Short Conceptual Overview

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GM1 and GM2 gangliosides: recent developments

Abstract: GM1 and GM2 gangliosides are important components of the cell membrane and play an integral role in cell signaling and metabolism. In this conceptual overview, we discuss recent developments in our understanding of the basic biological functions of GM1 and GM2 and their involvement in several diseases. In addition to a well-established spectrum of disorders known as gangliosidoses, such as Tay-Sachs disease, more and more evidence points at an involvement of GM1 in Alzheimer's and Parkinson's diseases. New emerging methodologies spanning from single-molecule imaging *in vivo* to simulations *in silico* have complemented standard studies based on ganglioside extraction.

Keywords: GM1; GM2; membrane raft; neurodegenerative diseases; polarization.

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Introduction

GM1 and GM2 are monosialic gangliosides, a class of glycosphingolipids that are found predominantly in the outer leaflet of the plasma membrane and, to a lesser extent, in intracellular membranes. Gangliosides are amphipathic molecules with a negatively charged head group modified with carbohydrate groups that vary among the more than 200 identified species of ganglioside. In the case of GM1 and GM2, the head group consists of a single sialic acid. Two hydrocarbon chains of the ceramide moiety anchor gangliosides in the plasma membrane. Gangliosides are found in the plasma membrane of vertebrate cells and are particularly enriched in the nervous system.

Gangliosides are constantly synthesized and catabolized by highly regulated pathways. Ceramide, which forms the hydrophobic backbone of gangliosides, is synthesized in the endoplasmic reticulum, and glycosylated and sialylated in the Golgi apparatus. Glycoslytransferases add the final complement of carbohydrate groups to form individual gangliosides before vesicles of the secretory pathway transport the gangliosides to the cell surface.

Gangliosides undergo catabolism via the lysosomal recycling pathway. Endocytosis and endosomal sorting pathways chaperone gangliosides to endosomes and eventually lysosomes, where they are sequentially degraded by a series of hydrolytic enzymes assisted by lipid-binding proteins. Defects in the catabolic pathway lead to an accumulation of ganglioside species and result in lysosomal storage disorders and gangliosidoses, including Tay-Sachs disease (1).

In this paper, we survey the latest methods and developments in our understanding of the gangliosides GM1 and GM2, from their basic biochemistry and cellular function to the interactions with amyloid β (Aβ) peptide in Alzheimer's disease. We also focus on the influence of GM1 and GM2 in other diseases including cancer, viral infection, and diabetes.

New approaches to study the cell biology and membrane biochemistry of gangliosides

The gangliosides GM1 and, to a lesser extent, GM2 are primarily recognized as essential components of membrane rafts. Membrane rafts, or lipid rafts, are heterogeneous clusters of cholesterol, sphingolipids, gangliosides, and membrane-associated proteins, including G protein-coupled receptors (GPCRs). These clusters form stabilized, liquid-ordered nanostructures important in a variety of physiological processes including signal transduction, protein and lipid sorting, and trafficking. Here, we mention the most innovative methods that have been recently used to gain new knowledge on the complex biology of gangliosides (Table 1).

The segregation of plasma membrane lipids into membrane microdomains has been reviewed extensively (2). A new study demonstrates the colocalization of cholesterol

Table 1 Updated methods to study GM1.

Ganglioside investigation method	Application
Extraction for the analysis of disease-associated changes (11)	*In vitro*
Biological membrane model (3, 4, 20, 22, 23, 26, 32)	*In vitro*
SIMS of individual isotope-labeled lipid components (3)	*In vitro*
Column of immobilized beads functionalized with a target protein and mass spectrometry (6)	*In vitro*
Single fluorescent molecule imaging and tracking (9, 28, 29)	*In vivo*
Molecular dynamics (5, 35, 36)	*In silico*

and GM1 in membrane microdomains with unprecedented precision using secondary ion mass spectrometry (SIMS) of individual isotope-labeled lipid components in model membranes (3). The results suggest several regimes of membrane domains classified by size: broad micrometer-scale domains and nanometer-scale domains that can be found either within the larger domains or outside of them. The micrometer-scale domains contained cholesterol and GM1 to the exclusion of other species. Nanometer-scale domains within larger domains contained increased palmitoyl sphingomyelin, whereas the nanometer-scale domains outside the larger domains have increased GM1. The detailed molecular information made visible by the SIMS technique represents a new step into the conceptual overview of membrane raft distribution.

Liquid-ordered (L_o) domains in model membranes have also been shown recently to respond to acidic gradients in a GM1-dependent manner (4). GM1-containing domains (but not GM1-free or asialo-GM1, which lacks the acidic head group) reorganized into larger clusters facing away from the source of the gradient. The authors speculate that this could constitute a potential mechanism by which membranes segregate into polarized regions during cell polarization.

GM1 in membrane raft domains has been shown to influence the functions of lipid raft-associated proteins. Mahmood et al. have recently demonstrated a direct relationship between the lipid composition in model bilayers and the distinct conformational states of a GPCR, the β_2 adrenergic receptor (5). The addition of GM1 to these synthetic membranes increased the stability of both the unbound and the ligand-bound β_2 adrenergic receptor. Their report suggests that beyond the role that lipid rafts play in recruiting membrane receptors and cofactors into close proximity, they may also play a direct role in the activation of membrane receptors. At the same time, another group has described a new method for identifying interactions between gangliosides, including GM1 and GM2, and membrane-associated proteins (6). Gangliosides extracted from a cell pellet are purified and passed through a column of immobilized beads functionalized with a target protein. Mass spectrometry allows the identification of minute amounts of an array of ganglioside species. The protocol improves upon earlier methods in its sensitivity to low concentrations of ganglioside species and has the potential to identify other GPCRs with activity-modulating interactions with GM1 or GM2.

GM1 has also been shown to regulate the formation of cell-cell junctions. Cell-cell junctions promote cell adhesion in tissues and play important roles in collective cell migration and the invasion of cancer cells in metastasis. New results indicate that flotillin mediates the interaction of cadherin with GM1 during the formation of cell-cell junctions (7). Another group demonstrated that GM1 localizes rapidly (within 10 s) to newly formed focal adhesions induced by a fibronectin-coated nanoelectrode (8). They further show that after recruitment of GM1, focal adhesions act as mechanosensors, transmitting signals from mechanical perturbations across the cell length.

GM1 gangliosides have also been shown to be central in cell polarization and motility. GM1 accumulates at the leading edge of migrating cells, and we have recently shown that this polarization is dependent on activation of phosphatidylinositide 3-kinases (PI3K), but not mitogen-activated protein kinase (MEK)/extracellular-signal-regulated kinases (ERK) (9). GM1 polarization was also demonstrated to be mechanistically and biochemically independent of the polarization of the Golgi apparatus, suggesting that *de novo* synthesis and transport are not responsible for the polarized localization. Other recently published results suggest that actin filaments form nucleation sites at the plasma membrane that enrich GM1-containing microdomains (10). Stabilized actin filaments with attachments to the plasma membrane at the leading edge are a common feature of polarized cell architecture, so these results indicate a plausible mechanism for enrichment of GM1 at the leading edge.

A general protocol for GM1 extraction that can potentially be applied to the analysis of disease-associated changes to GM1-enriched intracellular membranes has been recently proposed by Waugh (11).

Pathological involvement of GM1 and GM2

GM1 in Alzheimer's disease and other amyloid pathologies

A growing body of data point at GM1 as one of the crucial factors involved with the development of amyloid disorders such as Alzheimer's disease and type II diabetes (12–18). In the latter two pathologies, the binding of aggregates formed by the Aβ peptides (1–40 and 1–42) and amylin (also known as human islet polypeptide, hIAPP) to the plasma membrane triggers pathways eventually leading to the impairment and death of neuronal and pancreatic β cells (19), respectively. Both the formation of these aggregates and their interaction with the plasma membrane have been proposed to be mediated by GM1 (12, 20, 21). Experiments carried out *in vitro* show that the presence of GM1 enhances the seeding and aggregation of Aβ and amylin peptides on synthetic membranes (20, 22, 23). These results are in agreement with *in vivo* studies where aggregation seems to be increased at the level of membrane rafts (21, 24, 25). However, the binding of preformed Aβ oligomers and amylin aggregates to synthetic lipid vesicles, an event that induces membrane permeabilization, appears to be driven by GM1 (21, 26). It has also been demonstrated that exogenous Aβ1–42 oligomers applied to cultured neurons tend to accumulate on the membrane at the level of rafts enriched in GM1 (25). By contrast, a protective role for GM1 in Alzheimer's disease is proposed in a work performed using triple transgenic APP/PSEN1/GD3S-/- mice, where a dramatic decrease in cognitive dysfunction and Aβ plaque burden was observed despite a significant increase in GM1 levels (27).

Innovative approaches have been recently used to improve the understanding of the interaction between amyloid aggregates and GM1. Single-particle tracking experiments in living cells have revealed that amyloid aggregates can change the lateral diffusion of GM1 molecules labeled with cholera toxin B coupled to quantum dots (28, 29). Preformed amylin aggregates and Aβ1–42 oligomers added to living neuroblastoma cells display a low mobility on the plasma membrane (30). We have shown that GM1 interacts with the aggregates of both peptides and undergoes a dramatic reduction in diffusion rate (29). The altered mobility of GM1 may have consequences on its regulatory role in neurodevelopment and neuroprotection (31) or affect cellular pathways dependent on raft dynamics. An example demonstrating that the binding of amyloid aggregates can imply a loss of function for molecules linked to lipid rafts is represented by the binding of Sup35 amyloid fibrils to GM1 on the plasma membrane. The consequent accumulation of Fas receptors associated with GM1 appears to induce the activation of extrinsic apoptotic pathways (28).

These results are in agreement with data obtained by Sasahara et al. on the influence of Aβ aggregation on membrane fluidity *in vitro* (32). They examined the aggregation of Aβ on supported lipid bilayers containing the typical raft components and found an enhancement in phase separation of lipids as a result of interactions between aggregating Aβ and GM1. The sequestration of GM1 into Aβ aggregates resulted in induced membrane damage.

GM1 has been also found to be involved in the processing of the amyloid precursor protein (APP), a transmembrane protein that can be cleaved by alternative proteases, leading to the release of toxic Aβ peptide. In particular, the addition of exogenous GM1 promotes Aβ production and decreases the secretion of sAPPα in neuroblastoma cells and primary cultures of rat cortical neurons (33).

Evangelisti et al. have shown that GM1 has a pivotal role also on the cellular binding and toxicity of amyloid aggregates formed by a model protein not associated to disease (17). Moreover, the same group has demonstrated that modest depletion of GM1 content decreases the interaction of Aβ oligomers with the plasma membrane in fibroblasts of patients with familial Alzheimer's disease and in rat brain cortical neurons, causing a reduction in cytotoxicity (34).

Atomistic-scale computer simulations have been used to investigate the behavior of Aβ monomers and dimers in GM1-containing raft-like membrane. The oligosaccharide head group of GM1 was observed to act as a scaffold for Aβ binding and subsequent structural rearrangement, an event that did not occur in the absence of GM1 (35). In another molecular dynamics study, the authors report that in the presence of ganglioside GM1, monomeric Aβ1–40 seems to be released more frequently from the plasma membrane, whereas the aggregated form of Aβ develops more rapidly than in other membrane environments and remains bound to the membrane (36).

Although at the level of the central nervous system GM1 is predominately found in the white matter (37), GM1 appears to be redistributed in cells located in the frontal gray matter of patients affected by Alzheimer's disease, possibly reflecting a pathological connection (38).

GM1 in other neurodegenerative pathologies

GM1 appears to be involved in two additional neurodegenerative disorders related to protein aggregation:

Huntington's and Parkinson's diseases. A reduced synthesis of the ganglioside GM1 has been found in fibroblasts obtained from Huntington's disease patients, leading to increased cell susceptibility to apoptosis (39). Restoration of GM1 levels in these cells promotes phosphorylation of mutant Htt, inducing a reduction in toxicity and increased survival. Moreover, intraventricular infusion of GM1 appears to restore normal motor function when administered to symptomatic Huntington's disease mice. These studies suggest a potential therapy for Huntington's disease based on the posttranslational modification of mutant huntingtin (40).

During the past 20 years, several studies have tried to clarify the role of GM1 in Parkinson's disease. Immunohistochemical analysis of paraffin sections from Parkinson's disease patients has revealed significant GM1 deficiency in nigral dopaminergic neurons. In agreement with this finding, B4galnt1(-/-) genetically engineered mice devoid of GM1 have been found to acquire the symptoms characteristic of this disorder (41). The symptoms in the mice were reduced with administration of analogs of GM1. One hypothesis on the protective role of GM1 is that ganglioside treatment can promote autophagy and clearance of α-synuclein (42), the accumulation of which is associated with Parkinson's disease. By contrast, another study reveals that GM3, rather than GM1, can specifically regulate the permeabilization of the membrane caused by α-synuclein pore formation (43). GM1 has also been used in human clinical trials to treat Parkinson's disease. The results suggest that long-term GM1 use is safe and may provide some clinical benefit for Parkinson's disease patients (44, 45).

Multifocal motor neuropathy, a rare autoimmune disease, appears to be linked to GM1. Anti-GM1 antibodies can be found in some patients with multifocal motor neuropathy, but it is unclear whether these antibodies are pathogenic. Antibodies against gangliosides are associated with a wide range of inflammatory neuropathies, including the Guillain-Barré syndrome, and growing evidence points at ganglioside-specific IgG antibodies as culprits. Although the conventional hypothesis claims that the primary pathology is segmental demyelination, recent research raises the possibility of a primary axonopathy related to the anti-GM1 antibodies (46).

GM1 and GM2 in infections, cancer, and insulin metabolism

Gangliosides have long been known to play a central role in cholera infection, but recently, new reports suggest

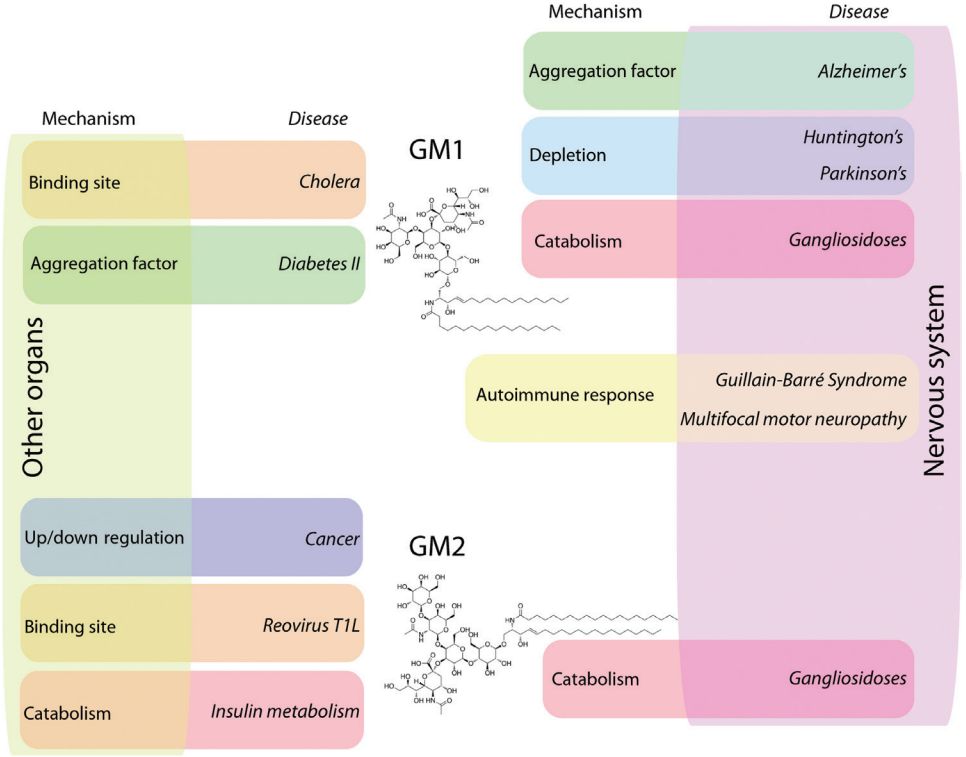

Figure 1 Pathological involvement of GM1 and GM2.

apparent roles in diseases as diverse as cancer (47–49), serotype 1 reovirus infection (50), and insulin secretion and regulation (51). GM2 appears to play an important role in adhesion, motility, and proliferation in tumor cells through interactions with growth factor receptors and focal adhesion proteins, including integrins, and caveolins [for a review, see (47)]. GM2 plays a protective role, and when its expression is decreased, characteristics of greater cancer malignancy are observed. More recently, analysis of glycosphingolipid profiles, including GM1 and GM2, in cancer stem cells revealed that GM2 and GM1 are upregulated in breast cancer stem cells compared to cancer non-stem cells and may provide a useful target against the development of cancer stem cell phenotypes (49). Interestingly, hexosaminidase subunit β (HEXB), which is involved in the catabolism of GM2, was found to be upregulated, presumably along with a downregulation of GM2 in blood vessels associated with invasive human breast cancer (48). Depletion of HEXB via siRNA was found to decrease the angiogenic potential. Another study using GM2 and GM3 synthase double knockout oncogene-transformed fibroblasts in a cancer model in mice found that downregulation of GM1 induces strikingly slower tumor growth (52). Although the precise role of GM2 in cancer progression is still not completely understood, it may prove to be an interesting therapeutic target.

GM2 was also identified recently to be a specific receptor for reovirus strain type 1 Lang (T1L) (50). Given the uneven distribution of GM2 in different tissue types, with a prominent expression in neural tissues, this finding could open the door to understanding other viral tissue infection patterns. It is also particularly interesting as reoviruses are currently being developed as delivery systems for cancer therapy, and given that GM2 expression is altered in many cancer types, understanding the interaction between reoviruses and GM2 could prove essential to these cancer therapies.

Finally, the GM2 activator protein (GM2AP), which acts as a cofactor to HexA in the catabolism of GM2, has been recently identified to be an adipokine that increases insulin secretion while at the same time impairing insulin and nerve growth factor signal transduction. Insulin receptors are localized in lipid rafts, and diabetes and insulin resistance have been hypothesized to be related to membrane microdomain function (51). GM2AP now appears to play a significant role in insulin metabolism, although a direct connection to GM2 has not yet been observed.

Considerations on the role of gangliosides in disease

Gangliosides are involved in important aspects of homeostasis, and levels of GM1 and GM2 gangliosides must be tightly and accurately regulated. Misregulation of GM1 or GM2 is implicated in a diverse array of diseases mostly associated with the nervous system (Figure 1). An accumulation of GM1 in neurons can lead to the deleterious effects observed in gangliosidoses. By contrast, GM1 depletion is associated to Parkinson's and Huntington's diseases, and administration of exogenous GM1 seems to reduce the pathological symptoms (in humans and mice) in both cases. Moreover, interaction of virus components and amyloid species with GM1 can trigger pathological pathways in cholera infection and Alzheimer's disease, respectively. Finally, high levels of anti-ganglioside antibodies are frequently found in the serum of patients affected by autoimmune neuropathy, where they are suggested to play a pathogenic role. The importance of gangliosides, especially GM1, is evident from these types of diseases, showing that perturbations in one sense or in the other can result in dramatic consequences for the organism.

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