Synthetic gangliosides and analogs : Versatile probes to elucidate the cell functions of sialoglycans

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Profile

Makoto Kiso was born in Kyoto in 1947, and received his B.Sc. (1970) and Ph.D. (1975) degrees in Agricultural Chemistry from Kyoto University. He then joined the group of Professor Akira Hasegawa at Gifu University. After working as a research fellow (1977-78) at University of Wisconsin, Madison (Prof. Laurens Anderson), he was promoted to associate professor in 1979, and professor in 1990. He is a recipient of Japan Society for Bioscience, Biotechnology and Agrochemistry (JSBBA) Award for the Encouragement of Young Scientists (1983), JSBBA Award (2002), and Gifu Newspaper Grand Award (2007), being one of the ISI Highly Cited Researchers since 2001. He is also working as satellite PI of the WPI program-Institute of Integrated Cell-Material Sciences (WPI-iCeMS), Kyoto University since 2007. His research interests include the chemical synthesis of biofunctional carbohydrates, especially sialoglycans and sialoglycoconjugates such as gangliosides, focusing on their cell functions and applications in medicinal chemistry and cell biology.

Sialic acid-containing oligosaccharides (sialoglycans) carry a variety of cell functions as the components of terminating branches of *N*-/*O*-glycans and glycosphingolipids (gangliosides). Since 1988 [1], we have developed [2)-4)] efficient methods for systematically synthesizing sialoglycans and gangliosides, involving their analogs and derivatives, over 800 species (GSC series), which have widely been utilized for glycobiology researches by many collaborations in and out of the country.

Among the lacto- and neolacto-series gangliosides (Figure 1. Lower column), sialyl lacto-/neolacto-tetraosylceramides (SPGs) were highly effective for analyzing the receptor-binding specificity of influenza virus (J. Virol., 74, 11825, 2000; Nature, 444, 378, 2006; Nature Biotechnol., 27, 797, 2009; J. Virol., 84, 12069, 2010). Since 1990, the selectin ligands: sialyl Lewis X (sLe^x), sialyl 6-sulfo Lewis X (6-sulfo sLe^x), and related gangliosides have played important roles not only for basic researches on lymphocyte homing, inflammation, and cancer metastasis, but also for various applications in medicinal chemistry [5)] and cell biology. (PNAS, 88, 10372, 1991; J. Cell Biol., 117, 895, 1992; Glycobiology, 3, 633, 1993; BBRC, 240, 748, 1997; JBC, 273, 11225, 1998; Angew. Chem. Int. Ed., 38, 1131, 1999; Blood, 107, 3197, 2006 etc.).

It has been found that sialyl Lewis a (sLe^a), a ligand for E-selectin, and disialyl Lewis a ($DsLe^a$) are associated with human colon cancers (Cancer Res., 64, 4498, 2004), and the $DsLe^a$ structure in colon cancer cell is produced only from disialyl lactotetraosyl ceramide (DSLc4), which is a high affinity ligand for siglec-7 (JBC, 278, 22787, 2003; Biochem. J., 397, 271, 2006).

Among the ganglio-series gangliosides (Fig.1 Upper column), GT1b has successfully been utilized for elucidating the binding mechanism of siglec-7 (JBC, 281, 32774, 2006), bacterial toxins (JBC, 276, 32274, 2001; PLoS Pathogens, 4, 1, 2008) and viral infections (PLoS Pathogens, 8, e1002738, 2012) by X-ray crystallography. The α-series gangliosides GD1α, GT1aα, and GQ1bα have been studied as high affinity ligands for myelin-associated glycoprotein (MAG, siglec-4) [6)].

GM3 and GM1, which is well known as the receptor of cholera toxin, have been suggested to serve as coordinators of multiple receptor functions in the membrane system. We have recently developed a variety of fluorescent GM3 and GM1 gangliosides, in which a fluorescent group is linked to the nonreducing end of the glycans, to search the functional roles of gangliosides in the membrane microdomain called raft.

By conducting comprehensive syntheses and intensive screening of diverse sialic acid derivatives, we have developed several sialoglycans which function as high affinity ligands for CD22 (siglec-2) (JMC, 51, 6665, 2008; Tetrahedron Lett., 50, 4488, 2009; Bioorg. Med. Chem., 19, 1966, 2011; Current Med. Chem., 18, 3537, 2011). Very recently, nanomolar CD22 ligands were discovered from a library of MAG antagonists [7)]. A set of C9 *N*-acyl Neu5Ac2en mimetics were also evaluated as viral sialidase selective inhibitors (Int. J. Med. Chem., 2011).

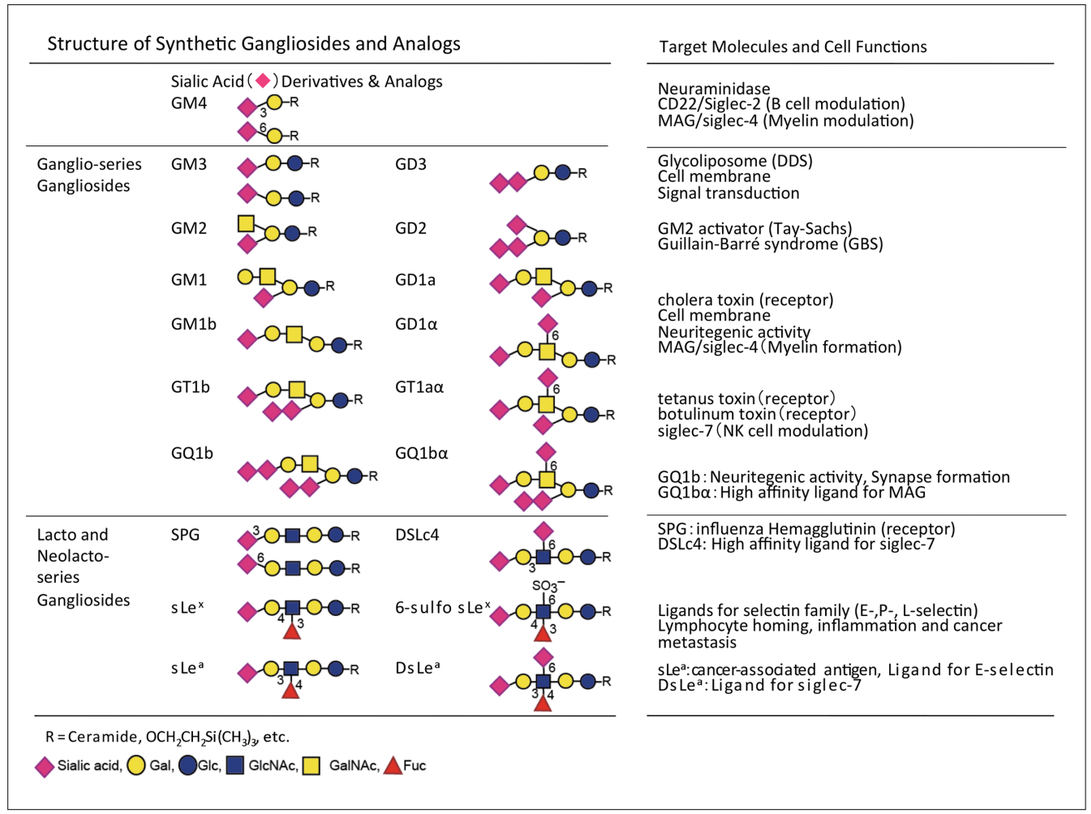

Figure 1. Typical Synthetic Gangliosides and Analogs

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