ELSEVIER

Biochimica et Biophysica Acta 1585 (2002) 108–113

BIOCHIMICA ET BIOPHYSICA ACTA
BBA

www.bba-direct.com

Review

Lysophosphatidic acid as a novel cell survival/apoptotic factor

Xiaoqin Ye, Isao Ishii[1], Marcy A. Kingsbury, Jerold Chun*

Department of Pharmacology, School of Medicine, University of California, San Diego, La Jolla, CA 92093-0636, USA

Received 1 February 2002; received in revised form 29 May 2002; accepted 30 October 2002

Abstract

Lysophosphatidic acid (LPA) activates its cognate G protein-coupled receptors (GPCRs) LPA_{1-3} to exert diverse cellular effects, including cell survival and apoptosis. The potent survival effect of LPA on Schwann cells (SCs) is mediated through the pertussis toxin (PTX)-sensitive $G_{i/o}$/phosphoinositide 3-kinase (PI3K)/Akt signaling pathways and possibly enhanced by the activation of PTX-insensitive Rho-dependent pathways. LPA promotes survival of many other cell types mainly through PTX-sensitive $G_{i/o}$ proteins. Paradoxically, LPA also induces apoptosis in certain cells, such as myeloid progenitor cells, hippocampal neurons, and PC12 cells, in which the activation of the Rho-dependent pathways and caspase cascades has been implicated. The effects of LPA on both cell survival and apoptosis underscore important roles for this lipid in normal development and pathological processes.

Keywords: LPA; LPA receptor; Schwann cell; Survival; Apoptosis

1. Introduction

Lysophosphatidic acid (1-acyl-2-*sn*-glycerol-3-phosphate) (LPA) is a simple lipid naturally produced during phospholipid biosynthesis of cell membranes [1]. LPA is also produced extracellularly from activated platelets, leukocytes, epithelial cells, neuronal cells, and tumor cells [2–7]. LPA is a potent signaling molecule involved in a variety of physiological and pathological processes, such as cell differentiation and proliferation, cytoskeletal rearrangement, cell–cell communication, and cell invasion [8] (reviewed in Refs. [9–13]). The signaling activities of LPA are mediated by a family of cognate G protein-coupled receptors (GPCRs), currently including LPA_1/LP_{A1}/VZG-1/MREC1.3/EDG-2 [14,15], LPA_2/LP_{A2}/EDG-4 [16,17], and LPA_3/LP_{A3}/EDG-7 [18,19] in mammals. These GPCRs couple to at least three different types of G proteins ($G_{q/11/14}$, $G_{12/13}$, and $G_{i/o}$) [20] to activate various downstream signaling pathways which induce the diverse cellular effects (reviewed in Refs. [9,11,21–25]).

Since the identification of the first LPA receptor, LPA_1, from developing cortical neuroblasts [14], studies investigating the roles of LPA in neural cell signaling found that LPA signaling mediated through LPA_1 protected rodent Schwann cells (SCs) from apoptosis [4,5,26,27]. In normal rat development, SC apoptosis occurs in the early postnatal period as SCs are matched in a 1:1 ratio with axons [28–30]. This process is controlled by both axonal and autocrine signals [31,32], and possibly by interactions with the extracellular matrix (ECM) [33]. While various peptide growth factors, such as neuregulins (NRGs) [34], insulin-like growth factor (IGF) [35], platelet-derived growth factor (PDGF) [36], and fibroblast growth factor (FGF) [37], are believed to elicit axonal and/or autocrine signals for SC survival, LPA is the first lipid molecule shown to mediate SC survival [26].

Here we review roles of LPA as a survival or apoptotic factor, with a particular emphasis on SCs. We also summarize the current LPA signaling cascades that are involved in cell survival and apoptosis.

2. LPA as a SC survival factor

2.1. LPA promotion of SC survival

Previous studies in rat postnatal SCs have shown that serum contains cell survival factor(s) [29]. Together, three

* Corresponding author. Present address: Department of Molecular Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA. Tel.: +1-858-784-8410; fax: +1-858-784-2988.
E-mail address: jchun@scripps.edu (J. Chun).
[1] Present address. Department of Molecular Genetics, National Institute of Neuroscience, 4-1-1, Ogawahigashi, Kodaira, Tokyo 187-8502, Japan.

1388-1981/02/$ - see front matter © 2002 Published by Elsevier Science B.V.
PII: S1388-1981(02)00330-X

lines of evidence suggest that LPA could be a potential candidate for mediating this survival effect of serum. First, LPA is present in serum at micromolar concentrations [7]. Second, the nervous system is a rich source of lipids [38]. Third, *lpa*$_1$ is highly expressed in SCs throughout sciatic nerve development and in SC cultures [5,26].

Indeed, the serum-mediated survival effect in rat postnatal SCs is attributable to LPA [26]. When cultured in serum-containing medium, most SCs survived after 72 h of culture [26,29]. However, upon serum withdrawal, 60–75% of SCs underwent apoptosis by 48 h, and up to 80–90% by 72 h [26,29]. Under serum deprivation, LPA at concentrations as low as 10 nM significantly rescued SCs from apoptosis and the effect was concentration-dependent [26]. The reduced cell death following LPA treatment was the result of cell survival rather than cell proliferation, as BrdU incorporation was not increased by LPA treatment [26]. Interestingly, LPA (1 μM) had comparable efficacy in promoting SC survival as did NRG-β (at 100 ng/ml), a potent peptide SC survival factor [26,39]. Treatment with either molecule was observed to inhibit ~50% of the apoptosis induced by serum deprivation, although these molecules did not act synergistically at their maximal effective concentrations, suggesting that they activated convergent signaling pathways [26].

Not all bioactive lysophospholipids (LPs) act as SC survival factors [26]. Sphingosine 1-phosphate (S1P) is another serum born bioactive LP that induces diverse physiological effects on many cell types (reviewed in Refs. [22,25,40,41]). S1P activates five cognate GPCRs encoded by: *s1p*$_1$/*lp*$_{B1}$/*edg-1*, *s1p*$_2$/*lp*$_{B2}$/*edg-5*, *s1p*$_3$/*lp*$_{B3}$/*edg-3*, *s1p*$_4$/*lp*$_{C1}$/*edg-6*, and *s1p*$_5$/*lp*$_{B4}$/*edg-8*, all of which are members of the same gene family as LPA receptors (reviewed in Refs. [22,25,40,41]). However, although at least three S1P receptors (*s1p*$_1$, *s1p*$_2$, *s1p*$_3$) were expressed in SCs both in vivo and in vitro [5,26], S1P did not promote SC survival [26].

2.2. Signaling cascades

2.2.1. Involvement of LPA_1

It is necessary to have the presence of endogenous LPA and the expression of LPA receptors for receptor-mediated LPA signaling. Activity specific to LPA was detected in conditioned medium from in vitro SC cultures [5], suggesting that secreted LPA may serve as an autocrine signal for SCs. In terms of receptor expression, *lpa*$_1$ was expressed at high levels in mouse and rat SCs, *lpa*$_2$ was detectable in mouse SCs by RT-PCR but not in rat SCs by Northern analysis, and *lpa*$_3$ was undetectable [5,26]. Because of the high levels of *lpa*$_1$ expression, the roles of this receptor were further explored [26]. Exogenous overexpression of LPA_1 in SCs significantly reduced apoptosis upon serum withdrawal, indicating that LPA promotion of SC survival was, at least partially, mediated by the LPA_1 receptor [26].

Direct evidence for the involvement of LPA_1 was derived from experiments using *lpa*$_1$ knockout mice [27]. These experiments revealed an approximately 80% increase in sciatic nerve SC apoptosis in $lpa_1^{(-/-)}$ homozygous knockout mice compared to wild-type mice [27]. In spite of this observation [5,26,27], the myelination of the peripheral nervous system and the structure of the sciatic nerves appeared to be normal in $lpa_1^{(-/-)}$ mice [5,27]. Since the sciatic nerves normally have a low level of cell death, the lack of a myelination phenotype in $lpa_1^{(-/-)}$ mice may not be surprising, despite the 80% increase in sciatic nerve SC apoptosis. However, the lack of phenotype may also be related to compensation by other receptor-mediated signals, such as LPA signaling through the LPA_2 receptor, and/or the actions of peptide growth factors [39] that are known to promote SC survival through downstream signaling pathways similar to that activated by LPA (see below).

2.2.2. $G_{i/o}$ and PI 3-kinase/Akt signaling pathways

The effect of LPA on SC survival is mediated by the $G_{i/o}$/phosphoinositide 3-kinase (PI3K)/Akt signaling pathways. The involvement of the PTX-sensitive $G_{i/o}$ protein was shown by the complete abolishment of the LPA survival effect following pretreatment with PTX [26]. The essential role of PI3K, one of the downstream targets of $G_{i/o}$, was established by the total loss of the LPA survival effect following pretreatment with two distinct PI3K inhibitors, wortmannin and LY294002 [26]. The activation of Akt/PKB (protein kinase B), an effector of PI3K [42], was demonstrated by a rapid and transient accumulation of phospho-Akt in response to LPA [26]. The Akt activation was blocked by PI3K inhibitors, but not by PD98059, a mitogen-activated protein kinase kinase (MAPKK) inhibitor, indicating that Akt was downstream of PI3K, but probably not downstream of MAPK. Furthermore, Akt activation was indispensable for the LPA survival effect since introduction of a kinase-inactive Akt mutant into rat SCs significantly reduced the survival effect of LPA [26]. However, the detailed mechanisms by which Akt activation leads to SC survival remain unknown.

The activation of the PI3K/Akt pathways for SC survival appears to be shared by numerous factors. In addition to the involvement of these pathways in the LPA_1-mediated LPA survival effect, these pathways also mediated SC survival induced by peptide growth factors even though these factors function through their own cognate receptors that are not GPCRs. For example, the effects of NRG are mediated by a subfamily of receptor protein-tyrosine kinases called the "ErbBs" [39]. Interestingly, like LPA_1, ErbBs also activated PI3K/Akt pathways to promote rat SC survival [34]. The common activation of these pathways may explain the inability of LPA and NRG-β to act synergistically at their maximal effective concentrations [26] and raises the possibility of cross-talk amongst different survival signals in SCs. Other SC survival factors, such as IGF-I [43] and *T. cruzi*

trans-sialidase (a neuraminidase from the protozoan parasite) [44], also promoted the survival of rat SCs and human SCs, respectively, by means of activating the PI3K/Akt pathways.

2.2.3. Rho pathways

Since loss of contact with the ECM can induce anoikis (a form of apoptosis caused by disruption of cell–matrix interactions) (reviewed in Ref. [45]), LPA-activated Rho pathways in SCs may potentially inhibit apoptosis [5,46,47]. This is suggested by the observation that LPA treatment enhanced cell adhesion to the ECM through the activation of the small GTPase Rho [5]. In addition, when SCs were grown on dishes coated with laminin, an important component of the ECM, LPA's ability to promote SC survival was increased [5]. This finding indicated that the enhancement of ECM-mediated cell adhesion through the activation of the Rho pathways facilitated LPA's ability to promote SC survival. This facilitation was through the activation of the PI3K/Akt pathways [5,26], suggesting possible cross-talk between the Rho pathways and the PI3K/Akt pathways. The cross-talk between these pathways has been clearly demonstrated in primary fibroblasts, in which loss of attachment to ECM resulted in diminished Akt activity through inhibition of Rho GTPase, thus leading to apoptosis [48]. These studies suggest that the activation of Rho-mediated pathways may be another important mechanism for the survival action of LPA in SCs [5,46,47].

3. LPA and survival/apoptosis in other cell types

3.1. Effects of LPA on other cell types

It has been reported that LPA can promote either survival or apoptosis in different cell types, and it may also have dual effects in the same cell type under different conditions (Table 1). In addition to SCs, LPA has been reported to promote survival of ovarian cancer cells [49,50], mouse renal proximal tubular (MPT) cells [51], murine macrophages [52], 3T3 fibroblasts [53], Jurkat and HeLa cells [53], neonatal rat cardiac myocytes [54], and mesangial cells [55]. In contrast, LPA also has been reported to induce apoptosis in hippocampal neurons [56], nerve growth factor-differentiated PC12 cells [57], human airway smooth muscle (HASM) cells [58], and myeloid progenitor TF-1 and D2 cells [59]. Interestingly, LPA had dual effects in human $CD4^{+}8^{+}3^{low}$ T lymphoblasts [60]: LPA promoted apoptosis in the absence of other molecules that induced apoptosis in these cells, but it inhibited apoptosis induced by the antibodies Fas, CD2, or a combination of CD3 and CD28.

3.2. Mechanisms of LPA-promoted cell survival

3.2.1. LPA receptors and cell type-specific effects

Different cell types express different combinations of the three LPA receptors, and different receptors may have

Table 1
The effects of LPA on cell survival and apoptosis

Cell type	LPA effect(s)	Apoptosis induced by	Effective [LPA] employed	Signaling elements identified	Reference
Schwann cells	survival	serum withdrawal	10 nM–1 μM	$LPA_1/G_{i,o}$/PI3K/Akt; LPA_1/Rho	[5,26]
Macrophages	survival	serum withdrawal	50 nM–7.7 μM	LPA receptor(s)/PI3K /$pp70^{s6k}$ and others?	[52]
T lymphoblasts	survival	anti-Fas, anti-CD2, anti-CD3 + anti-CD28	0.1 nM–0.1 μM	LPA_1 and LPA_2; Bax; others?	[60]
Neonatal myocytes	survival	hypoxia	1 μM	unknown	[54]
MPT cells	survival	growth factor deprivation	6–12 μM	PI3K	[51]
Mesangial cells	survival	PDGF	30 μM	PI3K	[55]
3T3 fibroblasts	survival	serum withdrawal	5–45 μM	$G_{i/o}$/MAPK; $G_{i/o}$/PI3K/Akt; PTX-insensitive G protein(s)	[53]
Jurkat cells; HeLa cells	survival	serum withdrawal	unknown	unknown	[53]
Ovarian cancer cells	survival	*cis*-DDP	10 μM	LPA_2?	[49,50]
HASM cells	apoptosis	serum withdrawal	100 μM[a]	unknown	[58]
Hippocampal neurons	apoptosis	LPA	0.1 ~ 1 μM	mitochondrial membrane potential; caspases	[56,72]
PC12 cells	apoptosis	LPA	10–25 μM	oxidative stress; nitric oxide; mitochondrial dysfunction; caspases	[57,72]
TF-1; D2	apoptosis	PMA	0.5–20 μM	RhoA	[59]
T lymphoblasts	apoptosis	LPA	0.1 μM	unknown	[60]
Jurkat cells; Ovarian cancer cells	apoptosis	overexpression of LPA_1	0	LPA_1	[61]

PI3K: phosphoinositide 3-kinase. PTX: pertussis toxin. MAPK: mitogen-activated protein kinase. MPT: mouse renal proximal tubular cells. PDGF: platelet-derived growth factor. *cis*-DDP: *cis*-diamminedichloroplatinum. HASM: human airway smooth muscle cells. PMA: phorbol 12-myristate-13-acetate.

[a] In the absence of calcium.

cell type specific roles, suggesting that the effects of LPA signaling might be variable from cell to cell. For instance, in contrast to the survival role of LPA_1 in SCs [26,27], overexpression of LPA_1 in ovarian cancer cells (OCCs) induced apoptosis and anoikis [61], whereas LPA_2 appeared to mediate LPA-stimulated survival of OCCs [50]. In T lymphoblasts, however, both LPA_1 and LPA_2 were reported to play a role in LPA-promoted cell survival [60].

3.2.2. Comparison of LPA and S1P receptors in survival signaling

Despite certain similar functions and similar amino acid sequences (reviewed in Refs. [22,23,40,41]), LPA and S1P receptors are differentially regulated and, thus, could have different roles in mediating the survival or death signals of LPA and S1P, respectively. For example, the expression of LPA receptors, but not that of S1P receptors, was suppressed by C6 ceramide; therefore LPA, but not S1P, was no longer able to protect T lymphoblasts from apoptosis induced by C6 ceramide [60]. In SCs, the potent survival effect of LPA was mediated through the LPA_1 receptor, while S1P did not have an effect on SC survival, despite the expression of S1P receptors [5,26]. In addition, both LPA receptors and S1P receptors were expressed in PC12 cells [62,63]. However, LPA had either apoptotic activity or no effect in PC12 cells [57,64], whereas S1P promoted survival of these cells [64].

3.2.3. Signaling cascades for survival effects

Similar to SCs, the $G_{i/o}$/PI3K-dependent survival signaling pathways were also activated by LPA in MPT cells [51], murine macrophages [52], 3T3 fibroblasts [53], and mesangial cells [55]. However, the involvement of $G_{i/o}$/PI3K signaling and the downstream pathways in murine macrophages and 3T3 cell lines may be somewhat different compared to that shown in SCs [52,53]. As demonstrated in SCs, the survival activity of LPA in murine macrophages was also completely blocked by PI3K inhibitors, indicating a key role for PI3K [52]. This signal was further transduced partially through $pp70^{s6k}$, a PI3K downstream kinase [52]. The partial contribution of $pp70^{s6k}$ in cell survival would suggest the involvement of other PI3K downstream targets, without excluding Akt, since Akt can be an upstream signal for $pp70^{s6k}$ [65]. Alternatively, Akt and $pp70^{s6k}$ could be parallel substrates [66,67]. In 3T3 fibroblasts, PTX treatment blocked 75% of the survival activity of LPA, indicating that the PTX-sensitive $G_{i/o}$ protein(s) mediated the major survival activity of LPA, while PTX-insensitive G protein(s) mediated the remaining activity [53]. The $G_{i/o}$-dependent survival signal was mainly mediated by MAPK pathways with only a minor contribution from the PI3K/Akt pathways [53]. In contrast, the MAPK pathways were not involved in SC survival, as shown by the observation that a MAPKK inhibitor did not affect LPA survival signaling in SCs [26].

Though the upstream signaling pathways have yet to be elucidated for T lymphoblasts, LPA protected these cells from apoptosis by suppressing the expression of the pro-apoptotic protein Bax [60]. Bax was proposed to induce caspase activation and cytochrome *c* release [68]. The reduced expression of Bax upon LPA treatment could thus weaken the apoptotic signal and reduce apoptosis in T lymphoblasts [60]. In addition, other mechanism(s) to promote survival may co-exist in these cells since LPA at low concentrations, which did not affect Bax expression, still facilitated cell survival [60].

3.3. Mechanisms of LPA-induced apoptosis

3.3.1. Rho pathways

Rho-dependent pathways appear to mediate LPA-induced apoptosis in myeloid progenitor TF-1 and D2 cells [59]. It was reported that LPA alone did not have an apoptotic effect on these cells; it only promoted phorbol 12-myristate-13-acetate (PMA)-induced apoptosis in non-adherent cells [59]. Mechanistic studies indicated that LPA treatment activated RhoA, which in these cells had a negative effect on cell adhesion [59]. These observations suggest that the LPA-activated Rho signaling pathways probably attenuated the adhesion capability of PMA-treated TF-1 and D2 cells, therefore promoting apoptosis [59]. LPA-activated Rho pathways are thus involved in both SC survival and myeloid progenitor cell apoptosis; how activation of similar pathways leads to opposite effects in these cell types is unknown [5,59].

3.3.2. Caspase cascades

Caspases, whose activation leads to apoptosis (reviewed in Ref. [69]), were activated by LPA in both hippocampal neurons and PC12 cells [56,57]. Although the detailed signaling cascades have not been studied, several mitochondrial events, which could subsequently activate caspase cascades (reviewed in Refs. [70,71]), were detected following LPA treatment in both cell types [56,57]. LPA treatment induced nitric oxide (NO) and reactive oxygen species (ROS), the latter of which is primarily produced in mitochondria [56,57,72]. In addition, mitochondrial dysfunction, which could result from increased NO or ROS, was also related to LPA-induced apoptosis in hippocampal neurons and PC12 cells [56,57,70–73].

4. Closing remarks

LPA can serve as a novel and potent cell survival and/or apoptotic factor, showing some selectivity for different cell types. In SCs, LPA exerts its survival effect through LPA receptor(s)-mediated $G_{i/o}$/PI3K/Akt survival pathways and possibly facilitated by Rho-dependent cytoske-

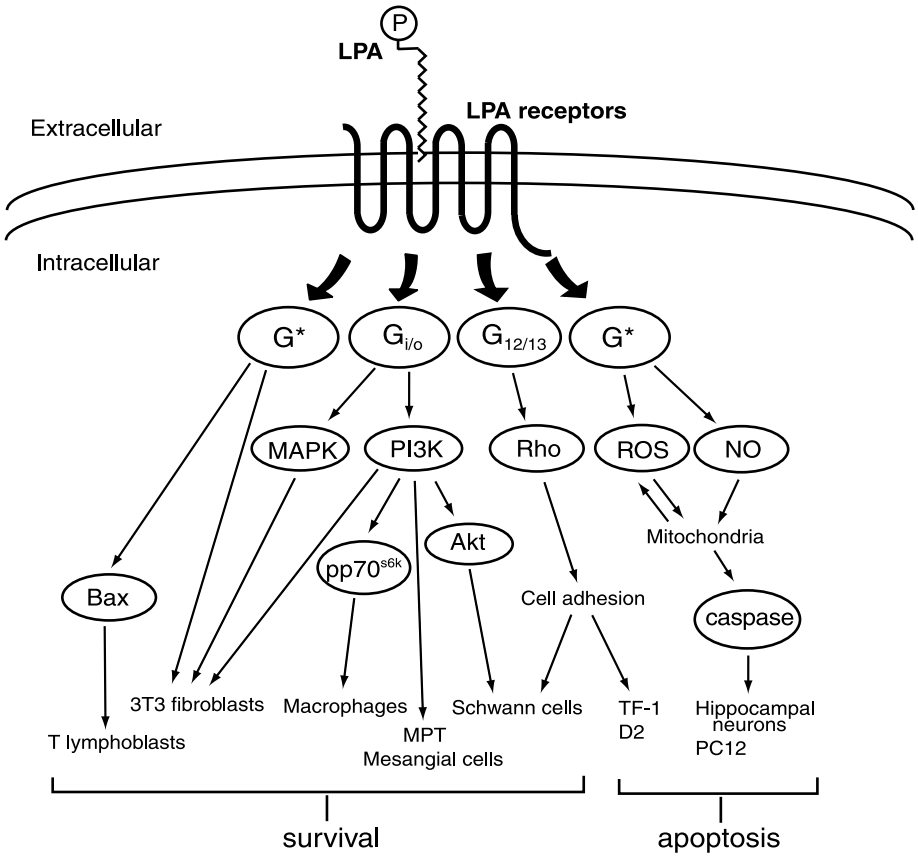

Fig. 1. LPA signaling pathways that mediate survival or apoptosis in various cell types (Refs.[5,26,27,51–53,56,57,59,60]). G*: unspecified G proteins. ROS: reactive oxygen species. NO: nitric oxide. MPT cells: mouse renal proximal tubular cells. TF-1, D2: myeloid progenitor cells.

letal signaling pathways. Various other signaling pathways are involved in mediating the survival and apoptotic effects of LPA in numerous cell types (Fig. 1). It is also possible that LPA regulates cell survival/apoptosis through the stimulation of release of some other cellular factors (e.g. protein growth factors/cytokines) [74].

A number of variables may account for the cell type-specific survival/apoptotic roles of LPA. First, there are qualitative and quantitative differences in the expression profiles of LPA receptors amongst different cell types [5,50]. Second, LPA receptors drive cell type-specific signaling cascades [26,50,60]. Third, each cell type has a unique gene expression and regulation pattern that can likely be altered by LPA signals. Fourth, the cross-talk amongst different signaling pathways could contribute to the final cellular outcome initiated by LPA signaling. Fifth, varying levels of cytoprotective factors, such as antioxidants in the cell, could influence LPA-induced apoptosis [57,75]. Sixth, the specific conditions under which LPA activities were examined could potentially modify the effects of LPA [58,60]. The near future should allow identification of additional biological, pathophysiological, and therapeutic roles for this simple bioactive lipid molecule in cell survival and apoptosis.

Acknowledgements

We thank Dr. N. Fukushima and A. Yang for critical comments on the manuscript. This work was supported by the NIMH, the HFSP, and an unrestricted gift from Merck Research Laboratories.

References

[1] R.A. Pieringer, H. Bonner Jr., R.S. Kunnes, J. Biol. Chem. 242 (1967) 2719–2724.
[2] F. Gaits, O. Fourcade, F. Le Balle, G. Gueguen, B. Gaige, A. Gassama-Diagne, J. Fauvel, J.P. Salles, G. Mauco, M.F. Simon, H. Chap, FEBS Lett. 410 (1997) 54–58.
[3] E.J. Goetzl, Prostaglandins Other Lipid Mediat. 64 (2001) 11–20.
[4] N. Fukushima, J.A. Weiner, J. Chun, Dev. Biol. 228 (2000) 6–18.
[5] J.A. Weiner, N. Fukushima, J.J. Contos, S.S. Scherer, J. Chun, J. Neurosci. 21 (2001) 7069–7078.
[6] X. Fang, D. Gaudette, T. Furui, M. Mao, V. Estrella, A. Eder, T. Pustilnik, T. Sasagawa, R. Lapushin, S. Yu, R.B. Jaffe, J.R. Wiener, J.R. Erickson, G.B. Mills, Ann. N.Y. Acad. Sci. 905 (2000) 188–208.
[7] T. Eichholtz, K. Jalink, I. Fahrenfort, W.H. Moolenaar, Biochem. J. 291 (Pt 3) (1993) 677–680.
[8] N. Yanai, N. Matsui, T. Furusawa, T. Okubo, M. Obinata, Blood 96 (2000) 139–144.

[9] W.H. Moolenaar, Ann. N.Y. Acad. Sci. 905 (2000) 1–10.
[10] J. Chun, Crit. Rev. Neurobiol. 13 (1999) 151–168.
[11] J.J. Contos, I. Ishii, J. Chun, Mol. Pharmacol. 58 (2000) 1188–1196.
[12] J.T. Swarthout, H.W. Walling, Cell. Mol. Life Sci. 57 (2000) 1978–1985.
[13] D. English, J.G. Garcia, D.N. Brindley, Cardiovasc. Res. 49 (2001) 588–599.
[14] J.H. Hecht, J.A. Weiner, S.R. Post, J. Chun, J. Cell. Biol. 135 (1996) 1071–1083.
[15] S. An, M.A. Dickens, T. Bleu, O.G. Hallmark, E.J. Goetzl, Biochem. Biophys. Res. Commun. 231 (1997) 619–622.
[16] S. An, T. Bleu, O.G. Hallmark, E.J. Goetzl, J. Biol. Chem. 273 (1998) 7906–7910.
[17] J.J. Contos, J. Chun, Genomics 64 (2000) 155–169.
[18] K. Bandoh, J. Aoki, H. Hosono, S. Kobayashi, T. Kobayashi, K. Murakami-Murofushi, M. Tsujimoto, H. Arai, K. Inoue, J. Biol. Chem. 274 (1999) 27776–27785.
[19] D.S. Im, C.E. Heise, M.A. Harding, S.R. George, B.F. O'Dowd, D. Theodorescu, K.R. Lynch, Mol. Pharmacol. 57 (2000) 753–759.
[20] I. Ishii, J.J. Contos, N. Fukushima, J. Chun, Mol. Pharmacol. 58 (2000) 895–902.
[21] J. Chun, J.J. Contos, D. Munroe, Cell Biochem. Biophys. 30 (1999) 213–242.
[22] N. Fukushima, I. Ishii, J.J. Contos, J.A. Weiner, J. Chun, Annu. Rev. Pharmacol. Toxicol. 41 (2001) 507–534.
[23] W.H. Moolenaar, Exp. Cell Res. 253 (1999) 230–238.
[24] O. Kranenburg, W.H. Moolenaar, Oncogene 20 (2001) 1540–1546.
[25] T. Hla, M.J. Lee, N. Ancellin, J.H. Paik, M.J. Kluk, Science 294 (2001) 1875–1878.
[26] J.A. Weiner, J. Chun, Proc. Natl. Acad. Sci. U. S. A. 96 (1999) 5233–5238.
[27] J.J. Contos, N. Fukushima, J.A. Weiner, D. Kaushal, J. Chun, Proc. Natl. Acad. Sci. U. S. A. 97 (2000) 13384–13389.
[28] J.B. Grinspan, M.A. Marchionni, M. Reeves, M. Coulaloglou, S.S. Scherer, J. Neurosci. 16 (1996) 6107–6118.
[29] D.E. Syroid, P.R. Maycox, P.G. Burrola, N. Liu, D. Wen, K.F. Lee, G. Lemke, T.J. Kilpatrick, Proc. Natl. Acad. Sci. U. S. A. 93 (1996) 9229–9234.
[30] J. Nakao, J. Shinoda, Y. Nakai, S. Murase, K. Uyemura, J. Neurochem. 68 (1997) 1853–1862.
[31] J.T. Trachtenberg, W.J. Thompson, Nature 379 (1996) 174–177.
[32] L. Cheng, F.S. Esch, M.A. Marchionni, A.W. Mudge, Mol. Cell. Neurosci. 12 (1998) 141–156.
[33] M.B. Bunge, M.B. Clark, A.C. Dean, C.F. Eldridge, R.P. Bunge, Ann. N.Y. Acad. Sci. 580 (1990) 281–287.
[34] Y. Li, G.I. Tennekoon, M. Birnbaum, M.A. Marchionni, J.L. Rutkowski, Mol. Cell. Neurosci. 17 (2001) 761–767.
[35] H.L. Cheng, M.L. Steinway, X. Xin, E.L. Feldman, J. Neurochem. 76 (2001) 935–943.
[36] C.S. Lobsiger, B. Schweitzer, V. Taylor, U. Suter, Glia 30 (2000) 290–300.
[37] R. Shaw, R. Cianchetti, D. Pleasure, B. Kreider, J. Neurosci. Res. 47 (1997) 400–404.
[38] W. Stoffel, A. Bosio, Curr. Opin. Neurobiol. 7 (1997) 654–661.
[39] K. Adlkofer, C. Lai, Glia 29 (2000) 104–111.
[40] S. Spiegel, S. Milstien, Biochim. Biophys. Acta 1484 (2000) 107–116.
[41] S. Pyne, N. Pyne, Pharmacol. Ther. 88 (2000) 115–131.
[42] B.M. Marte, J. Downward, Trends Biochem. Sci. 22 (1997) 355–358.
[43] W.M. Campana, S.J. Darin, J.S. O'Brien, J. Neurosci. Res. 57 (1999) 332–341.
[44] M.V. Chuenkova, F.B. Furnari, W.K. Cavenee, M.A. Pereira, Proc. Natl. Acad. Sci. U. S. A. 98 (2001) 9936–9941.
[45] S.M. Frisch, R.A. Screaton, Curr. Opin. Cell Biol. 13 (2001) 555–562.
[46] R.P. Bunge, M.B. Bunge, C.F. Eldridge, Annu. Rev. Neurosci. 9 (1986) 305–328.
[47] R.P. Bunge, M.B. Bunge, J. Cell. Biol. 78 (1978) 943–950.
[48] O. Zugasti, W. Rul, P. Roux, C. Peyssonnaux, A. Eychene, T.F. Franke, P. Fort, U. Hibner, Mol. Cell. Biol. 21 (2001) 6706–6717.
[49] A. Frankel, G.B. Mills, Clin. Cancer Res. 2 (1996) 1307–1313.
[50] E.J. Goetzl, H. Dolezalova, Y. Kong, Y.L. Hu, R.B. Jaffe, K.R. Kalli, C.A. Conover, Cancer Res. 59 (1999) 5370–5375.
[51] J.S. Levine, J.S. Koh, V. Triaca, W. Lieberthal, Am. J. Physiol. 273 (1997) F575–F585.
[52] J.S. Koh, W. Lieberthal, S. Heydrick, J.S. Levine, J. Clin. Invest. 102 (1998) 716–727.
[53] X. Fang, S. Yu, R. LaPushin, Y. Lu, T. Furui, L.Z. Penn, D. Stokoe, J.R. Erickson, R.C. Bast Jr., G.B. Mills, Biochem. J. 352 (Pt 1) (2000) 135–143.
[54] J.S. Karliner, N. Honbo, K. Summers, M.O. Gray, E.J. Goetzl, J. Mol. Cell. Cardiol. 33 (2001) 1713–1717.
[55] C.N. Inoue, I. Nagano, R. Ichinohasama, N. Asato, Y. Kondo, K. Iinuma, Clin. Sci. (Lond.) 101 (2001) 11–19.
[56] F.W. Holtsberg, M.R. Steiner, J.N. Keller, R.J. Mark, M.P. Mattson, S.M. Steiner, J. Neurochem. 70 (1998) 66–76.
[57] F.W. Holtsberg, M.R. Steiner, A.J. Bruce-Keller, J.N. Keller, M.P. Mattson, J.C. Moyers, S.M. Steiner, J. Neurosci. Res. 53 (1998) 685–696.
[58] T.L. Ediger, M.L. Toews, Biochim. Biophys. Acta 1531 (2001) 59–67.
[59] J.M. Lai, C.Y. Lu, H.F. Yang-Yen, Z.F. Chang, Biochem. J. 359 (2001) 227–233.
[60] E.J. Goetzl, Y. Kong, B. Mei, J. Immunol. 162 (1999) 2049–2056.
[61] T. Furui, R. LaPushin, M. Mao, H. Khan, S.R. Watt, M.A. Watt, Y. Lu, X. Fang, S. Tsutsui, Z.H. Siddik, R.C. Bast, G.B. Mills, Clin. Cancer Res. 5 (1999) 4308–4318.
[62] G.J. Della Rocca, S. Maudsley, Y. Daaka, R.J. Lefkowitz, L.M. Luttrell, J. Biol. Chem. 274 (1999) 13978–13984.
[63] D.J. Fischer, N. Nusser, T. Virag, K. Yokoyama, D. Wang, D.L. Baker, D. Bautista, A.L. Parrill, G. Tigyi, Mol. Pharmacol. 60 (2001) 776–784.
[64] L.C. Edsall, G.G. Pirianov, S. Spiegel, J. Neurosci. 17 (1997) 6952–6960.
[65] S.A. Shah, M.W. Potter, R. Ricciardi, R.A. Perugini, M.P. Callery, J. Surg. Res. 97 (2001) 123–130.
[66] T.O. Chan, S.E. Rittenhouse, P.N. Tsichlis, Ann. Rev. Biochem. 68 (1999) 965–1014.
[67] P. Flynn, M. Wongdagger, M. Zavar, N.M. Dean, D. Stokoe, Curr. Biol. 10 (2000) 1439–1442.
[68] H.J. Kim, J.Y. Mun, Y.J. Chun, K.H. Choi, M.Y. Kim, FEBS Lett. 505 (2001) 264–268.
[69] J.C. Reed, Trends Mol. Med. 7 (2001) 314–319.
[70] J. Chandra, A. Samali, S. Orrenius, Free Radic. Biol. Med. 29 (2000) 323–333.
[71] H.T. Chung, H.O. Pae, B.M. Choi, T.R. Billiar, Y.M. Kim, Biochem. Biophys. Res. Commun. 282 (2001) 1075–1079.
[72] M.R. Steiner, F.W. Holtsberg, J.N. Keller, M.P. Mattson, S.M. Steiner, Ann. N.Y. Acad. Sci. 905 (2000) 132–141.
[73] G. Kroemer, Biochem. Soc. Symp. 66 (1999) 1–15.
[74] Y.L. Hu, M.K. Tee, E.J. Goetzl, N. Auersperg, G.B. Mills, N. Ferrara, R.B. Jaffe, J. Natl. Cancer Inst. 93 (2001) 762–768.
[75] J. Iglesias, V.E. Abernethy, Z. Wang, W. Lieberthal, J.S. Koh, J.S. Levine, Am. J. Physiol. 277 (1999) F711–F722.