06 ABSTRACT

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Life without Gangliosides

profile

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Dr. Richard L. Proia received a B.A. degree from Bates College in Lewiston, Maine in 1976. From 1976-1980 he performed his graduate studies at the University of Texas Southwestern Medical Center in Dallas, Texas where he was awarded a Ph.D. in Immunology. He did post-doctoral work with Dr. Elizabeth Neufeld at National Institutes of Health from 1981-1983. He eventually earned tenure and is now the Chief of the Development and Disease Branch, National Institute of Diabetes and Digestive and Kidney Diseases.

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Gangliosides — a subfamily of the larger group of glycosphingolipids (GSLs) — are composed of a ceramide anchor attached to an oligosaccharide chain of variable complexity. They are distinguished by the presence of one or more sialic acid residues [1]. The abundance and diversity of gangliosides is greatest in the nervous system. However, these lipids are found on all mammalian cell plasma membranes where they are concentrated within microdomains — rafts and caveolae — specialized for cell signaling. Gangliosides have been implicated as playing roles in fundamental cell processes such as growth, differentiation and adhesion [2].

Targeted disruption of genes in the biosynthesis pathway for gangliosides in mice has yielded new insight into their function (Figure 1). We have disrupted the gene encoding glucosylceramide synthase (UDP-glucose:ceramide glucosyltransferase), the enzyme required for the synthesis of all glucose-based GSLs [3]. Glucosylceramide synthase knockout (KO) mice died during mid-gastrulation with massive apoptosis within the ectoderm. Furthermore, embryonic stem cells completely deficient in glucosylceramide synthase activity lacked the ability to form mature, well-differentiated tissues. These results indicated that GSL synthesis is fundamentally important for early development and differentiation.

Mice with a disrupted GalNAcT (GM2 synthase/ UDP-GalNAc:lactosylceramide/GM3/GD3 β-1,4-N-acetylgalactosaminyltransferase) gene were unable to synthesize complex gangliosides [4, 5]. These mice were viable, although the males were infertile. They exhibited neurologic abnormalities including impaired nerve conductance, Wallerian degeneration and age-related motor function defects [6, 7]. A disturbance of the interaction of complex gangliosides with myelin-associated glycoprotein (MAG) may be responsible for some of these defects.

Disruption of the GD3 synthase(CMP-sialic acid:GM3 α-2,8-sialyltransferase) gene produced mice without b-series gangliosides. These mice were viable and without apparent major neurologic abnormalities [8, 9]. However, these mice did exhibit impaired regeneration of the hypoglossal nerve after lessioning [9].

Interestingly, the GalNAcT and GD3 synthase double KO mice — expressing only GM3 ganglioside — demonstrated an adult lethal phenotype and exquisite sensitivity to audiogenic seizures [8]. This very severe phenotype of the double KO mice illustrates that gangliosides are essential for central nervous system function.

Collectively the results from mice lacking gangliosides demonstrate the fundamental importance of these lipids in a variety of biological processes. Research is now focused on how their functions might impact important diseases such as cancer and diabetes.

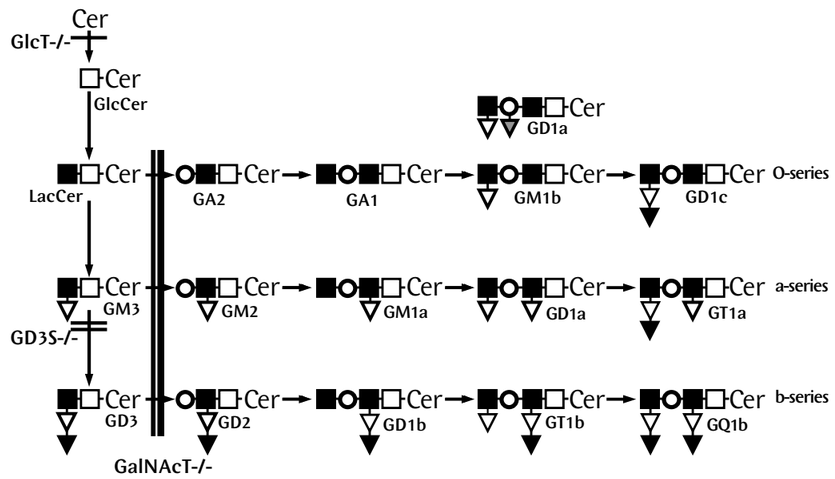

Figure 1. Biosynthetic pathway of gangliosides.
Shown are the steps blocked in mouse KOs of individual glycosyltransferase genes. GlctT: gene encoding glucosylceramide synthase; GalNAcT: gene encoding GM2 synthase. GD3S: gene encoding GD3 synthase.

Figure 2. GD3 synthase expression in embryonic mice.

References

1) Kolter T, Proia RL, Sandhoff K: Combi-natorial Ganglioside Biosynthesis Minireview. *J. Biol. Chem*, **277**:25859-25862, 2002
2) Hakomori S: Traveling for the glyco-sphingolipid path. *Glycoconj. J.* **17**:627-647, 2000
3) Yamashita T, Wada R, Sasaki T, Deng C, Bierfreund U, Sandhoff K, Proia RL: A vital role for glycosphingolipid synthesis during development and differentiation. *Proc. Natl. Acad. Sci .USA* **96**:9142-9147., 1999
4) Takamiya K, Yamamoto A, Furukawa K, Yamashiro S, Shin M, Okada M, Fukumoto S, Haraguchi M, Takeda N, Fujimura K, Sakae M, Kishikawa M, Shiku H, Aizawa S: Mice with disrupted GM2/GD2 synthase gene lack complex gangliosides but exhibit only subtle defects in their nervous system. *Proc. Natl. Acad. Sci. USA* **93**:10662-10667., 1996
5) Liu Y, Wada R, Kawai H, Sango K, Deng C, Tai T, McDonald MP, Araujo K, Crawley JN, Bierfreund U, Sandhoff K, Suzuki K, Proia RL: A genetic model of substrate deprivation therapy for a glycosphingolipid storage disorder. *J .Clin. Invest* **103**:497-505, 1999
6) Sheikh KA, Sun J, Liu Y, Kawai H, Craw-ford TO, Proia RL, Griffin JW, Schnaar RL: Mice lacking complex gangliosides develop Wallerian degeneration and myelination defects. *Proc Natl. Acad. Sci. USA* **96**:7532-7537., 1999
7) Chiavegatto S, Sun J, Nelson RJ, Schnaar RL: A functional role for complex gangliosides: motor deficits in GM2/GD2 synthase knockout mice. *Exp. Neurol.* **166**:227-234., 2000
8) Kawai H, Allende ML, Wada R, Kono M, Sango K, Deng C, Miyakawa T, Crawley JN, Werth N, Bierfreund U, Sandhoff K, Proia RL: Mice expressing only monosialoganglioside GM3 exhibit lethal audiogenic seizures. *J. Biol. Chem.* **276**:6885-6888., 2001
9) Okada M, Itoh Mi M, Haraguchi M, Okajima T, Inoue M, Oishi H, Matsuda Y, Iwamoto T, Kawano T, Fukumoto S, Miyazaki H, Furukawa K, Aizawa S:b-series Ganglioside deficiency exhibits no definite changes in the neurogenesis and the sensitivity to Fas-mediated apoptosis but impairs regeneration of the lesioned hypoglossal nerve. *J. Biol. Chem.* **277**:1633-1636., 2002