokinase-type plasminogen activator proteases are regulated by RA [9,23–25]. Glucocorticoids, RA, and vitD3 also regulate the expression of several adhesion molecules that may contribute to the angiogenic process: intracellular adhesion molecule-1 [26], vascular cellular adhesion molecule-1 [27], E-selectin [28], L-selectin [29], tenascin [30], and E-cadherin [31]. In most cases expression of these molecules is repressed by hormone-bound nuclear receptors. Repression of gene transcription by nuclear hormone receptors is mainly conducted either by binding to negative elements in target genes or, more frequently, by interference with transcription factors such as AP-1, NF-κB, or others [32]. The precise mechanism of this antagonistic effect has not been elucidated yet. Protein-protein interactions or competition for co-activators such as the cyclic AMP response element binding protein (CREB) binding protein (CBP) have been proposed, though not convincingly demonstrated [32]. We and others have described that nuclear hormone receptor antagonism with AP-1 in epithelial cells and macrophages is a consequence, at least in part, of the inhibition of the c-Jun N-terminal kinase (JNK) pathway by nuclear hormone receptors [33–36]. As a number of pro-angiogenic factors act through activation of AP-1, we sought to determine whether the anti-angiogenic effect of glucocorticoids, RA, or vitD3 may be mediated by the inhibition of any of the signalling pathways leading to the activation of members of the mitogen-activated protein kinase (MAPK) family: JNK, extracellular-regulated kinase (ERK), and p38 mitogen-activated protein kinase (p38MAPK). We show here that glucocorticoids and RA inhibit JNK activation by tumor necrosis factor-α (TNFα) and also reduce ERK activation by TNFα or VEGF in several endothelial cell lines. In contrast, the activation of the p38MAPK cascade by different stimuli is not affected by these hormones.

2. Materials and methods

2.1. Materials

Dexamethasone (Dex), all-*trans* RA, phosphatase and protease in-

*Corresponding author. Fax: (34) (91) 5854587.
E-mail: amunoz@biomed.iib.uam.es

Abbreviations: CBP, cyclic AMP response element binding protein binding protein; DMEM, Dulbecco's modified Eagle's medium; ERK, extracellular-regulated kinase; FCS, fetal calf serum; GR, glucocorticoid receptor; JNK, c-Jun N-terminal kinase; RA, retinoic acid; RAR, retinoic acid receptor; TNF, tumor necrosis factor; TPA, 12-*O*-tetradecanoyl phorbol 13-acetate; VEGF, vascular endothelial growth factor; vitD3, vitamin D3; VDR, vitamin D receptor

PII: S0014-5793(99)01257-0

hibitors (sodium pyrophosphate, sodium fluoride (NaF), β-glycerophosphate, sodium orthovanadate, phenylmethylsulfonyl fluoride (PMSF), aprotinin, and leupeptin), myelin basic protein (MBP), protein A-Sepharose, and 12-*O*-tetradecanoyl phorbol 13-acetate (TPA) were from Sigma Chemical Co. (St. Louis, MO, USA). TNFα and VEGF were purchased from PeproTech Inc. (NJ, USA). VitD3 (1,25-dihydroxyvitamin D3) was a kind gift from Productos Roche (Madrid, Spain). Dulbecco's modified Eagle's medium (DMEM), fetal calf serum (FCS), glutamine and antibiotics (penicillin, streptomycin) were all from Life Technologies Ltd. (Paisley, UK). Autoradiography films and the chemiluminescence ECL detection system were from Amersham (London, UK).

2.2. Cell culture

The immortalized human microvascular endothelial cell line HMEC-1 [37] was provided by Dr. T. Lawley (National Center for Infectious Disease, Center for Disease Control, Atlanta, GA, USA), and the murine microvascular MS-1 [38] and hemangioma-derived EOMA [39] endothelial cell lines were provided by Dr. J. Folkman (Harvard Medical School, Boston, MA, USA). All three cell lines, as well as human cervical HeLa and mouse mammary epithelial EpH4 cells, were grown in DMEM supplemented with 10% FCS plus glutamine and antibiotics.

2.3. RNA preparation and Northern analysis

Purification of poly(A)$^+$ RNA, Northern blotting, and hybridization were performed as described [40]. Filters were washed twice for 30 min each in 1% SDS and 40 mM sodium phosphate, pH 7.2 at 65°C. Membranes were exposed to Hyperfilm MP films. Densitometric analysis was performed in a La Cie scanner connected to a Power Macintosh G3 computer using Adobe Photoshop 3.0 and NIH Image programs. Probes used were a 1264 bp 3′ fragment from the rat glucocorticoid receptor (GR) cDNA donated by Dr. D. Barettino (Instituto de Investigaciones Biomédicas, Valencia, Spain), the full-length human retinoic acid receptor (RAR) α cDNA donated by Dr. R.M. Evans (The Salk Institute, San Diego, CA, USA), and the full-length human cDNA vitamin D3 receptor (VDR) donated by Dr. M. Zenke (Max Delbrück Center, Berlin, Germany).

2.4. Protein kinase assays

For JNK and ERK assays subconfluent endothelial cells (one p60 per determination) were preincubated overnight in DMEM supplemented with 0.5% FCS. Hormone treatments were carried out for 45 min before stimulation with 10 ng/ml TNFα or VEGF. At indicated times after stimulation the cells were solubilized in NP40 lysis buffer (1% NP40, 150 mM NaCl, 20 mM Tris-HCl pH 7.5, 2 mM EDTA) supplemented with phosphatase inhibitors (10 mM sodium pyrophosphate, 50 mM NaF, 25 mM β-glycerophosphate, 1 mM sodium orthovanadate) and protease inhibitors (1 mM PMSF and 10 μg/ml each of aprotinin and leupeptin). Lysates were cleared of insoluble material by centrifugation and incubated for 2 h at 4°C in the presence of 0.4 μg/ml anti-ERK2 or anti-JNK1 antibodies (sc 154 and sc 474, Santa Cruz Biotechnology Inc.), followed by 1 h incubation at 4°C with protein A beads. Immunoprecipitates were washed four times with NP40 lysis buffer and once with kinase reaction buffer (50 mM HEPES pH 7.5, 10 mM $MgCl_2$, 12.5 mM β-glycerophosphate, 0.1 mM sodium orthovanadate). Samples were resuspended in 40 μl of kinase buffer containing 20 μM cold ATP and 1 μCi γ-[^{32}P]ATP. For ERK or JNK assays we used as substrates 10 μg MBP or 1 μg of GST-c-Jun (1–79) protein, respectively. The reactions were incubated at 30°C for 30 min and terminated by addition of 5×electrophoresis sample buffer. Total amounts of JNK and ERK were analyzed by Western blotting using the previously mentioned anti-ERK2 or anti-JNK1 antibodies. Membranes were exposed to Hyperfilm MP films. Quantitation was performed as for Northern blots.

For p38MAPK assays, cells were lysed in Triton buffer (1% Triton X-100, 150 mM NaCl, 20 mM Tris-HCl pH 7.5, 2 mM EDTA) supplemented with protease and phosphatase inhibitors as above. Kinase activation was assessed by Western blot using an anti-phospho-specific p38 antibody (9210, New England Biolabs). Membranes were stripped and reprobed with an anti-p38MAPK antibody (sc 535, Santa Cruz Biotechnology Inc.) for loading control. Western blots were developed using the ECL detection system and horseradish peroxidase-conjugated anti-rabbit antibodies (55689, ICN).

3. Results

3.1. Expression of nuclear hormone receptors in endothelial cell lines

We studied the expression of hormone receptors in human HMEC-1, and murine EOMA and MS-1 endothelial cell lines, to characterize their hormone responsiveness. The levels of RNA expression of GR, RAR-α, and VDR were assessed by Northern blotting. All three endothelial cell lines expressed substantial levels of GR and RAR-α RNA, comparable to those found in HeLa or EpH4 cells (Fig. 1). These two cell types were chosen as controls in view of the previously described hormone interference with AP-1 activation [31]. In contrast, VDR RNA expression was only relevant in HMEC-1 cells while it was undetectable in EOMA and MS-1 lines. Consequently, we studied the effects of Dex and RA on the three MAPK signalling pathways: JNK, ERK, and p38MAPK in all three endothelial cell lines, but that of vitD3 exclusively in HMEC-1 cells.

3.2. Activation of the JNK pathway by TNFα in endothelial cell lines is inhibited by glucocorticoids and retinoic acid

We first investigated the effect of the synthetic glucocorticoid Dex and RA on the activation of JNK by TNFα. A short (45 min) pretreatment with Dex led to an efficient inhibition (3-fold) of JNK activation induced by TNFα in human HMEC-1 cells (Fig. 2A). In this same cell line RA also had a less pronounced inhibitory effect (Fig. 2B). Both hormones, Dex and RA, similarly reduced JNK activation by other stimuli such as ultraviolet radiation (data not shown). The effect of vitD3 was analogous to that of RA, leading to a slight overall inhibition of JNK activation by TNFα in HMEC-1 cells (Fig. 2B).

The inhibitory action of Dex on JNK activation by TNFα was also found in EOMA and MS-1 endothelial cell lines (2–3-fold) (Fig. 2C,D). In contrast, RA was less effective in EOMA and MS-1 cells as compared to human HMEC-1 cells causing only a minimal inhibition of JNK activation (not shown). This result correlated with the lower expression or RARα RNA found in these rodent cell lines (Fig. 1).

As described previously in HeLa cells [33], the same inhibitory effects were found by preincubation of HMEC-1 cells with Dex or RA for longer periods of up to 18 h indicating

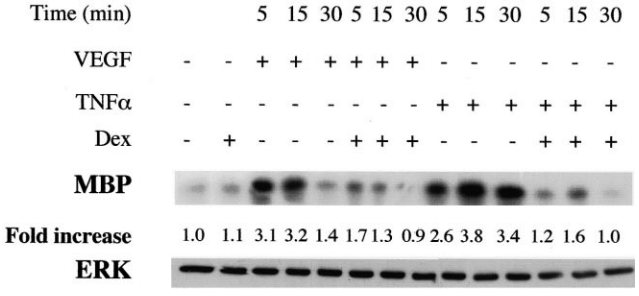

Fig. 1. Expression of GR, RARα, and VDR mRNA in HMEC-1, EOMA, and MS-1 endothelial cell lines. Poly(A)$^+$ RNA (10 μg/lane) was analyzed by Northern blot using specific probes as described in Section 2. RNA samples from human HeLa and mouse EpH4 cells were included as controls. Filters were stripped and rehybridized with a cDNA probe of the 18S ribosomal RNA for loading control. Sizes of corresponding bands are indicated.

that a short incubation is sufficient for their maximal action (not shown).

3.3. ERK activation by TNFα and VEGF is inhibited by glucocorticoids in human endothelial cells

A number of pro-angiogenic factors like basic fibroblast growth factor, platelet-derived growth factor, TNFα, and VEGF activate the ERK isoforms [41–43]. Moreover, induction of endothelial cell proliferation by VEGF requires ERK activation [43], suggesting a relevant role of ERK signalling cascade on angiogenesis. Therefore, we next investigated the possibility of an antagonistic action of glucocorticoids on the activation of ERK signalling pathways.

Dex inhibited (2–3-fold) ERK activation by TNFα or VEGF in HMEC-1 cells (Fig. 3). Furthermore, ERK activation by serum and the phorbol ester TPA was also inhibited by both Dex and, albeit to a lesser extent, RA (data not shown).

3.4. Dexamethasone did not affect p38MAPK activation induced by TNAα

To complete the analysis of hormone effects on MAPK signalling pathways, we also examined the putative regulation of p38MAPK activity. However, we found that Dex did not inhibit p38MAPK activation induced by TNFα in HMEC-1 cells (Fig. 4). Likewise, Dex did not interfere with the activation of p38MAPK by other stress stimuli such as ultraviolet radiation or osmotic shock caused by sorbitol or sodium chloride in either HMEC-1 or HeLa cells (not shown). In line with these results, RA and vitD3 also failed to inhibit p38MAPK activation in HMEC-1 or HeLa cells (not shown).

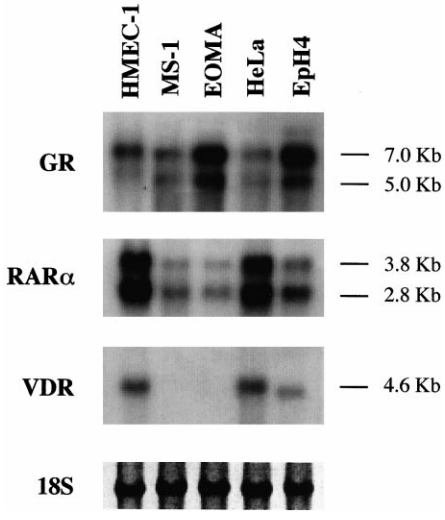

Fig. 2. Activation of the JNK pathway by TNFα is inhibited by Dex and RA. Cells were incubated in serum-free medium for 16 h before addition of vehicle (−) or 1 μM Dex or RA as indicated. After 45 min cells were stimulated with 10 ng/ml TNFα. JNK activity was measured in cell extracts prepared at indicated times after TNFα treatment as described in Section 2. A: HMEC-1 cells, Dex treatment. B: HMEC-1 cells, RA and vitD3 treatments. C: EOMA cells, Dex treatment. D: MS-1 cells, Dex treatment. Quantitation of the total amount of JNK protein present in each cell extract as estimated by Western blotting is shown at the bottom of each panel. Representative results corresponding to one out of three independent experiments are shown in each panel.

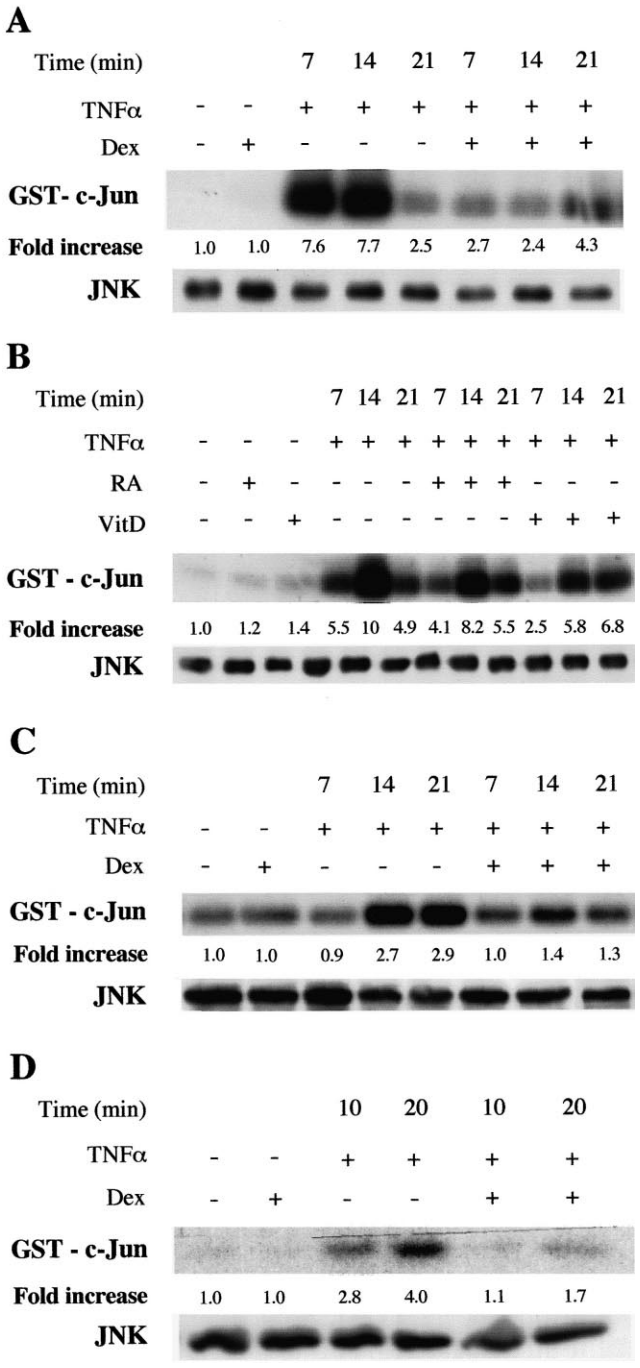

Fig. 3. ERK activation by TNFα or VEGF is inhibited by Dex in HMEC-1 cells. Cells were incubated in serum-free medium for 16 h before addition of vehicle (−) or 1 μM Dex as indicated. After 45 min cells were stimulated with 10 ng/ml TNFα or VEGF. ERK activity was measured in cell extracts prepared at indicated times after TNFα of VEGF treatment as described in Section 2. Bottom: Quantitation of the total amount of ERK protein present in each cell extract as estimated by Western blotting. Three independent experiments gave similar results.

4. Discussion

We present evidence that glucocorticoids and retinoids inhibit the activation of members of the MAPK signalling modules in endothelial cells. Inhibitory effects of these hormones on JNK activation by stress stimuli have been recently de-

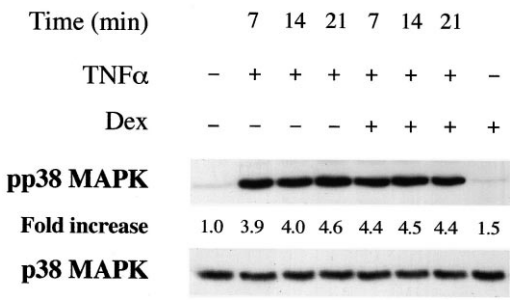

Fig. 4. Dex does not affect p38MAPK activation induced by TNFα. HMEC-1 cells were incubated in serum-free medium for 16 h before addition of vehicle (−) or 1 μM Dex as indicated. After 45 min cells were stimulated with 10 ng/ml TNFα. p38MAPK activation was estimated in cell extracts prepared at indicated times after TNFα treatment by immunoblotting using an anti-phospho-specific p38MAPK antibody as described in Section 2. Bottom: Quantitation of the total amount of p38MAPK protein present in each cell extract by immunoblotting using an anti-total p38 antibody. The same result was found in three independent experiments.

scribed in epithelial (HeLa, EpH4, hepatocytes) and hematopoietic (macrophages) cells, suggesting that it is a wide mechanism of action for hormones acting through nuclear receptors [33–36]. However, this is the first demonstration that glucocorticoids and retinoids can inhibit JNK and ERK activation in endothelial cells by pro-angiogenic agents.

The precise mechanism by which hormone-activated nuclear receptors inhibit JNK or ERK activation is presently unknown. Although a direct interaction of hormone receptors with signalling elements in the JNK cascade (in the case of GR) or with the kinases themselves cannot be ruled out, this possibility has not been proved yet [33–36]. Alternatively, uncharacterized regulatory factor(s) could mediate the interference with the JNK/ERK signalling modules upon hormone binding to their receptors. Other possible mechanisms include the activation of one or more protein phosphatases or the blockade of the stimulus-induced nuclear translocation of JNK/ERK.

While VEGF is considered to be a major pro-angiogenic agent [1], TNFα seems to have a dual role in angiogenesis, as a number of studies have proposed its role as a pro-angiogenic factor [44,45], while others suggest an anti-angiogenic role for this molecule [46,47]. Among other effects, TNFα induces the activation of AP-1 transcription factor through the activation of JNK [48,49]. In contrast, VEGF preferentially activates ERK and so, supposedly these two factors use distinct signalling pathways to increase AP-1 activity. As in other cell systems, the inhibitory effect of Dex and RA on JNK/ERK may at least in part underlie the antagonistic effects of these hormones on AP-1 activity. Given the roles of VEGF and TNFα in the angiogenic process, our data suggest that this antagonistic effect can be part of the mechanism by which several hormones with nuclear receptors behave as anti-angiogenic agents in vivo.

Our results suggest that the inhibition of MAPK signalling pathways is a general mechanism of hormone action which shows a partial specificity, there being a preference for the inhibition of certain signalling modules most probably depending on the stimulus and cell type, amount of receptors expressed, and perhaps interaction with other effectors. Thus, it has been reported that Dex does not block ERK activation by LPS in macrophages [34], whereas RA inhibits growth factor activation of ERK in normal human bronchial epithelial cells [34]. Our data indicate that endothelial cells are sensitive to Dex and RA inhibition of both JNK and ERK. In contrast, p38MAPK activation by diverse stimuli appears to be insensitive to these hormones in endothelial cells as well as in other cell types.

Hormones with nuclear receptors such as glucocorticoids, retinoids, and vitamin D3 are potent therapeutic agents and have even been considered in some cases to be putative chemopreventive agents [50]. In the context of tumor angiogenesis the inhibition of MAPK signalling pathways is a potential mechanism that would explain their anti-angiogenic effect, for instance by inhibiting the overexpression of genes encoding proteases which become induced by pro-angiogenic factors through AP-1-responsive sites in their promoter regions or by modulating the expression of molecules regulating cell adhesion and migration.

Acknowledgements: We acknowledge Margarita González and Teresa Martínez for their technical assistance. We also thank those who appear in Section 2 for providing us with cells or plasmids, and Productos Roche (Madrid) for the gift of 1,25-dihydroxyvitamin D3. This research was supported by Grant SAF98-0060 from the Plan Nacional de Investigación y Desarrollo, Comisión Interministerial de Ciencia y Tecnología, and the Comunidad Autónoma de Madrid, Spain. M.V.G. and J.M.G-S. were supported by post-doctoral contracts from the Comunidad Autónoma de Madrid.

References

[1] Bouck, N., Stellmach, V. and Hsu, S. (1996) Adv. Cancer Res. 69, 135.
[2] Folkman, J. (1995) Nature Med. 1, 27–30.
[3] Hanahan, D. and Folkman, J. (1996) Cell 86, 353–364.
[4] Boehm, T., Folkman, J., Browder, T. and O'Reilly, M.S. (1997) Nature 390, 404–407.
[5] Bergers, G., Javaherian, K., Lo, K.M., Folkman, J. and Hanahan, D. (1999) Science 284, 808–812.
[6] Wolf, J.E., Guerin, C., Laterra, J., Bressler, J., Indurti, R.R. and Goldstein, G.W. (1993) Brain Res. 604, 79–85.
[7] Folkman, J., Langer, R., Linhardt, R.J., Haudenschild, C. and Taylor, S. (1983) Science 221, 719–725.
[8] Kaye, A. and Laws, E. (1995) Brain Tumours: An Encyclopedic Approach, Churchill Livingstone, New York.
[9] Pepper, M.S., Vassalli, J.D., Wilks, J.W., Schweigerer, L., Orci, L. and Montesano, R. (1994) J. Cell Biochem. 55, 419–434.
[10] Lingen, M.W., Polverini, P.J. and Bouck, N.P. (1996) Lab. Invest. 74, 476–483.
[11] Lingen, M.W., Polverini, P.J. and Bouck, N.P. (1996) Cancer Res. 58, 5551–5558.
[12] Majewski, S., Marczak, M., Szmurlo, A., Jablonska, S. and Bollag, W. (1995) Cancer Lett. 89, 17–24.
[13] Fujioka, T., Hasegawa, M., Ishikura, K., Matsushita, Y., Sato, M. and Tanji, S. (1998) J. Urol. 160, 247–251.
[14] Mangelsdorf, D.J., Thummel, C., Beato, M., Herrlich, P., Schütz, G., Umensono, K., Blumberg, G., Kastner, P., Mark, M., Chambon, P. and Evans, R.M. (1995) Cell 83, 835–839.
[15] Gloddek, J., Pagotto, U., Paez Pereda, M., Artz, E., Stalla, G.K. and Renner, U. (1999) J. Endocrinol. 160, 483–490.
[16] Weninger, W., Rendl, M., Mildner, M. and Tschachler, E. (1998) J. Invest. Dermatol. 111, 907–911.
[17] Cai, J., Zheng, T., Lotz, M., Zhang, Y., Masood, R. and Gill, P. (1997) Blood 89, 1491–1500.
[18] Yoshizawa, M., Miyazaki, H. and Kojima, S. (1998) J. Cell Physiol. 176, 565–573.
[19] García-Cabanes, C., Palmero, M., Bellot, J.L. and Orts, A. (1999) Ophthalmic Res. 31, 42–46.
[20] Jun, S.S., Chen, Z., Pace, M.C. and Shaul, P.W. (1999) Circ. Res. 84, 193–200.

[21] Inoue, H., Umesono, K., Nishimori, T., Hirata, Y. and Tanabe, T. (1999) Biochem. Biophys. Res. Commun. 254, 292–298.
[22] Frank, S., Madlener, M., Pfeilschifter, J. and Werner, S. (1998) J. Invest. Dermatol. 111, 1058–1064.
[23] Lansink, M. and Kooistra, T. (1996) Blood 88, 531–541.
[24] Kooistra, T., Lansing, M., Arts, J., Sitter, T. and Toet, K. (1995) Eur. J. Biochem. 232, 425–432.
[25] Bulens, F., Ibañez-Tallon, I., Van Acker, P., De Vriese, A., Nelles, L., Belayew, A. and Collen, D. (1995) J. Biol. Chem. 270, 7167–7175.
[26] Chadwick, C.C., Shaw, L.J. and Winneker, R.C. (1998) Exp. Cell Res. 239, 423–429.
[27] Gille, J., Paxton, L.L., Lawley, T.J., Caughman, S.W. and Swerlick, R.A. (1997) J. Clin. Invest. 99, 492–500.
[28] Ray, K.P., Farrow, S., Daly, M., Talabot, F. and Searle, N. (1997) Biochem. J. 328, 707–715.
[29] Filep, J.G., Delalandre, A., Payette, Y. and Foldes-Filep, E. (1997) Circulation 96, 295–301.
[30] González-Sancho, J.M., Alvarez-Dolado, M. and Muñoz, A. (1998) FEBS Lett. 426, 225–228.
[31] Ryuto, M., Jimi, S., Ono, M., Naito, S., Nakayama, Y., Yamada, Y., Komiyama, S. and Kuwano, M. (1997) Jpn. J. Cancer Res. 88, 982–991.
[32] Göttlicher, M., Heck, S. and Herrlich, P. (1998) J. Mol. Med. 76, 480–489.
[33] Caelles, C., González-Sancho, J.M. and Muñoz, A. (1997) Genes Dev. 11, 3351–3364.
[34] Swantek, J.L., Cobb, M.H. and Geppert, T.D. (1997) Mol. Cell. Biol. 17, 6274–6282.
[35] Lee, H.Y., Sueoka, N., Hong, W.K., Mangelsdorf, D.J., Claret, F.X. and Kurie, J.M. (1999) Mol. Cell. Biol. 19, 1973–1980.
[36] Ventura, J.J., Roncero, C., Fabregat, I. and Benito, M. (1999) Hepatology 29, 849–857.
[37] Ades, E.W., Candal, F.J., Swelick, R.A., George, V.G., Summers, S., Bosse, D.C. and Lawley, T.J. (1992) J. Invest. Dermatol. 99, 683–690.
[38] Arbiser, J.L., Moses, M.A., Fernández, C.A., Ghiso, N., Cao, Y., Klauber, N., Frank, D., Brownlee, M., Flynn, E., Parangi, S., Byers, H.R. and Folkman, J. (1997) Proc. Natl. Acad. Sci. USA 94, 861–866.
[39] Obeso, J., Weber, J. and Auerbach, R. (1990) Lab. Invest. 63, 259–269.
[40] López-Barahona, M., Fialka, I., González-Sancho, J.M., Asunción, M., González, M., Iglesias, T., Bernal, J., Beug, H. and Muñoz, A. (1995) EMBO J. 14, 1145–1155.
[41] D'Angelo, G., Struman, Y., Martial, W. and Weiner, R.I. (1995) Proc. Natl. Acad. Sci. USA 92, 6374–6378.
[42] Modur, V., Zimmerman, G.A., Precott, J.M. and McIntyre, T.M. (1996) J. Biol. Chem. 271, 13094–13102.
[43] Pedram, A., Razandi, M. and Levin, E.R. (1998) J. Biol. Chem. 273, 26722–26728.
[44] Pandey, A., Shao, H., Marks, R.M., Polverini, P.J. and Dixit, V.M. (1995) Science 268, 567–569.
[45] Montrucchio, G., Lupia, E., Battaglia, E., Passerini, G., Bussolino, F., Emanuelli, G. and Camussi, G. (1994) J. Exp. Med. 180, 337–382.
[46] Feleszko, W., Balkowiec, E.Z., Sieberth, E., Marfczak, M., Dabrowska, A., Giermasz, A., Czajka, A. and Jakobisiak, M. (1999) Int. J. Cancer 81, 560–567.
[47] Ruegg, C., Yilmaz, A., Bieler, G., Bamat, J., Chaubert, P. and Lejeune, F.J. (1998) Nature Med. 4, 408–414.
[48] Westwick, J.K., Weitzel, C., Minden, A., Karin, M. and Brenner, D.A. (1994) J. Biol. Chem. 269, 26396–26401.
[49] Sluss, H.K., Barrett, T., Dérijard, B. and Davis, R. (1994) Mol. Cell. Biol. 14, 8376–8384.
[50] Bollag, W. (1994) J. Cell Biochem. 56, 427–435.