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The Evolutionary Emmergence Of N-Acetylneuraminic Acid (Sialic Acid)-Containing Glycosphingolipids From Deuterosome Echinodermata Starfish

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Abbreviations: NeuAc: N-acetylneuraminic Acid; NeuGc: N-glycolylneuraminic Acid; GalNAc: N-Acetylgalactosamine; Gal: Galactose; Glc: Glucose

Sialic acid-containing glycosphingolipids, gangliosides are characterized by the core sugar structures and ubiquitous in mammals with anionic N-acetylneuraminic acid (NeuAC) or sialic acid in glycan to a ceramide. On the outer leaflet of the plasma membrane, they are working as cellular communicators [1,2]. The occurrence of the gangliosides is initially started from the phylum deuterosome Echinodermata such as starfish [3] and sea urchin [4,5], as the sialic acids appeared late in evolution, and only in vertebrates and higher invertebrates. During the past half-century, over 40 gangliosides have been isolated from marine echinodermata phylum. This old type or ancient type structures of starfish gangliosides has the lactose in the sugar part and specifically carrying 2 different types of termial sugars: 1) sialic acids of NeuAc and N-glycolylneuraminic acid (NeuGc) and 2) N-acetylgalactosamine (GalNAc) bound to the carbon No 3 of galactose (Gal)-glucose (Glc) of lactose [6]. In literature, the gangliosides as functionally bioactive biomolecules have been reported in the echinoderm starfishes such as *Asterina pectinifera* [7,8] and *Asterias orbesi* [9]. Unlikely to higher vertebrates, the lipid-based polar phase contained the structurally unique gangliosides. For the modified class of NeuAc, the NeuGc-based gangliosides have also been found from the starfish [10]. The presend editorial has been focused on diverse evolutionay origins in the lower animal Echinodermata of the sialic acids derivatives and mimetics.

Evolutionally Occurrence of Methyl Sialic Acids Started from Deuterosome Echinoderms is the Biological Adaptation Process

The O-acetyl and methyl sialic acids are found in the deuterosome starfish as components of gangliosides with esterifying, de-esterifying and methyltransferase enzymes [11,12]. The structurally unique 8-O-methyl sialic acids are at first found, indicating that the echinoderm phylum is specific for the methylation, although the trace levels are found in higher animals [13]. However, N-acetyl hydroxylation and *O*-acetylation of sialic acids are generally conserved both in echinoderms and higher animals [14]. Threfore, it can be speculated that evolutionary on/off mechanism(s) involves this differential modification of sialic acids between lower echinoderms and higher animals. Therefore, the different midification types allow the acquisition of the protective adaptation against the pathogenic exosialidase actions. *O*-methyl sialic acids are resistant to environmental or phathogenic sialidases. 8-O-methyl sialic acids are also reported as the stop signal for glycan elongation in echinoderm by Schauer *et al.* [13]. It is, therefore, proposed that the sialidase-resistant gangliosides or sialyl glycoconjugates can keep their biological functions of starfish from the environmental invasion or attacks.

Unique Gangliosides from the Chloroform/Methanol (C/M) Polar Lipid Phase in Deuterosome Echinoderms

GM3-type ganglioside

Recently, monomethyl and monosialyl GM_3-type gangliosides have been isolated from the polar lipid phase of the C/M extracts of the starfish *Luidia maculate* [15]. The ceramide moieties have also their unique chemical structures, comprising of unsubstituted fatty acid, 2-hydroxy fatty acid, sphingosine and phytosphingosine chains [15].

GD3-type Ganglioside with neurite forming capacity

From *L. maculata*, disialyl GD3-type ganglioside (originally named LMG) was also purified using the polar lipid phase. Interestingly, the GD3-type has the neuritogenic activity, increasing the neurite formation of the rat heochromocytoma PC12 cells in the condition of nerve growth factor (NGF) [15]. Similarly from the feather star *Comanthus japonica*, the trisialo inositolphosphoceramide-type ganglioside (originally named CJP) showed the neurite forming-neuritogenic activity in the PC12 cells with NGF [16]. Another ganglioside LLG isolated from the water soluble lipid fraction of the starfish *Linckia laevigata* and *A. pectinifera*, has the neurite forming-neuritogenic activity [17,18]. The neurite forming activity as measured by cell numbers having the neurites longer than the diameter of the cell body was higher than the NGF control. The level is much higher than that of brain GM1. Another glycosyl inositolphosphoceramide-type ganglioside (originally named CSP) of the *Comanthina schlegeli* has the 9-O-methyl-(N-acetyl-α-D-neuraminosyl)-(2-3)-inositolphosphoceramide as the monosialyl type with the neurite forming activity [19]. Since these gangliosides exhibited potent neurite forming capacity for the neurite-axon plasticity in the neuron-like rat adrenal pheochromocytoma PC-12 cells [6,20], the initial type gangliosides are attracting for the neuronal renegeration in central neuronal system and peripheral neuronal system [16].

Hematoside-type and GM4-type gangliosides

A hematoside-type ganglioside (originally LLG1), *O*-[N-glycolyl-α-D-neuraminosyl-(2-3)-β-D-galactopyranosyl-(1-4)-β-D-glucopyranosyl]-ceramide was purified from the polar lipid phase of *Linckia laevigata* [21].

GM4-type ganglioside was, for the first time, identified from the pyloric caeca of the Okinawan starfish *Protoreaster nodosus*.

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The structures have O-[8-O-methyl-N-acetyl-α-neuraminosyl-2,3β-Gal]-R, 1-*O*-[β-Gal-1,3α-Gal-1,4-8-*O*-methyl-N-acetyl-α-neuraminosyl-2,3β-Gal]-R, and 1-*O*-[β-Gal-1,3αGal-1,9N-acetyl-α-neuraminosyl-2,3βGal]-R [22]. Historically, it was reported in 1964 that GM4 exists in human brain as a minor form [23] and the human myelin has abundantly GM4 [24]. GM4 specifically interact with myelin protein and protect neuraminidase digestion of gangliosides [25]. Therefore, GM4 is a ganglio-specifc biomarker for human myelin and oligodendroglial perikarya [26]. In human brain myelin, GM4 suppresses the immune reaction through tetanus toxoid-provoked cytotoxic CD8 specific T-cells response [27,28]. Recently, it was known that GM4 is found in various animals including chicken thymus, chicken embryonic liver, rat kidney, shark liver, and red sea bream intestine [29-33]. GM4 isolated from lower animals of bony fish and frog liver is regarded as lower animal-specific ganglioside [34], even though the reason why GM4 is specific in invertebrates remains unknown.

Therapuetic gangliosides and GM3-like mimetic

The gangliosides regulate cell functions in the tumor microenvironments [35]. GM3 modulates the function of several receptors for the insulin-like growth factor-1, basic fibroblast growth factor, epidermal growth factor, platelet-derived growth factor, vascular endothelial growth factor (VEGF), and cell adhesion molecules including the integrins [35,36]. GM3 inhibits VEGF-stimulated VEGF receptor activation in vascular endothelial cells [35] through blocking its dimerization and binding through interaction with the extracellular domain. For the mechanistic hypothesis, the conformational and stereo-selectivity of the GM3 structure with α2-3 Sia-lactosylceramide is raised during interaction with its cell membrane receptors. It can incubate several theapeutic technologies that GM3-modified mimetics might have therapeutic potential against human diseases including eye disease, obesity and autoimmune diseases, leukemia and cancers [37-40].

References

1. Kim CH (2013) Controversial sialoglycosphingolipids Functions in tumor biology. J. Glycobiology 2: 107.
2. Kim CH (2014) Sialic Acid (N-acetylneuraminic acid) as the functional molecule for differentiation between animal and plant kingdom. J Glycomics Lipidomics 4: e116
3. Zhukova IG, Bogdanovskaia TA, Smirnova GP, Chekareva NV, Kochetkov NK (1973) [Structure of sialoglycolipid from the digestive gland of the starfish Distolasterias nipon]. Dokl Akad Nauk SSSR 208: 981-984.
4. Hoshi M, Nagai Y (1975) Novel sialosphingolipids from spermatozoa of the sea urchin Anthocidaris crassispina. Biochim Biophys Acta 388: 152-162.
5. Kochetkov NK, Zhukova IG, Smirnova P, Glukhoded IS (1973) Isolation and characterization of a sialoglycolipid from the sea urchin Strongylocentrotus intermedius. Biochim Biophys Acta 326: 74-83.
6. Higuchi R, Inagaki M, Yamada K, Miyamoto T (2007) Biologically active gangliosides from echinoderms. J Nat Med 61: 367-370.
7. Sugita M, Hori T (1976) New types of gangliosides in starfish with sialic acid residues in the inner part of their carbohydrate chains. J Biochem 80: 637-640.
8. Sugita M (1979) Studies on the glycosphingolipids of the starfish, Asterina pectinifera. II. Isolation and characterization of a novel ganglioside with an internal sialic acid residue. J Biochem 86: 289-300.
9. Warren L (1964) N-Glycolyl-8-O-Methylneuraminic Acid, A New Form of Sialic Acid in the Starfish Asterias Forbesi. Biochim Biophys Acta 83: 129-132.
10. Smirnova GP, Kochetkov NK, Sadovskaya VL (1987) Gangliosides of the starfish Aphelasterias japonica, evidence for a new linkage between two N-glycolylneuraminic acid residues through the hydroxy group of the glycolic acid residue. Biochim Biophys Acta 920: 47-55.
11. Hayes BK, Varki A (1989) O-acetylation and de-O-acetylation of sialic acids. Sialic acid esterases of diverse evolutionary origins have serine active sites and essential arginine residues. J Biol Chem 264: 19443-19448.
12. Kelm A, Shaw L, Schauer R, Reuter G (1998) The biosynthesis of 8-O-methylated sialic acids in the starfish Asterias rubens--isolation and characterisation of S-adenosyl-L-methionine:sialate-8-O-methyltransferase. Eur J Biochem 251: 874-884.
13. Kelm A, Shaw L, Schauer R, Reuter G (1998) The biosynthesis of 8-O-methylated sialic acids in the starfish Asterias rubens--isolation and characterisation of S-adenosyl-L-methionine:sialate-8-O-methyltransferase. Eur J Biochem 251: 874-884.
14. Schauer R (1991) Biosynthesis and function of N- and O-substituted sialic acids. Glycobiology 1: 449-452.
15. Kawatake S, Inagaki M, Isobe R, Miyamoto T, Higuchi R (2002) Isolation and structure of monomethylated GM3-type ganglioside molecular species from the starfish Luidia maculata. Chem Pharm Bull (Tokyo) 50: 1386-1389.
16. Arao K, Inagaki M, Miyamoto T, Higuchi R (2004) Constituents of Crinoidea. 3. Isolation and structure of a glycosyl inositolphosphoceramide-type ganglioside with neuritogenic activity from the feather star Comanthus japonica. Chem Pharm Bull (Tokyo) 52: 1140-1142.
17. Inagaki M, Miyamoto T, Isobe R, Higuchi R (2005) Biologically active glycosides from asteroidea, 43. Isolation and structure of a new neuritogenic-active ganglioside molecular species from the starfish Linckia laevigata. Chem Pharm Bull (Tokyo) 53: 1551-1554.
18. Higuchi R, Inoue S, Inagaki K, Sakai M, Miyamoto T, et al. (2006) Biologically active glycosides from asteroidea, 42. Isolation and structure of a new biologically active ganglioside molecular species from the starfish Asterina pectinifera. Chem Pharm Bull (Tokyo) 54: 287-291.
19. Inagaki M, Shiizaki M, Hiwatashi T, Miyamoto T, Higuchi R (2007) Constituents of Crinoidea. 5. Isolation and structure of a new glycosyl inositolphosphoceramide-type ganglioside from the feather star Comanthina schlegeli. Chem Pharm Bull (Tokyo) 55: 1649-1651.
20. Kaneko M, Yamada K, Miyamoto T, Inagaki M, Higuchi R (2007) Neuritogenic activity of gangliosides from echinoderms and their structure-activity relationship. Chem Pharm Bull (Tokyo) 55: 462-463.
21. Inagaki M, Saito T, Miyamoto T, Higuchi R (2009) Isolation and structure of hematoside-type ganglioside from the starfish Linckia laevigata. Chem Pharm Bull (Tokyo) 57: 204-206.
22. Pan K, Tanaka C, Inagaki M, Higuchi R, Miyamoto T (2012) Isolation and structure elucidation of GM4-type gangliosides from the Okinawan starfish Protoreaster nodosus. Mar Drugs 10: 2467-2480.
23. Kuhn R, Wiegandt H (1964) Weitere Ganglioside Aus Menschenhirn. Z Naturforsch 19: 256-257.
24. Ledeen RW, Yu RK, Eng LF (1973) Gangliosides of human myelin: sialosylgalactosylceramide (G7) as a major component. J Neurochem 21: 829-839.
25. Yohe HC, Jacobson RI, Yu RK (1983) Ganglioside-basic protein interaction: protection of gangliosides against neuraminidase action. J Neurosci Res 9: 401-412.
26. Yu RK, Iqbal K (1979) Sialosylgalactosyl ceramide as a specific marker for human myelin and oligodendroglial perikarya: gangliosides of human myelin, oligodendroglia and neurons. J Neurochem 32: 293-300.
27. Ladisch S, Becker H, Ulsh L (1992) Immunosuppression by human gangliosides: I. Relationship of carbohydrate structure to the inhibition of T cell responses. Biochim Biophys Acta 1125: 180-188.
28. Ladisch S, Hasegawa A, Li R, Kiso M (1995) Immunosuppressive activity of chemically synthesized gangliosides. Biochemistry 34: 1197-1202.
29. Narasimhan R, Murray RK (1978) Comparative study of the glycosphingolipids of chicken bursa of Fabricius and of chicken, rat and human thymus. Biochem J 173: 475-482.
30. Saito M, Rosenberg A (1982) Sialosylgalactosylceramide (GM4) is a major ganglioside in chicken embryonic liver. J Lipid Res 23: 9-13.

31. Saito M, Sugiyama K (2001) Gangliosides in rat kidney: composition, distribution, and developmental changes. Arch Biochem Biophys 386: 11-16.

32. Li YT, Sugiyama E, Ariga T, Nakayama J, Hayama M, et al. (2002) Association of GM4 ganglioside with the membrane surrounding lipid droplets in shark liver. J Lipid Res 43: 1019-1025.

33. Chisada S, Horibata Y, Hama Y, Inagaki M, Furuya N, et al. (2005) The glycosphingolipid receptor for Vibrio trachuri in the red sea bream intestine is a GM4 ganglioside which contains 2-hydroxy fatty acids. Biochem Biophys Res Commun 333: 367-373.

34. Saito M, Kitamura H, Sugiyama K (2001) Liver gangliosides of various animals ranging from fish to mammalian species. Comp Biochem Physiol B Biochem Mol Biol 129: 747-758.

35. Chung TW, Kim SJ, Choi HJ, Kim KJ, Kim MJ, et al. (2009) Ganglioside GM3 inhibits VEGF/VEGFR-2-mediated angiogenesis: direct interaction of GM3 with VEGFR-2. Glycobiology 19: 229-239.

36. Choi HJ, Chung TW, Kang SK, Lee YC, Ko JH, et al. (2006) Ganglioside GM3 modulates tumor suppressor PTEN-mediated cell cycle progression--transcriptional induction of p21(WAF1) and p27(kip1) by inhibition of PI-3K/AKT pathway. Glycobiology 16: 573-583.

37. Kelly MS (2005) Echinoderms: their culture and bioactive compounds. Prog Mol Subcell Biol 39: 139-165.

38. Jin UH, Chung TW, Song KH, Kwak CH, Choi HJ, et al. (2014) Ganglioside GM3 is required for caffeic acid phenethyl ester-induced megakaryocytic differentiation of human chronic myelogenous leukemia K562 cells. Biochem Cell Biol 92: 243-249.

39. Chung TW, Choi HJ, Kim SJ, Kwak CH, Song KH, et al. (2014) The ganglioside GM3 is associated with cisplatin-induced apoptosis in human colon cancer cells. PLoS One 9: e92786.

40. Kim SJ, Chung TW, Choi HJ, Jin UH, Ha KT, et al. (2014) Monosialic ganglioside GM3 specifically suppresses the monocyte adhesion to endothelial cells for inflammation. Int J Biochem Cell Biol 46: 32-38.