Gangliosides: Synthesis and Function in Nervous Tissues

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Abstract

Gangliosides, sialic acid-containing glycosphingolipids, have been considered to be involved in the development and functions of the nervous system. Recent progress in the genetic analysis of gangliosides in cultured cells and experimental animals revealed their roles in the maintenance of integrity of nervous tissues and neuroregeneration. The fact that ganglioside-deficient mice exhibited milder abnormalities than expected suggests that compensatory actions of remaining glycolipids might be present, and complex knockout of multiple glycosyltransferase genes might be useful to clarify essential roles of gangliosides.

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Introduction

Since are highly expressed in nervous tissues, they have been considered to be involved in the development and function of the central (CNS) and peripheral nerves (Yu et al. 2012). A number of cell biology (Schengrund 1990) and molecular biology studies (Furukawa et al. 2004) have been performed to investigate the roles of gangliosides in nervous tissues, and virtually it has been concluded that gangliosides are essential for the maintenance and regeneration of neural cells and nervous tissues (Furukawa et al. 2007). Consequently, ganglioside deficiency induced neuroinflammation and subsequent (Ohmi et al. 2009) as demonstrated in the analysis of various ganglioside-deficient mutant mice (Ohmi et al. 2011). In this chapter, synthesis of gangliosides and their implication in the nervous tissues with focus on their roles in the membrane microdomains were summarized.

Ganglioside Synthetic Enzymes (Genes)

Glucosylceramide (GlcCer), which is synthesized by the conjugation of glucose to ceramides, is an essential structure from which almost all glycosphingolipids are synthesized (Fig. 1). Among four major series of glycolipids, gangliosides are synthesized mainly via the synthesis of GM3 from LacCer. Namely, GM3 synthase (ST3SIA5) is an essential enzyme for the synthesis of ganglio-series gangliosides. However, GM2/GD2 synthase (B4GALNT1) is also important to generate asialo-series gangliosides, starting from the synthesis of GA2 (asialo-GM2) from LacCer (Yamashiro et al. 1995). In addition to ST3SIA5 and B4GALNT1, GD3 synthase (ST8SIA1) (Haraguchi et al. 1994) and GM1/GD1b/GA1 synthase (B4GALT4) are also critical for the synthesis of complex gangliosides. Furthermore, a-series gangliosides with alpha2-6-sialylated GalNAc structures are present even in human bodies, while their functions have not yet been well understood. The responsible enzymes (genes) are ST6GALNAC5 and ST6GALNAC6. In particular, the latter one is also involved in globo-series disialyl gangliosides and lacto-series disialyl gangliosides. Fundamental features of these enzymes are essentially the same as reported previously (Lloyd and Furukawa 1997; Furukawa and Furukawa 2008).

Abnormal Phenotypes of Ganglioside-Deficient Mice

Majority of gene-disrupted mutant mice of s involved in the synthesis of gangliosides showed neurodegeneration and/or poor neuroregeneration (Inoue et al. 2002; Okada et al. 2002; Takamiya et al. 1996) except for ST3GAL5 KO mice (Yamashita et al. 2003). Even GlcCer synthase KO mice showed

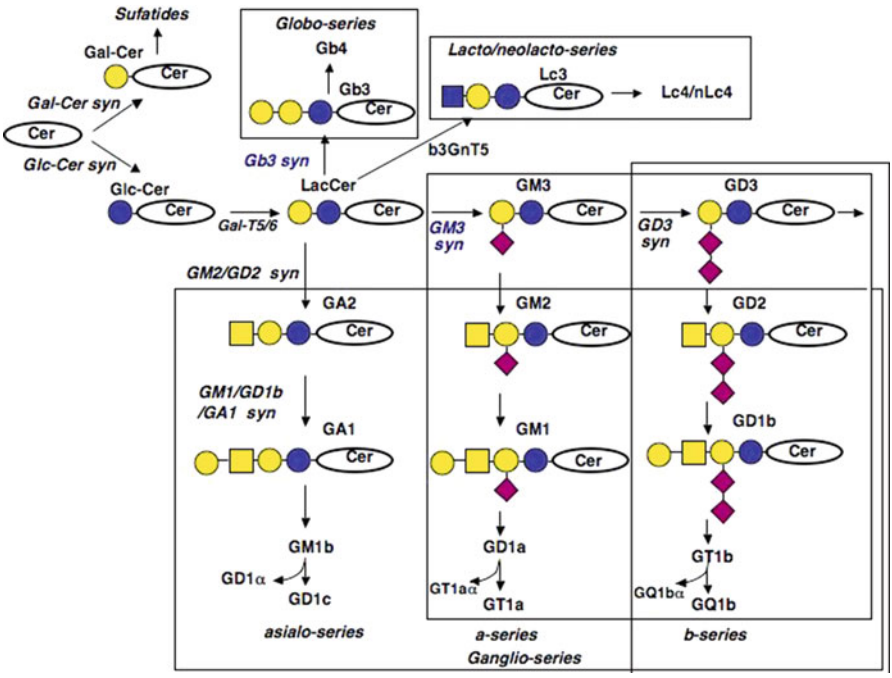

Fig. 1 Synthetic pathway and effects of of genes. Deleted structures in the individual mice were encircled by different colors. Symbols for individual sugars depend on those indicated in the site, http://www.ncbi.nlm.nih.gov/books/NBK1931/figure/ch1.f5/?report=objectonly (Reprinted from Lipid Rafts: Properties, Controversies and Roles in Signal Transduction, The Role of Glycosphingolipids in Lipid Rafts: Lessons from Knockout Mice, p. 10, copyright (2014), author(s): Koichi Furukawa, Yusuke Ohmi, Yuji Kondo, Yuki Ohkawa, Noboru Hashimoto, Orie Tajima, Keiko Furukawa. With permission from Nova Science Publishers, Inc.)

neurodegeneration when it was disrupted conditionally after birth (Jennemann et al. 2005), while whole-body KO mice of GlcCer synthase resulted in the embryonal lethality at E6.5-7.5 (Yamashita et al. 1999).

Generally, abnormal phenotypes of ganglioside synthetic enzyme-deficient mice were attributed to the altered architectures and functions of membrane microdomains, lipid rafts (Simons and Sampaio 2011). Aberrant glycosylation of glycosphingolipids resulted in the abnormal natures of lipid rafts, leading to the uncontrolled cell signaling transduced via cell membrane (Ohmi et al. 2012). In particular, disrupted rafts induced altered location and function of complement-regulatory molecules such as DAF and CD59, resulting in the increased sensitivity of cells to the self-attack of the complement system (Ohmi et al. 2011). Many of them belong to GPI-anchored proteins, resident molecules in lipid rafts. Gradual destruction of lipid rafts in nervous tissues depending on the intensity of deletion of ganglioside species was demonstrated using various KO mice of ganglioside synthase genes including ST8SIA1 KO, B4GALNT1 KO, and double KO (DKO) of both genes (Ohmi et al. 2011).

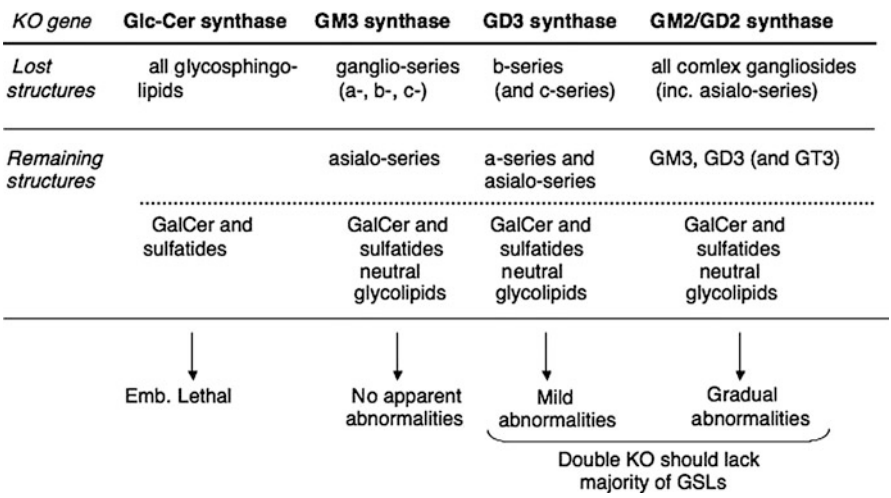

Fig. 2 Deleted and remaining structures in various KO mice. Profiles of glycosphingolipids in the individual KO mice revealed increased levels of precursor structures that might compensate for the lost glycolipids in the individual KO mice (Reprinted from Lipid Rafts: Properties, Controversies and Roles in Signal Transduction, The Role of Glycosphingolipids in Lipid Rafts: Lessons from Mice, p. 10, copyright (2014), author(s): Koichi Furukawa, Yusuke Ohmi, Yuji Kondo, Yuki Ohkawa, Noboru Hashimoto, Orie Tajima, Keiko Furukawa. With permission from Nova Science Publishers, Inc.)

Critical roles of the complement system in the neurodegeneration were confirmed by generating triple KO mice of B4GALNT1, ST8SIA1, and complement component C3 (Ohmi et al. 2009). This has been demonstrated in both the cerebellum and spinal cord (Ohmi et al. 2009, 2014). In the triple KO mice, both inflammatory reaction such as gliosis and increased cytokines and neurodegeneration as indicated by reduced Purkinje cells were restored except for persistent astrocytosis (Ohmi et al. 2011). Thus, activation of the complement system and subsequent inflammation seemed to be responsible for the neurodegeneration due to ganglioside deficiency. However, it seems difficult to conclude that only dysregulation of complement-regulatory proteins is responsible for the inflammation/ of nervous tissues observed in ganglioside-deficient mice (Fukumoto et al. 2000; Wu et al. 2009). Defects in the modulatory function of gangliosides for various membrane proteins need to be considered in the interpretation of phenotypes observed in KO mice of ganglioside synthase genes.

Lessons from Ganglioside-Deficient Mice

The fact that ST3GAL5 KO mice showed no apparent abnormal phenotypes suggested that complementary roles of similar gangliosides with the lost structures due to the gene disruption should be effective enough to keep the homeostasis of ganglioside-deficient mice. Namely, asialo-series gangliosides such as GM1b and

GD1α might be able to replace the functions of ganglioside-series gangliosides (Fig. 2). These results also suggested that specific function for each ganglioside structure may be limited, if present. Consequently, there might be two different modes of action for gangliosides in membrane microdomains, i.e., low specific function to form membrane environment and specific function exerted via the interaction with specific ligand(s) (Furukawa et al. 2014).

Neurodegenerative changes in complex ganglioside-deficient mice (Takamiya et al. 1996; Sugiura et al. 2005) could be almost restored by transgenic expression of B4GALNT1 cDNA in neurons, not in oligodendrocytes/Schwann cells (Yao et al. 2014). This fact suggests that gangliosides expressed in neurons are primarily important for the maintenance of the integrity in nervous tissues. However, effects of B4GALNT1 expression in astrocytes have not been examined yet. Differential roles of gangliosides in individual neural cell lineages remain to be clarified.

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