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Control of cell proliferation via transduction of sPLA$_2$-I activity and possible PPAR activation at the nuclear level

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Abstract Pancreatic phospholipase A$_2$ (PLA$_2$-I) stimulates U$_{III}$ cells proliferation, a rat uterine cell line, after binding to membrane receptors, internalization and translocation. Here, we demonstrate that during these steps of internalization, PLA$_2$-I retains its hydrolytic activity and thus could exert its proliferative effect via nuclear phospholipids hydrolysis. Since fatty acids and eicosanoids released by such activity are known to be ligands of PPAR, we study the expression of these nuclear receptors and demonstrate that, in the experimental conditions where PLA$_2$-I stimulates U$_{III}$ cells proliferation, PLA$_2$-I also regulates PPAR expression indicating a possible mechanism of its proliferative effect.

Key words: Phospholipase A$_2$; Proliferation; Stromal cell; Nuclear activity; Rat uterus; Signal transduction

1. Introduction

Phospholipases A$_2$ (PLA$_2$) are implicated in a great diversity of cell functions and particularly they play a crucial role in signal transduction [1]. These lipolytic enzymes (EC 3.1.1.4) of which different forms have been described in various tissues, hydrolyze the sn-2 acyl ester bond in glycerophospholipids. They are traditionally classified according to their primary structure and their sensitivity towards intracellular concentrations of calcium [2]. The calcium-dependent enzymes have been subdivided into two main groups. The secretory forms (sPLA$_2$) are low molecular mass (13–18 kDa), extracellular secreted enzymes acting at millimolar concentrations of calcium, including pancreatic and *Naja* venom PLA$_2$ (type I), *Crotalus* venom and inflammatory PLA$_2$ (type II), bee venom PLA$_2$ (type III), and the PLA$_2$ recently identified in the heart and the lung (type V) [3]. On the other hand, intracellular cytosolic PLA$_2$ (cPLA$_2$) constitutes the high molecular mass (85 kDa) type IV group of molecules sensitive to micromolar concentrations of calcium [4]. The calcium-independent PLA$_2$s (iPLA$_2$) with molecular mass varying in the range of 29–120 kDa have recently been described in a variety of tissues [5]. In almost every cell studied, multiple PLA$_2$s exist but their relative contribution to the cell function is not yet understood.

The pancreatic type PLA$_2$-I, which has long been thought to act only as a digestive enzyme, has been shown to stimulate cell proliferation via a specific membrane receptor [6]. Cloning of PLA$_2$ receptors from several species has revealed a structural organization of the protein which is highly similar to that of mannose receptors [7]. It has been proposed that the physiological role of this PLA$_2$ receptor is to internalize and deliver PLA$_2$-I to specific intracellular compartments where the enzyme can exert its activity [8].

We have recently demonstrated that nanomolar concentrations of pancreatic PLA$_2$ stimulate the proliferation of U$_{III}$ cells, a stromal cell line (U$_{III}$) derived from normal rat uterus [9,10]. Analysis of cellular uptake of exogenous PLA$_2$-I by U$_{III}$ cells in culture revealed the presence of membrane receptors for PLA$_2$-I, which were responsible for internalization of the ligand [11]. The number of PLA$_2$ receptors is closely associated with the proliferative state of U$_{III}$ cells [10]. Moreover, subsequent studies showed that the internalized enzyme migrates to the nucleus, suggesting that the proliferative effect of pancreatic PLA$_2$ in U$_{III}$ cells is mediated by a direct action of the enzyme at the nuclear level [12]. To investigate whether PLA$_2$-I has retained its hydrolytic activity during the steps of internalization and nuclear migration, we studied PLA$_2$ activity in purified nuclear preparations and we demonstrated that, after translocation into the nucleus, the PLA$_2$-I was still able to hydrolyze phospholipids. The hydrolytic activity of PLA$_2$-I could lead to the release of fatty acids and production of eicosanoids at the nuclear level. Since these products have been shown to stimulate peroxisome proliferator-activated receptors (PPARs) [13] and in order to get further information on the mechanism of action of the enzyme at the nuclear level, we also studied the PPAR expression in U$_{III}$ cells. Our results indicate that the proliferative effect of PLA$_2$-I may be mediated by differential regulation of PPAR-α and -γ expression.

2. Materials and methods

2.1. Cell culture

For stock culture, rat uterine stromal cells (U$_{III}$ cells) were grown in Falcon plastic flasks (75 cm^2) in a 95% air–5% CO$_2$ humidified atmosphere at 37°C. The medium was M199 supplemented with 10% fetal calf serum, 2 mM L-glutamine, 100 U/ml penicillin and 100 μg/ml streptomycin. Medium was changed every 48 h. Confluent cells were subcultured by incubation with 0.25% trypsin, centrifuged and seeded

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Abbreviations: PLA$_2$, phospholipase A$_2$; PPAR, peroxisome proliferator-activated receptor

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at 1:2 ratio. Cell viability, determined by the trypan blue exclusion method, was consistently greater than 95%.

2.2. Isolation of nuclei

Procedures of cell homogenization using ionic salt solutions were avoided since they often induce artefactual transfer of molecules from the nuclear compartment to the cytoplasm. Nuclei were prepared according to the method of Nicotera and al. [14] with some modifications. U_{III} cells from subconfluent stock cultures were trypsinized and centrifuged at $800\times g$ for 5 min. The pellet was rinsed twice with phosphate-buffered saline and resuspended into three volumes of TKM solution (50 mM Tris–HCl, pH 7.5, 25 mM KCl, 5 mM $MgCl_2$, 2 μg/ml leupeptin and pepstatin with 0.1% Triton X-100) supplemented with 0.25 M sucrose, briefly sonicated using a microprobe and centrifuged again at $700\times g$ for 10 min at 4°C. The resulting pellet was resuspended into two volumes of the above TKM–0.25 M sucrose solution, then one volume of sample was gently mixed with two volumes of TKM supplemented with 2.3 M sucrose. TKM–2.3 M sucrose (one volume) was placed into centrifuge tubes (ultraclear no. 344057, Beckman) and two volumes of experimental sample were layered on the top. The tube was centrifuged at $37\,000\times g$ for 45 min at 4°C. The supernatant was discarded and the nuclei pellet was resuspended in TKM solution and pelleted at $1000\times g$ for 5 min at 4°C. The final pellet was resuspended into 50 mM Tris–HCl, pH 7.5 and analyzed. DNA content of the sample was determined on an aliquot by a fluorometric procedure as described previously [15]. The purity of the nuclear preparations was analyzed by measuring 5′-nucleotidase and glucose 6-phosphatase activities. In all experiments, these enzymatic activities in nuclear fractions were less than 2% of that observed in the cellular homogenate indicating the almost complete absence of contamination by plasma membrane and by microsomes. The yield of extractions, determined by measuring DNA amount in nuclear and in cell homogenates, was $15.3\pm1.4\%$ for 10 independent extractions (mean ± S.E.M.). Some experiments were done to increase this yield, but this was detrimental for the purity of nuclear preparation.

2.3. PLA_2 activity measurement

Secreted PLA_2 activity in the nuclear preparations was determined by using a fluorometric method derived from the technique of Radvanyi and al. [16]. For PLA_2 activity measurement, 100 μl of 2 mM PG substrate (1-hexadecanoyl-2-(10-pyrenedecanoyl)-sn-glycero-3-phosphoglycerol, ammonium, Interchim, Montluçon, France) stored at −80°C in toluene-isopropanol (50/50 v/v) was evaporated under nitrogen and dissolved in 1 ml ethanol. 100 μl of this solution was mixed with 10 ml of 50 mM Tris–HCl buffer, 100 mM NaCl, 1 mM EGTA, pH 7.5, vortexed for 2 min and maintained at room temperature.

Incubation medium was prepared in a fluorometric cuve by adding successively 1940 μl of the PG substrate (2 μM final concentration) and 20 μl of fatty acid free bovine serum albumin (BSA) solution (0.1% final concentration). 10–50 μl aliquots of nuclei kept at 0°C were added and equilibrated at room temperature for 1 min. The reaction started by adding 20 μl of 1 M $CaCl_2$ and fluorescence was measured continuously with a spectrofluorometer Jobin Yvon JY3D. Secreted PLA_2 activity was estimated by measuring the slope of the curve and expressed as nmol of substrate hydrolyzed/min/mg DNA. Effect of antibodies against PLA_2 on the nuclear PLA_2 activity was measured after preincubation for 12 h at 4°C with a polyclonal antibody produced in our laboratory [17] and purified on a DEA chromatography column [18]. These antibodies are specific for PLA_2-I and inhibit the binding of the enzyme to its receptor [17].

2.4. Fluorescence microscopy

For immunofluorescence studies, cells were seeded (5×10^4 cells per well) and cultured in 4-well plastic culture dishes as previously described [12]. Briefly, staining was performed by incubating cells overnight at 4°C with polyclonal antibodies against the whole PPARs [20], PPAR-α and PPAR-γ_2 (a subtype of PPAR-γ differing by add of 30 amino acids in N-terminal domain to the PPAR-γ_1) [19] (dilution 1/20). The staining was followed by four washes with HBSS–1% BSA. The cells were then exposed for 30 min at 4°C to the secondary fluorescent TRITC-conjugated antibody in HBSS–1% BSA (dilution 1/20) and washed four times in the same solution without the antibody. The cell preparations were analyzed using a fluorescence microscope (Leitz Laborlux).

2.5. Statistical analysis

Data are expressed as the mean ± S.E.M. Statistical significance ($\alpha = 0.05$) was tested using Mann–Whitney or Kruskal–Wallis nonparametric rank tests [21].

3. Results and discussion

U_{III} cells express specific membrane receptors for PLA_2-I which undergo cycles of binding, intracellular transfer and release of the enzyme [11]. The internalized enzyme then migrates to the nucleus [12]. The number of receptors and thus the capacity of the cells to internalize PLA_2-I decrease when cells progress from a non-confluent proliferating state to a confluent contact inhibited monolayer [10]. Consequently, the intracellular concentration of PLA_2-I is significantly reduced, about 3-fold, in confluent cells. This reduction affects almost exclusively the nuclear content of the enzyme which is much more concentrated in the nuclear fraction of non-confluent cells [12]. To investigate whether the PLA_2-I located in the nuclear compartment still expresses its hydrolytic activity, confluent and non-confluent cells were incubated for 48 h with or without 30 nM porcine pancreatic PLA_2. At the end of incubation, cells were washed several times and nuclei were prepared. Secreted PLA_2 activity was measured in the different nuclear preparations. In the absence of calcium, no detectable PLA_2 activity was observed in the nuclear samples analyzed. In the presence of calcium, a significant enzyme activity was measured in all samples and the results are summarized in Fig. 1. Enzyme activity was greater (3.1-fold) in nuclei from non-confluent cells (NC−) compared to nuclei from confluent cells (C−). Moreover, when non-confluent cells were incubated with 30 nM porcine pancreatic PLA_2-I for 48 h, nuclear enzyme activity was increased by more than 5-fold (NC+ versus NC−). When confluent cells were preincubated with exogenous PLA_2-I, nuclear enzyme activity was also increased

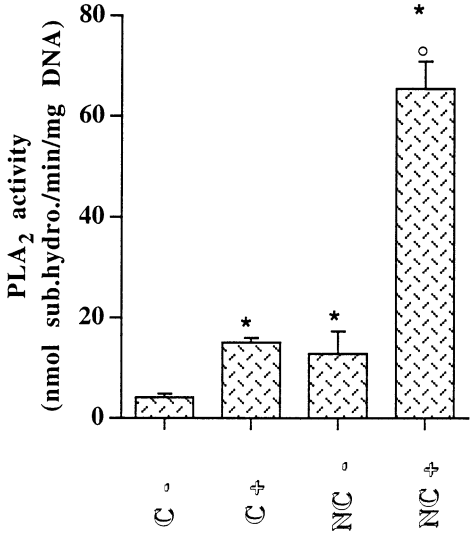

Fig. 1. PLA_2 activity in nuclear preparations from confluent and non-confluent cells. Confluent cells (C) or non-confluent cells (NC) were incubated for 48 h without (−) or with 30 nM of PLA_2-I (+). The PLA_2 activities, expressed as nmol of hydrolyzed substrate per minute and per mg of DNA, are means ± S.E.M. of six and 18 independent measures for confluent and non-confluent cells, respectively. *Significantly different from control C−, $P<0.05$. °Significantly different from control NC−, $P<0.05$.

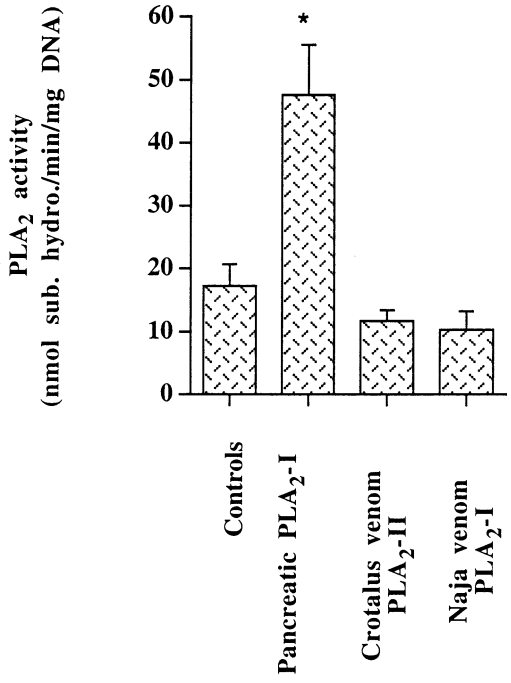

Fig. 2. Effect of various exogenous secreted PLA_2s on PLA_2 activity of nuclear preparations. Non-confluent cells were incubated during 48 h without (controls) or with 30 nM of pancreatic PLA_2-I, *Crotalus* PLA_2-II or *Naja* PLA_2-I. The PLA_2 activities, expressed as nmol of hydrolyzed substrate per minute and per mg of DNA, are means ± S.E.M. of four independent measures. *Significantly different of controls, $P < 0.05$.

but less than in non-confluent cells (about 3-fold). When non-confluent cells were incubated for 48 h with 30 nM *Naja naja mocambique* venom PLA_2 (type I PLA_2) or *Crotalus atrox* venom PLA_2 (type II PLA_2), two secreted PLA_2s showing a much lower affinity for U_{III} cell PLA_2 binding sites than the pancreatic enzyme [11], no increase in nuclear enzyme activity was observed (Fig. 2).

Taken together, these results strongly suggest that PLA_2-I retains its hydrolytic activity during the steps of binding, internalization and nuclear migration. In rat mesangial cells, PLA_2-I was shown to stimulate prostaglandin biosynthesis by induction of PLA_2-II expression via a specific binding site [22]. PLA_2-I was also shown to release arachidonic acid from NIH 3T3 cells via a receptor-mediated mechanism [23]. The authors suggested that PLA_2-I may induce the expression of a Ca^{2+}-independent PLA_2 that in turn mediates arachidonic acid release. In order to be sure that the increase in nuclear enzyme activity, observed after incubation of cells with pancreatic PLA_2, resulted from the accumulation of the exogenous enzyme in an active form in the nuclear compartment, the non-confluent cells, preincubated with 30 nM pancreatic PLA_2, were incubated with increasing amounts of anti-PLA_2-I antibodies before measurement of enzyme activity. Results (Fig. 3) show a dose-dependent decrease of enzyme activity while non-immune immunoglobulins were without effect, demonstrating the presence of active PLA_2-I in U_{III} cells nuclei and that the increasing enzyme activity was not the result of the expression of another PLA_2. Moreover the hydrolytic activity of nuclei isolated from control non-confluent cells was completely abolished by the incubation with the anti-PLA_2-I antibodies. This result suggests that the PLA_2-I is the only secreted PLA_2 present and/or active in the nuclear compartment. As PLA_2-II has already been detected in U_{III} cells [12], this means that it is either absent or inactive in the nucleus.

The presence of lipids inside the nucleus that could be potential substrates for PLA_2 was reported long ago [24,25] but has not received much attention. Initially considered as structural elements [26] these nuclear phospholipids may also be involved in the control of genomic activities as suggested by their higher concentration in active chromatin [27]. Cell cycle-dependent changes in synthesis rates of the chromatin-associated pools of phospholipids have been reported [28] and changes in fatty acid composition of nuclear phospholipids have also been described during liver regeneration [29]. This suggests a direct involvement of nuclear matrix lipids in cell proliferation. On the other hand, fatty acids are now considered as intracellular second messengers which can be involved in the regulation of cell growth by a direct genomic action [30]. An arachidonic acid response element has recently been identified [31]. Numerous data have also shown that fatty acids are able to directly interact with nuclear receptors and regulate transcription, sharing true properties of hormones [32]. In particular, long chain fatty acids and eicosanoids have been described as ligands for nuclear PPARs [13]. PPARs are members of the well-known steroid receptor super family, three subtypes have been identified and cloned: PPAR-α, -β and -γ (the latter exists as two isoforms, γ_1 and γ_2) and a well documented literature has recently been published about their tissue distribution and functions [32,33].

Taking into account all these data, a working hypothesis for the mechanism of action of PLA_2-I in U_{III} cells could be that the enzyme hydrolyzes nuclear phospholipids leading to the generation of specific ligands for PPAR and resulting in

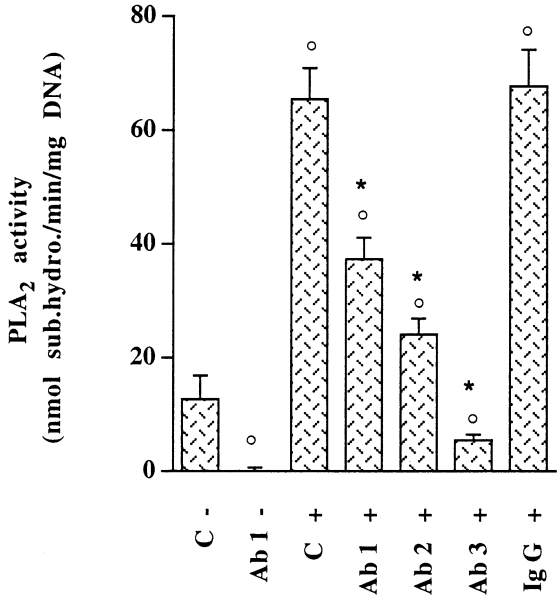

Fig. 3. Inhibition of nuclear PLA_2 activity by antibodies against PLA_2-I. Nuclear preparations, obtained from cells preincubated during 48 h without (−) or with 30 nM PLA_2-I (+), were incubated overnight without (C) or with 45 nM (Ab 1), 67 nM (Ab 2), 90 nM (Ab 3) of anti-PLA_2-I antibodies or with 90 nM of rabbit IgG (IgG). The PLA_2 activities, expressed as nmol of hydrolyzed substrate per minute and per mg of DNA, are means ± S.E.M. of two independent measures. °Significantly different from control C−, $P < 0.05$. *Significantly different from control C+, $P < 0.05$.

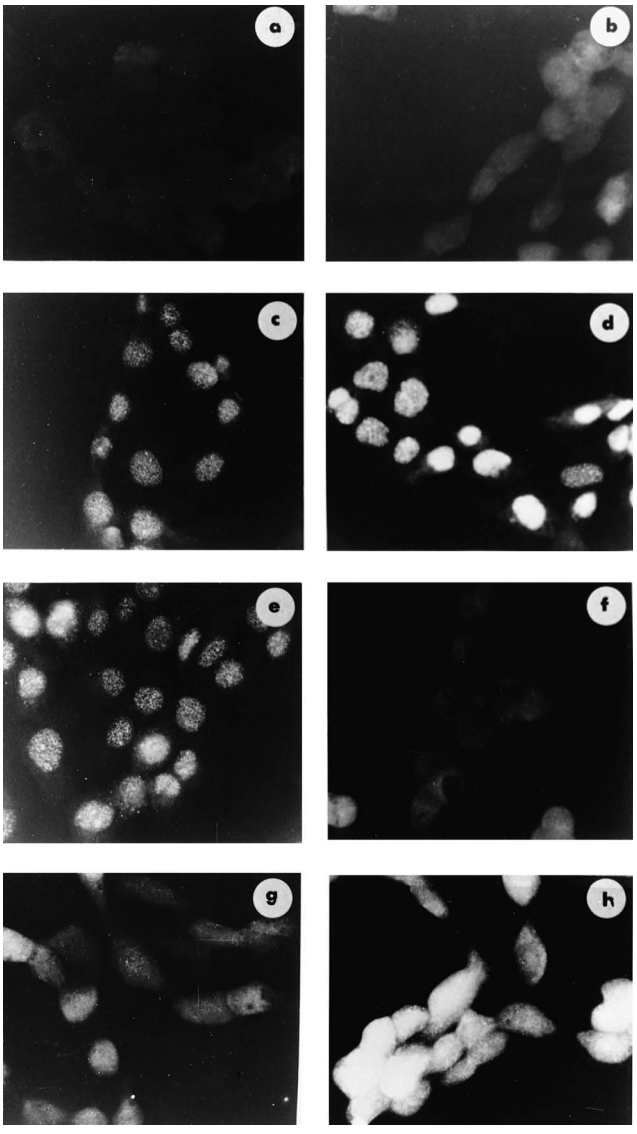

Fig. 4. Effect of PLA_2-I on PPAR expression in U_{III} cells. Expression of PPAR in non-confluent cells, preincubated 2 h without (a, c, e, g) or with 30 nM PLA_2-I (b, d, f, h), was analyzed by immunocytochemistry as described in Section 2. Cells, treated without (a), with preimmune rabbit serum (b) or with non-specific immune serum against the whole of PPARs (c, d), or with specific immune serum anti-PPAR-α (e, f) and anti-PPAR-γ_2 (g, h) were observed in fluorescence microscopy.

transcriptional activation of gene expression. In order to test this hypothesis, we first investigated the expression of PPAR in non-confluent cells incubated in the presence or absence of 30 nM pancreatic PLA_2. Data presented in Fig. 4 show that U_{III} cells express PPAR-α and -γ_2 in a constitutive manner. When U_{III} cells were preincubated for 2 h with exogenous PLA_2-I, the whole PPAR expression was enhanced (Fig. 4d versus Fig. 4c).

However a differential regulation of PPAR-α and PPAR-γ_2 expression was apparent since the expression of PPAR-α was reduced in cells preincubated with the exogenous enzyme (Fig. 4f versus Fig. 4e) while that of PPAR-γ_2 was greatly increased (Fig. 4h versus Fig. 4g). The presence of PPAR-α in U_{III} cells is in accordance with its ubiquitous pattern of expression and its presence in the rat uterus as has already been described [20]. The inhibitory effect of PLA_2 on PPAR-α expression is also in accordance with a number of data showing that glucocorticoids, which are well-known to inhibit the secreted form of PLA_2 [34], also activate PPAR-α expression [32]. Since PPAR-γ expression is more restricted, the presence of PPAR-γ_2 in U_{III} cells and the induction of its expression by PLA_2-I seems to be of great interest. Although, PPAR-γ is generally considered as a key transcription factor involved in adipocyte differentiation [33,35,36]. It has also been described in non-adipose tissues such as the spleen, mucosa of duodenum and retina [37], indicating that PPAR-γ is probably more widely distributed than it was initially considered. Interestingly, recent evidence has been demonstrated that PPAR-γ is highly expressed in colon and breast cancer cells [38,39]. The PLA_2-I-induced PPAR-γ_2 expression in U_{III} cells leads us to attribute a more general function to PPAR-γ_2 in controlling cell behavior for differentiation or proliferation. Then, the proliferative effect of the PLA_2-I on U_{III} cells could be exerced, after binding to its membrane receptor, internalizing and migrating toward the nucleus, via PPAR-γ_2 and peroxisomes. Thus, we can suggest, like it was soon demonstrated in bacteria [40], that the proliferation in eukaryotes could also be induced by molecular hyperstructure associating DNA, proteins and lipids.

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References

[1] Murakami, M., Nakatani, Y., Atsumi, G.I., Inoue, K. and Kudo, I. (1997) Crit. Rev. Immunol. 17, 225–283.
[2] Six, D.A. and Dennis, E.A. (2000) Biochim. Biophys. Acta 1488, 1–19.
[3] Murakami, M., Kudo, I. and Inoue, K. (1995) J. Lipid Mediat. Cell Signal. 12, 119–130.
[4] Clark, J.D., Schievella, A.R., Nalefski, E.A. and Lin, L.L. (1995) J. Lipid Mediat. Cell Signal. 12, 83–117.
[5] Winstead, M.V., Balsinde, J. and Dennis, E.A. (2000) Biochim. Biophys. Acta 1488, 28–39.
[6] Arita, H., Hamasaki, K., Nakano, T., Oka, S., Teraoka, H. and Matsumoto, K. (1991) J. Biol. Chem. 266, 19139–19141.
[7] Ohara, O., Ishizaki, J. and Arita, H. (1995) Prog. Lipid Res. 34, 117–138.
[8] Zvaritch, E., Lambeau, G. and Ladzunski, M. (1996) J. Biol. Chem. 271, 250–257.
[9] Cohen, H., Pageaux, J.F., Melinand, C., Fayard, J.M. and Laugier, C. (1993) Eur. J. Cell. Biol. 61, 116–125.
[10] Tessier, C., Rossini, G.P., Pageaux, J.F., Cohen, H., Lagarde, M., Laugier, C. and Fayard, J.M. (1996) FEBS Lett. 390, 311–314.
[11] Rossini, G.P., Fayard, J.M., Tessier, C. and Laugier, C. (1996) Biochem. J. 315, 1007–1014.
[12] Fayard, J.M., Tessier, C., Pageaux, J.F., Lagarde, M. and Laugier, C. (1998) J. Cell Sci. 111, 985–994.
[13] Krey, G., Braissant, O., L'Horset, F., Kalkhoven, E., Perroud, M., Parker, M.G. and Wahli, W. (1997) Mol. Endocrinol. 11, 779–791.
[14] Nicotera, P., McConkey, D.J., Jones, D.P. and Orrenius, S. (1989) Proc. Natl. Acad. Sci. USA 86, 453–457.
[15] Labarca, C. and Paigen, K. (1980) Anal. Biochem. 102, 344–352.
[16] Radvanyi, F., Jordan, L., Russo-Marie, F. and Bon, C. (1989) Anal. Biochem. 177, 103–109.
[17] Prigent-Tessier, A., Pageaux, J.F., Fayard, J.M., Lagarde, M.,

Laugier, C. and Cohen, H. (1996) Mol. Cell. Endocr. 122, 101–108.
[18] Delves, P.J. (1997) J. Wiley and sons Ltd., West Essex.
[19] Huin, C., Corriveau, L., Bianchi, A., Keller, J.M., Collet, P., Kremarik-Bouillaud, P., Domenjoud, L., Becuwe, P., Schohn, H., Menard, D. and Dauça, M. (2000) J. Histochem. Cytochem. 48, 1–9.
[20] Braissant, O., Foufelle, F., Scotto, C., Dauça, M. and Wahli, W. (1996) Endocrinology 137, 354–366.
[21] Conover, W.J. (1980) Wiley, New York.
[22] Kishino, J., Ohara, O., Nomura, K., Kramer, R.M. and Arita, A. (1994) J. Biol. Chem. 269, 5092–5098.
[23] Xing, M., Miele, L. and Mukherjee, A.B. (1995) J. Cell Physiol. 165, 566–575.
[24] Gurr, G.I., Finean, J.B. and Hawthorne, J.N. (1963) Biochim. Biophys. Acta 70, 406–416.
[25] Rose, H.G. and Frenster, J.H. (1965) Biochim. Biophys. Acta 106, 577–591.
[26] Manzoli, F.A., Muchmore, H.J., Bonora, B., Sabioni, A. and Stefoni, S. (1972) Biochim. Biophys. Acta 277, 251–255.
[27] Frenster, J.H. (1969) Handbook of Molecular Cytology (Lima-de-Faria, A., Ed.), pp. 251–276, North-Holland Publishing company, Amsterdam.
[28] Viola-Magni, M.P., Gahan, P.B. and Pacy, J. (1985) Cell Biochem. Funct. 3, 71–78.
[29] Ishihara, H., Tamiya-Koizumi, K., Kuriki, H., Yoshida, S. and Kojima, K. (1991) Biochim. Biophys. Acta 1084, 53–59.
[30] Jump, D.B. and Clarke, S.D. (1999) Annu. Rev. Nutr. 19, 63–90.
[31] Yoo, H.Y., Chang, M.S. and Rho, H.M. (1999) Gene 234, 87–91.
[32] Lemberger, T., Desvergne, B. and Wahli, W. (1996) Annu. Rev. Cell Signal. 12, 119–130.
[33] Schoonjans, K., Staels, B. and Auwerx, J. (1996) Biochim. Biophys. Acta 1302, 93–109.
[34] Olivier, J.L., Fan, Q., Salvat, C., Ziari, M., Kong, L., Mangeney, M. and Bereziat, G. (1994) Biochemistry 33, 7134–7145.
[35] Bastie, C., Holst, D., Gaillard, D., Jehl-Pietri, C. and Grimaldi, P.A. (1999) J. Biol. Chem. 274, 21920–21925.
[36] Oberfield, J.L., Collins, J.L., Holmes, C.P., Gorehem, D.M., Cooper, J.P., Cobb, J.E., Lenhard, J.M., Hull-Ryde, E.A., Mohr, C.P., Blanchard, S.G., Parks, D.J., Moore, L.B., Lehmann, J.M., Plunket, K., Miller, A.B., Milburn, M.V., Kliewer, S.A. and Wilson, T.M. (1999) Proc. Natl. Acad. Sci. USA 96, 6102–6106.
[37] Jain, S., Pulikuri, S., Zhu, Y., Qi, C., Kanwar, Y.S., Yeldandi, A.V., Rao, M.S. and Reddy, J.K. (1998) Am. J. Pathol. 153, 349–354.
[38] DuBois, R.N., Gupta, R., Brockman, J., Reddy, B.S., Krakow, S.L. and Lazar, M.A. (1998) Carcinogenesis 19, 49–53.
[39] Elstner, E., Müller, C., Koshizuka, K., Williamson, E.A., Park, D., Asou, H., Shintaku, P., Said, J.W., Heber, D. and Koeffer, H.P. (1998) Proc. Natl. Acad. Sci. USA 95, 8806–8811.
[40] Norris, V., Fralick, J. and Danchin, A. (2000) Mol. Microbiol. 37, 696–702.