ISSN 0006-2979, Biochemistry (Moscow), 2008, Vol. 73, No. 2, pp. 119-122. © Pleiades Publishing, Ltd., 2008.
Original Russian Text © E. V. Dyatlovitskaya, 2008, published in Biokhimiya, 2008, Vol. 73, No. 2, pp. 149-153.

REVIEW

Sphingolipid Receptors

E. V. Dyatlovitskaya

Shemyakin and Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences, ul. Miklukho-Maklaya 16/10, 117797 Moscow; E-mail: dyatl@ibch.ru

Received June 28, 2007

Abstract—The role of sphingolipids as receptors of bacteria, viruses, and toxins and also as ligands of proteinaceous receptors involved in the cell–cell signaling in animals is considered.

DOI: 10.1134/S0006297908020016

Key words: sphingosine-1-phosphate, sphingosine-1-phosphocholine, receptors, bacteria, viruses, toxins

The concept of "sphingolipid receptors" includes, on one hand, sphingolipids (glycosphingolipids) as receptors of toxins, viruses, and bacteria and, on the other hand, sphingolipids (sphingosine-1-phosphate, sphingosine-1-phosphocholine, psychosine) as ligands of some proteinaceous receptors and their complexes responsible for signaling functions in cells.

GLYCOSPHINGOLIPIDS AS RECEPTORS OF TOXINS, VIRUSES, AND BACTERIA

Neutral glycosphingolipids. The receptor role of neutral glycosphingolipids has been known for more than twenty years. Some experimental works are discussed in reviews [1, 2].

The present paper considers data on neutral glycosphingolipids as receptors published from the late 1980s up to now. In 1987, *Actinomyces naeslundii* was shown to bind with glycolipids including the group Galβ-3GalNAc- or GalNAcβ-3Gal- as a fragment [3]. Then LacCer and GalNAcβ1-4Galβ1-4Glcβ1-Cer (asialo-GM2) were reported to be receptors of *Neisseria gonorrheae* [4]. LacCer is also a receptor of *Cryptococcus neoformans*, *Candida albicans* [5], and also of the bacterium *Helicobacter pylori* responsible for disorders in the gastrointestinal tract [6]. In the last case, LacCer was shown to contain phytosphingosine and hydroxy acids. However, other neutral glycosphingolipids, such as GalCer, GlcCer [7], gangliotetraosyl ceramide (asialo-GM1) [8], and lactotetraosyl ceramide (paragloboside) [9], also act as receptors of *H. pylori*. Asialo-GM1 is a receptor of the bacterium *Halobacter mustelae* [8], which also is an agent of gastrointestinal diseases. Asialo-GM1 serves as a receptor of the bacterium *Pseudomonas aeruginosa* [10], GlcCer binds the bacterium *Salmonella enterica serovar* on the chicken oviduct surface [11]. Neutral glycosphingolipids also function as receptors of toxins. Thus, glycolipids of insects are receptors of *Bacillus thuringiensis* [12], and globotriaosyl ceramide is a receptor of *Shiga*-toxin in HeLa cells and not only binds the toxin with the cell but also promotes its penetration into the cell [13, 14]. Asialo-GM1 and asialo-GM2 are receptors of pathogens responsible for respiratory diseases [15, 16]. And finally, GalCer was shown to act as a receptor of human immunodeficiency virus [17].

Globotriaosyl- and globotetraosyl ceramide were identified as receptors of the toxin of the cabbage moth [18].

Gangliosides. Acidic glycosphingolipids, or sialic acid-containing gangliosides, also function as receptors. Data on receptor gangliosides are summarized in reviews [19-21]. The simplest ganglioside GM3 is a receptor of *Salmonella enterica serovar* on the chicken oviduct surface [11] and of *Theileria sergenti* infecting bovine erythrocytes, and in this case N-glycolyl-GM3 acts as a receptor [22]. However, in the case of *Salmonella enteridis FliC* gangliosides are coreceptors [23]. GM3 also plays an important role in recognition of the swine rotavirus [24]. Often more complicated gangliosides are used as receptors. Thus, neurotoxin of *Clostridium botulinum* binds with nerve endings through gangliosides GD1a and GT1b [25], and complicated gangliosides have been shown to be receptors in presynaptic membranes of animals [26]. Trisialo- and tetrasialogangliosides function as receptors

Abbreviations: Cer) ceramide; Gal) galactose; Glc) glucose; Lac) lactose; S1P) sphingosine-1-phosphate; S1PCh) sphingosine-1-phosphocholine.

of tetanus toxin [27, 28]. Ganglioside GM1 binds cholera toxin [29-31], but an NH_2-group is required for the reception [31]. Staphylococcal toxin is bound by gangliosides mainly containing N-glycolylneuraminic acid [32].

Because gangliosides are receptors of toxins, they were proposed to be used for detecting toxins [33].

Gangliosides are also receptors of viruses. It has been mentioned that GM3 ganglioside is necessary for recognition of the swine rotavirus [24]. The Sendai virus binds with GD1a, GT1b, and GQ1b [34, 35], and complex gangliosides have been shown to be receptors for the SV-40 and mouse polyoma viruses [36, 37]. Gangliosides also serve as receptors for respiratory tract pathogens [38], in particular such gangliosides as GM2 [39] and GM1b [40].

Thus, the data presented indicate that glycosphingolipids (neutral glycosphingolipids, gangliosides) actively contribute to various pathological processes in humans and other animals, and it seems that antibodies to glycosphingolipids are promising for withstanding these processes.

SPHINGOLIPIDS AS LIGANDS OF CELLULAR SIGNALING COMPLEXES

Two extracellular sphingolipids located in plasma lipoproteins, sphingosine-1-phosphate and sphingosine-1-phosphocholine, are ligands of cellular signaling complexes. On the cell surface for each of these sphingolipids there are some receptors coupled with G-proteins, which are responsible for the sphingolipid binding with the cell.

Reception of sphingosine-1-phosphate. Sphingosine-1-phosphate binds with different cells through five specific EDG receptors named after the encoding gene (*Endothelium Differentiation Gene*). The structure of these receptors is considered in detail in [41], and they are often designated by symbols S1P1, S1P2, S1P3, S1P4, and S1P5. Abbreviations EDG-1, EDG-2, etc. are also used for these receptors.

The presence of sphingosine-1-phosphate receptors on the cell surface was first reported in 1998 [42]. Data of subsequent experimental works are considered in reviews [43-52]. On the cell surface, a number of receptors have been detected activation of which results in different biological processes [53]. The difference in activities of sphingosine-1-phosphate receptors is especially pronounced in the case of mobility and migration of the cells [54, 55]. The binding of S1P with S1P1- or S1P3-receptors was shown to stimulate cell migration, whereas the binding with S1P2 inhibited it [56-60]. S1P2 also downregulates cell migration and proliferation induced by platelet-derived growth factor [61]. This receptor also plays an important role in the response of liver to acute poisoning [62]. The S1P2 receptor also influences activity of the vestibular apparatus [63]. The role of sphingosine-1-phosphate receptors is also essential in immunology [64-68], and drug effects on the receptors have been suggested to be a new form of immunotherapy [66]. Receptors of sphingosine-1-phosphate are extremely important for functioning of the vascular, and especially of the cardiovascular system [69]. In this case, S1P1, S1P2, and S1P3 act as major receptors [70-72]. S1P1 and S1P3 enhance proliferation and migration of endothelial and smooth muscle cells of blood vessels, whereas S1P2 inhibits migration of these cells [71]. S1P3 detected in the fraction of high-density lipoproteins contributes to the defense of the heart against ischemia [73]. S1P1 is required for angiogenesis of tumors because it stabilizes blood vessels [74]. Receptors of sphingosine-1-phosphate play a role in the pathobiology of kidney diseases [75, 76] and also modulate Ca^{2+} homeostasis [77, 78]. S1P1 is involved in activation of NO-synthase [79]. Note that sphingosine-1-phosphate receptors can produce dimers with receptors of lysophosphatidic acid [80].

Reception of sphingosine-1-phosphocholine. Receptors of sphingosine-1-phosphocholine (S1PCh) constitute a family of multifunctional receptors (OGR1, GPR4, GPR12, G2A, TDAG8) coupled with G-proteins and sensitive to protons [81]. They are also receptors of psychosine (galactosylsphingosine). These receptors stimulate various intracellular signaling pathways, and are therefore suggested to be involved in many physiological and pathological processes [81]. Some data concerning S1PCh receptors are presented in [82, 83].

The first S1PCh receptor (OGR1) was detected in a malignant tumor of ovary and its binding with the ligand was accompanied by activation of mitogen-activated protein kinase and inhibition of cell proliferation [84]. In the same tumor, another S1PCh receptor (GPR4) was identified and shown to be also a receptor of lysophosphatidylcholine and promote stimulation of proliferation and increase in the level of intracellular Ca^{2+} [85]. Both receptors are proton-sensitive [86]. GPR4 is important for angiogenesis, and interaction of S1PCh with the receptor results in activation of inositol-3 kinase and Akt [87]. Expression of GPR12 in the brain markedly influences differentiation and maturation of neurons [88]. The structure of OGR1 and GPR4 is similar to the proton-sensitive TDAG8 whose ligands are S1PCh and psychosine [89]. G2A-receptor is located on the surface of lymphocytes and is essential for their functioning [90]. It promotes an increase in the amount of intracellular Ca^{2+}, stimulates migration of T-cells, and activates ERK.

The presented data indicate a very important role of sphingolipid receptors in animal cells. On one hand, they are receptors of toxins, viruses, and bacteria (glycosphingolipids) and negatively influence the vital activity of the body. On the other hand, receptors of lysosphingolipids (sphingosine-1-phosphate and sphingosine-1-phosphocholine) are necessary for cell functioning and are involved in various biochemical and physiological processes.

REFERENCES

1. Lingwood, C. A. (1999) *Biochim. Biophys. Acta*, **1455**, 85-103.
2. Smith, D. C., Lord, J. M., Roberts, L. M., and Johannes, L. (2004) *Semin. Cell Dev. Biol.*, **15**, 397-408.
3. Brennan, M. J., Joralmon, R. A., Cisar, J. O., and Sandberg, A. L. (1987) *Infect. Immun.*, **55**, 487-489.
4. Stromberg, N., Deal, C., Nyberg, G., Normark, S., So, M., and Karlsson, K. A. (1988) *Proc. Natl. Acad. Sci. USA*, **85**, 4902-4906.
5. Jimenez-Lucho, V., Ginsburg, V., and Krivan, H. C. (1990) *Infect. Immun.*, **50**, 2085-2090.
6. Halvarsson, M. O., Danielsson, D., Naslund, I., Ljungh, A., Wadstrom, T., and Karlsson, K. A. (1998) *Glycobiology*, **8**, 297-309.
7. Abul-Mith, M., Barnett-Foster, D., and Lingwood, C. A. (2001) *Glycoconj. J.*, **18**, 253-260.
8. Gold, B. D., Huesca, M., Sherman, P. M., and Lingwood, C. A. (1993) *Infect. Immun.*, **61**, 2632-2638.
9. Teneberg, S., Leonardsson, I., Karlsson, H., Jovall, P. A., Angstrom, J., Danielsson, D., Naslund, I., Ljungh, A., Wadstrom, T., and Karlsson, K. A. (2002) *J. Biol. Chem.*, **277**, 19709-19719.
10. Hazlett, L. D., Masinick, S., Barrett, R., and Rosol, K. (1993) *Infect. Immun.*, **61**, 5164-5173.
11. Li, W., Watarai, S., and Kodama, H. (2003) *Vet. Microbiol.*, **93**, 73-78.
12. Griffitts, J. S., Haslam, S. M., Yang, T., Garczynski, S. E., Mulloy, B., Morris H., Cremer, P. S., Dell, A., Adang, M. J., and Aroian, R. V. (2005) *Science*, **307**, 922-925.
13. Falguieres, T., Romer, W., Amessou, M., Afonso, C., Wolf, C., Tabet, J. C., Lamaze, C., and Johannes, L. (2006) *FEBS J.*, **273**, 5205-5218.
14. Keusch, G. T., Jacewicz, M., Acheson, D. W., Donohue-Rolfe, A., Kane, A. V., and McCluer, R. H. (1995) *Infect. Immun.*, **63**, 1138-1141.
15. Gori, A. H., Ahmed, K., Martinez, G., Masaki, H., Watanabe, K., and Nagatake, T. (1999) *Am. J. Trop. Med. Hyg.*, **61**, 473-475.
16. Ahmed, K., Suzuki, Y., Miyamoto, D., and Nagatake, T. (2002) *Med. Microbiol. Immunol.*, **191**, 5-10.
17. Long, D., Berson, J. F., Cook, D. G., and Doms, R. W. (1994) *J. Virol.*, **68**, 5890-5898.
18. Matsushima-Hibiya, Y., Watanabe, M., Hidari, K. I., Miyamoto, D., Suzuki, Y., Kasama, T., Kasama, T., Koyama, K., Sugimura, T., and Wakabayashi, K. (2003) *J. Biol. Chem.*, **278**, 9972-9978.
19. Holmgren, J., Elwing, H., Fredman, P., Strannegard, O., and Svennerholm, L. (1980) *Adv. Exp. Med. Biol.*, **125**, 453-470.
20. Fishman, D. H., Pacuszka, T., and Orlandi, P. A. (1993) *Adv. Lipid Res.*, **25**, 165-187.
21. Suzuki, Y. (1994) *Progr. Lipid Res.*, **33**, 429-457.
22. Watarai, S., Sugimoto, C., Onoe, S., Onuma, M., and Yasuda, T. (1995) *J. Vet. Med. Sci.*, **57**, 17-22.
23. Ogushi, K., Wada, A., Niidoma, T., Okuda, T., Llanes, R., Nakayama, M., Nishi, Y., Kurazono, H., Smith, K. D., Aderem, A., Moss, J., and Hirayama, T. (2004) *J. Biol. Chem.*, **279**, 12213-12219.
24. Rolsma, M. D., Kuhlenschmidt, T. B., Gelberg, H. B., and Kuhlenschidt, M. S. (1998) *J. Virol.*, **72**, 9079-9091.
25. Tsukamoto, K., Konda, T., Mukamoto, M., Takeuchi, K., Ihara, H., Saito, M., and Kozaki, S. (2005) *J. Biol. Chem.*, **280**, 35164-35171.
26. Bullens, R. W., O'Hanlon, G. M., Wagner, E., Molenaar, P. C., Furukawa, K., Furukawa, K., Plomp, J. J., and Willison, H. J. (2002) *J. Neurosci.*, **22**, 6876-6884.
27. Waldon, K. M., Sandberg, K., Rogers, T. B., and Schnaar, R. L. (1988) *J. Biol. Chem.*, **263**, 2055-2063.
28. Williamson, L. C., Bateman, K. E., Clifford, J. C., and Neale, E. A. (1999) *J. Biol. Chem.*, **274**, 25173-25180.
29. Critchley, D. R., Streuli, C. H., Kellie, S., Ansell, S., and Patel, B. (1982) *Biochem. J.*, **204**, 209-219.
30. Spiegel, S. (1985) *Biochemistry*, **24**, 5947-5952.
31. Kanne, B., Schierbeck, B., and Angstrom, J. (1994) *J. Biochem. (Tokyo)*, **126**, 226-234.
32. Kato, I., and Naiki, M. (1976) *Infect. Immun.*, **13**, 289-291.
33. Singh, A. K., Harrison, S. H., and Schoeniger, J. S. (2000) *Analyt. Chem.*, **72**, 6019-6024.
34. Markwell, M. A., Svennerholm, L., and Paulson, J. C. (1981) *Proc. Natl. Acad. Sci. USA*, **78**, 5406-5410.
35. Epand, R. M., Nir, S., Padolin, M., and Flanagan, T. D. (1995) *Biochemistry*, **34**, 1084-1089.
36. Tsai, B., Gilbert, J. M., Stehle, T., Lencer, W., Benjamin, T. L., and Rapoport, T. A. (2003) *EMBO J.*, **22**, 4346-4355.
37. Low, J. A., Magnuson, B., Tsai, B., and Imperiale, M. J. (2006) *J. Virol.*, **80**, 1361-1366.
38. Fakih, M. G., Murphy, T. F., Pattopi, M. A., and Berenson, C. S. (1997) *Infect. Immun.*, **65**, 1695-1700.
39. Ahmed, K., Matsumoto, K., Rikitomi, N., and Nagatake, T. (1996) *FEMS Microbiol. Lett.*, **135**, 305-309.
40. Suzuki, Y., Matsunaga, M., Nagao, Y., Taki, T., Hirabayashi, Y., and Matsumoto, M. (1985) *Vaccine*, **3**, 201-203.
41. Torkhovskaya, T. I., Ipatova, O. M., Zakharova, T. S., Kochetova, M. M., and Khalilov, E. M. (2007) *Biochemistry (Moscow)*, **72**, 125-131.
42. Lee, M. J., van Brocklyn, J. R., Thangada, S., Liu, C. H., Hand, A. R., Menzeleev, R., Spiegel, S., and Hla, T. (1998) *Science*, **279**, 1552-1555.
43. Van Brocklyn, J. R., and Spiegel, S. (2000) *Meth. Enzymol.*, **312**, 401-406.
44. Pyne, S., and Pyne, N. J. (2000) *Biochem. J.*, **349**, 385-402.
45. Spiegel, S. (2000) *Ann. N. Y. Acad. Sci.*, **905**, 54-60.
46. Hla, T., Lee, M. J., Ancellin, N., Paik, J. H., and Kluk, M. J. (2001) *Science*, **294**, 1875-1878.
47. Angel, I., Bar, A., and Haring, R. (2002) *Curr. Opin. Drug Discov. Devel.*, **5**, 728-740.
48. Pyne, S., and Pyne, N. J. (2002) *Biochim. Biophys. Acta*, **1582**, 121-131.
49. Radeff-Huang, J., Seasholt, T. M., Matteo, R. G., and Brown, J. H. (2004) *J. Cell Biochem.*, **92**, 949-966.
50. Ishii, I., Fukushima, N., Ye, X., and Chun, J. (2004) *Annu. Rev. Biochem.*, **73**, 321-354.
51. Young N., and van Brocklyn, J. R. (2006) *Sci. World J.*, **6**, 946-966.
52. Meyer zu Heringdorf, D., and Jacobs, K. H. (2007) *Biochim. Biophys. Acta*, **1768**, 923-940.
53. Taha, T. A., Argraves, K. M., and Obeid, L. M. (2004) *Biochim. Biophys. Acta*, **1682**, 48-55.
54. Spiegel, S., English, D., and Milstien, S. (2002) *Trends Cell Biol.*, **12**, 236-242.

55. Balthasar, S., Samulin, J., Ahlgren, H., Bergelin, N, Lundqvist, M., Toescu, E. C., Eggo, M. C., and Tomquist, K. (2006) *Biochem. J.*, **398**, 547-556.
56. Kimura, T., Watanabe, T., Sato, K., Kon, J., Tamama, K., Kuwabara, A., Kanda, T., Kobayashi, I., Ohta, H., Ui, M., and Okajima, F. (2000) *Biochem. J.*, **348**, 71-76.
57. Hobson, J. P., Rosenfeldt, H. M., Barak, L. S., Olivera, A., Poulton, S., Caron, M. G., Milstien, S., and Spiegel, S. (2001) *Science*, **291**, 1800-1803.
58. Ankawa, K., Takuwa, N., Yamaguchi, H., Sugimoto, N., Kitayama, J., Nagawa, H., Takehara, K., and Takuwa, Y. (2003) *J. Biol. Chem.*, **278**, 32841-32851.
59. Yamaguchi, H., Kitayama, J., Takuwa, N., Arikawa, K., Inoki, I., Takehara, K., Nagawa, H., and Takuwa, Y. (2003) *Biochem. J.*, **374**, 715-722.
60. Shimizu, T., Nakazawa, T., Cho, A., Dastvan, F., Shilling, D., Daum, G., and Reidy, M. A. (2007) *Circ. Res.*, **101**, 995-1000.
61. Goparaju, S. K., Jolly, P. S., Watterson, K. R., Bektas, M., Alvarez, S., Sarkar, S., Mel, L., Ishii, I., Chun, J., Milstien, S., and Spiegel, S. (2005) *Mol. Cell Biol.*, **25**, 4237-4249.
62. Serriere-Linneau, V., Teixeira-Clerc, F., Li, L., Schippers, M., de Wries, W., Julien, B., Tran-Van-Nhieu, J., Manin, S., Poelstra, K., Chun, J., Carpentier, S., Levade, T., Miallat, A., and Lotersztain, S. (2007) *FASEB J.*, **21**, 2005-2013.
63. Herr, D. R., Grillet, N., Schwander, M., Rivera, R., Muller, U., and Chun, J. (2007) *J. Neurosci.*, **27**, 1474-1478.
64. Von Wenckstern, H., Zimmermann, K., and Kleuser, B. (2006) *Arch. Immunol. Ther. Exp.*, **54**, 239-251.
65. Maghazachi, A. A. (2003) *J. Leukoc. Biol.*, **74**, 16-24.
66. Goetzl, E. J., and Rosen, H. (2004) *J. Clin. Invest.*, **114**, 1531-1537.
67. Chun, J., and Rosen, H. (2006) *Curr. Pharm. Des.*, **12**, 161-171.
68. Keller, C. D., Rivera, Gil, P., Tolle, M., van der Giet, M., Chun, J., Radeke, H. H., Schafer-Korting, M., and Kleuser, B. (2007) *Am. J. Pathol.*, **170**, 281-290.
69. Brinkmann, V., and Baumruker, T. (2006) *Curr. Opin. Pharmacol.*, **6**, 244-250.
70. Wendler, C. C., and Rivkees, S. A. (2006) *Dev. Biol.*, **291**, 264-277.
71. Waeber, C., Blondean, N., and Salomone, S. (2004) *Drug News Perspect.*, **17**, 365-382.
72. Peters, S. L., and Alewijnse. A. E. (2007) *Curr. Opin. Pharmacol.*, **7**, 186-192.
73. Theilmeier, G., Schmidt, C., Herrmann, J., Keul, P., Schafers, M., Herrgott, I., Mersmann, J., Larmann, J., Herrman, S., Stypmann, J., Schober, O., Hildebrand, R., Schulz, R., Heusch, G., Haude, M., von Wnuck Lipinski, K., Herzog, C., Schmitz, M., Erbel, R., Chun, J., and Levkau, B. (2006) *Circulation*, **114**, 1403-1409.
74. Chae, S. S., Paik, J. H., Furneaux, H., and Hla, T. (2004) *J. Clin. Invest.*, **114**, 1082-1089.
75. Bischoff, A., Meyer zu Heringdorf, D., Jacobs, K. H., and Michel, M. C. (2001) *Br. J. Pharmacol.*, **132**, 1925-1933.
76. Kamanna, V. S., Bassa, B. V., Ganji, S. H., and Roh, D. D. (2005) *Histol. Histophatol.*, **20**, 603-613.
77. Sato, K., Kon, J., Tomura, H., Osada, M., Murata, N., Kawabara, A., Watanabe, T., Ohta, H., Ui, M., and Okajima, F. (1999) *FEBS Lett.*, **443**, 25-30.
78. Rappizi, E., Donati, C., Cencetti, E., Pinton, P., Rizzuto, R., and Bruni, P. (2007) *Biochem. Biophys. Res. Commun.*, **353**, 268-274.
79. Igarashi, J., Miyoshi, M., Hashimoto, T., Kubota, Y., and Kosaka, H. (2007) *Br. J. Pharmacol.*, **150**, 470-479.
80. Zaslavsky, A., Singh, L. S., Tan, H., Ding, H., Liang, Z., and Xu, Y. (2006) *Biochim. Biophys. Acta*, **1761**, 1200-1212.
81. Tomura, H., Mogi, C., Sato, K., and Okajima, F. (2005) *Cell Signal.*, **17**, 1466-1476.
82. Xu, Y. (2002) *Biochim. Biophys. Acta*, **1582**, 81-86.
83. Kostenis, E. (2004) *J. Cell Biochem.*, **92**, 923-936.
84. Xu, Y., Zhu, K., Hong, G. Y., Wu, W. H., Baudhuin, L. M., Xiao, Y. J., and Damron, D. S. (2000) *Nat. Cell Biol.*, **2**, 261-267.
85. Zhu, K., Baudhuin, L. M., Hong, G., Williams, F. S., Cristina, K. L., Kabarovski, J. H., Witte, O. N., and Xu, Y. (2001) *J. Biol. Chem.*, **276**, 41325-41335.
86. Ludwig, M. G., Vanek, M., Guerini, D., Gasser, J. A., Jones, C. E., Junker, U., Hofstetter, H., Wolf, R. M., and Seuwen, K. (2003) *Nature*, **425**, 93-98.
87. Kim, K. S., Ren, J., Jiang, Y., Ebrahem, Q., Tipps, R., Cristina, K., Xiao, Y. J., Qiao, J., Taylor, K. L., Lum, H., Anand-Apte, B., and Xu, Y. (2005) *FASEB J.*, **19**, 819-821.
88. Ignatov, A., Lintzel, J., Hermans-Borgmeyer, I., Kreienkamp, H. J., Joost, P., Thomsen, S., Methner, A., and Schaller, H. C. (2003) *J. Neurosci.*, **23**, 907-914.
89. Wang, J. Q., Kon, J., Mogi, C., Tobo, M., Damirin, A., Sato, K., Komachi, M., Malchnkhuu, E., Murata, N., Kimura, T., Kuwabara, A., Wakamatsu, K., Koizumi, H., Uede, T., Tsujimoto, G., Kurose, H., Sato, T., Harada, A., Misawa, N., Tomura, H., and Okajima, F. (2004) *J. Biol. Chem.*, **279**, 45626-45633.
90. Kabarowski, F. G., Zhu, K., Le, L. Q., Witte, O. N., and Xu, Y. (2001) *Science*, **293**, 702-705.