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Membrane Glycolipids: Functional Heterogeneity: A Review

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Abstract

Glycolipids are membrane components in species ranging from bacteria to man especially in those organisms which live in unusual harsh environments. The most probable function of glycolipids in membrane is based on their capability to undergo extensive interlipid hydrogen bonding via glycosyl head groups; therefore they impart structural integrity to the membranes of the organisms. Besides, being structural components of the cell membrane, they play an important role in cellular functions such as in cell-cell communication, as receptor components, as anchors for proteins and as regulators of signal transduction. In addition, glycolipids provide a molecular platform for clustering of signal transducers. The tight interactions between cholesterol and glycolipids in the membrane are the driving force that segregates them from phospholipids that remain fluid in nature.

Keywords: Glycolipids; Structural components; Cell-cell interaction

Glycolipids and their Classification

Glycolipids were discovered and named by Ernst Klenk after their isolation from brain tissue in 1942. They are ubiquitous membrane constituents, which are embedded in the cell plasma membrane. Glycolipids are glycosyl derivatives of lipids. They are collectively a part of a larger family of substances known as glycoconjugates. The term glycolipid designates any compound containing one or more monosaccharide residues bound by a glycosidic linkage to a hydrophobic moiety such as an acylglycerol, a sphingoid, a ceramide (N-acylsphingoid) or a prenyl phosphate. Glycolipids are classified as follows:

Glycoglycerolipids

The term glycoglycerolipid is used to designate glycolipids containing mono, di or trisaccharides linked glycosidically to the hydroxyl group of diglycerides (e.g. monogalacosyldiglycerides, digalacotosyldiglycerides). Monogalactosyldiacylglycerols and digalactosyldiacylglycerols are the main glycolipid components of the various membranes of chloroplasts and also these are the most abundant lipids in all photosynthetic tissues, including those of higher plants, algae and certain bacteria [1].

Glycosphingolipids

The term glycosphingolipid designates lipids containing at least one monosaccharide residue linked to ceramide moiety. Ceramides are amides of fatty acids with long chain di or trihydroxy bases. The acyl group of ceramides is generally a long chain saturated or monounsaturated fatty acids. The glycosphingolipids can be subdivided as follows:

Neutral glycosphingolipids: These glycolipids contain one or more glycosyl moieties linked to ceramide e.g. cerebrosides: Cerebrosides are monoglycosylceramides in which glucose or galactose sugar residue is attached by O-ester linkage to the primary alcohol of the ceramide. Galactosylceramides are found in all nervous tissues, but they can amount to 2% of the dry weight of grey matter and 12% of white matter [2]. Glucosylceramide (Glcß1-1'Cer) is found at low levels in animal tissues, such as spleen and erythrocytes, as well as in nervous tissues.

Oligoglycosylceramides: Glycosphingolipids containing more than one sugar moiety belongs to the oligoglycosylceramide group. They are vital components of cellular membranes of most eukaryotic organisms and some bacteria [2]. The most important and abundant of the oligosylceramides is β-D-galactosyl-(1-4)-β-D-glucosyl-(1-1')-ceramide, also called lactosylceramide (LacCer).

Acidic glycosphingolipids: They are divided into two groups:

- **Sulfoglycosphingolipids:** They are sometimes called "sulfatides" or "sulfatoglycosphingolipids" also. These are glycosphingolipids carrying a sulfate ester group attached to the carbohydrate moiety. Sulfated is mainly formed of 3-sulfate esters of galactosylcerebrosides (galactosyl-3-sulfate esters). They are mainly found in tissues that are very active in sodium transport such as kidneys, salt glands and gills [3].
- **Gangliosides:** This group of glycosphingolipids consists of molecules composed of ceramide linked by a glycosidic bond to an oligosaccharide chain containing hexose and sialic acid units. These lipids can amount to 6% of the weight of lipids from brain. One of the common monosialo-gangliosides is ganglioside GM1.

Distribution of Glycolipids in the Cell

Most of the glycolipids are distributed in membranous structures in the cell. Two-thirds of the total glycolipids are distributed in intracellular membranes such as golgi apparatus, endosomes, lysosomes, nuclear membrane, endoplasmic reticulum, and mitochondria [4]. Glycolipids are synthesized in golgi apparatus by the addition of saccharides one by one to the ceramide moiety. Most glycolipids are transported between membranes as small vesicles maintaining a bilayer structure. However, the first step of the biosynthesis of most glycosphingolipids i.e. transfer of a glycosyl residue to ceramide, occurs at the cytosolic surface of cis golgi and the other sugars are transferred at the luminal face of the golgi complex [5]. Some glycolipids are also distributed in cytosol. The

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soluble fraction of brain contains 5% of the total gangliosides and their composition is similar to that of the membrane fraction. Glycolipids are distributed prudentially into exofacial leaflets of plasma membrane and the luminal side of organelles [6]. In polarized epithelial cells, glycosphingolipid are enriched on apical side of the cells while cells with polarity, e.g. epithelial cells in intestine and kidney glycolipid composition differ at the apical and basolateral side.

Simons and Toomre [7] observed that in plasma membrane, glycosphingolipids along with cholesterol form clusters, called rafts. This region had relatively less phospholipids than other areas of plasma membrane. Approximately 70% of total cellular glycolipids are found in rafts. Rafts are lateral assemblies of sphingolipids and cholesterol that form tight hydrophobic interactions between these molecules. Brown and London [8] reported that sphingolipids associate laterally with one another through weak interactions between the carbohydrates heads of the glycosphingolipids and the hydrophobic interactions between their saturated side chains and any void between associated glycosphingolipids were filled by cholesterol molecules which interact with hydrophobic portions of glycolipids. The tight interactions between cholesterol and glycolipids in the membrane are the driving force that segregates them from phospholipids that remain fluid in nature [9].

Carbohydrate-Carbohydrate Interaction of Glycolipids

Cell-cell interactions play an important role in the development, maintenance, and host-pathogen interaction. They are highly dynamic processes, which include migration, recognition, signaling, adhesion, and finally attachment. Carbohydrates moieties of glycolipids, the most prominently exposed structures on the surface of living cells, with flexible chains and many potential binding sites are ideal to serve as important players in these events. Molecular interactions where carbohydrates are involved are usually considered as weak interactions, and therefore, there is biological relevance of carbohydrate-carbohydrate and carbohydrate-protein interactions [10].

Glycolipid-glycolipid interaction is a rapid process, as compared with protein-protein interaction, although the strength of the interaction is weaker than that of protein-protein interaction [10]. A synergistic effect between cell adhesion based on glycosphingolipids-glycosphingolipids interactions and adhesion based on integrins was observed by Bucior et al. [11]. They postulated that glycosphingolipid-glycosphingolipid interaction may define the initial specificity and direction of the cell recognition and regulate the adhesion process.

One of the important properties of the bilayer is the ability to orient and cluster glycolipid species in such a way so that interactions in the biological systems are maximized. The lipid moiety of glycolipids is generally buried in the cell membrane bilayer, leaving the oligosaccharide moieties exposed but in close proximity to the bilayer surface [12]. This represents a unique environment for carbohydrate interactions with other molecules. Glycolipids cause two types of interactions. They interact side by side within the same membrane to form clusters and by trans interactions in which two interfacing membrane interact through their surface carbohydrates [13]. They further reported that trans interactions between the glycolipids provides the basis for glycosphingolipids-dependent cell to cell adhesion, which takes place through specific complementary structures catalyzed in many cases by calcium ions. Therefore, cell surface complex carbohydrate has emerged as key recognition molecules, mediating physiological interactions between cells. Typically glycans on one cell surface engaged by complementary carbohydrate binding proteins on opposing cells, initiate a cellular responses [14]. The preliminary evidence for carbohydrate-carbohydrate interaction came from the studies of liposomes containing highly purified glycosphingolipids. Glycosphingolipids bind to the complementary glycosphingolipids through interaction between their carbohydrate moieties [15].

Cell surface carbohydrates play a major role in cell-cell or cell-substrate recognition. They suggested that melanoma cell adhesion to endothelial cells was based on GM3/LacCer interaction, which initiates metastatic deposition, and may trigger a series of "cascade" reactions leading to activation of endothelial cells and expression of Ig family or selectin receptors, thereby promoting adhesion and migration of tumor cells, hence demonstrated dramatic changes in surface carbohydrates during oncogenesis.

Boggs et al. [16] suggested that galactosyl ceramide and cerebroside sulfate present in high concentrations in multilayered myelin sheath was involved in carbohydrate- carbohydrate interactions between lipid head groups. The interaction resulted in dehydration of the sulfate, changes in the intermolecular hydrogen bonding, interactions of the sugar and other oxygens, decreased intermolecular hydrogen bonding of the amide C=O of GalC and dehydration of the amide region of one or both of the lipids, and disordering of the hydrocarbon chains of both lipids. The interaction between these two lipids could be either a lateral cis interaction in the same bilayer or a trans interaction between apposed bilayers and may be involved in stabilization of the myelin sheath.

Schnaar [17] observed that human leukocytes were recognized by E-selectins present on vascular endothelium during inflammation. The recruitment of neutrophils to sites of inflammation was mediated by endothelial leukocytes adhesion molecule-1(ELAM-1) expressed on activated endothelial cells of blood vessels walls. ELAM-1 is a member of the selectin family of adhesion molecules that contain a lectin motif thought to recognize carbohydrate ligands. They observed that cell adhesion by ELAM-1 was mediated by a carbohydrate ligand, sialyl-Lewis X (SLex; NeuAc alpha 2,3Gal beta 1,4(Fuc alpha 1,3)-GlcNAc-), a terminal structure found on cell-surface glycoprotein and glycolipid carbohydrate groups of neutrophils. The sialyl Lewis A and sialyl Lewis X, the carbohydrate determinants which are frequently expressed on human cancer cells, serve as ligands for a cell adhesion molecule of the selectin family, E-selectin, which is expressed on vascular endothelial cells. These carbohydrate determinants are involved in the adhesion of cancer cells to vascular endothelium and thus contribute to hematogenous metastasis of cancer by triggering the activation of integrin molecules through the action of several cytokines leading to extravasation of cancer cells.

Overall, it can be stated that carbohydrate-carbohydrate interactions play an important role in recognition and signaling events in a variety of biological phenomena.

Biological Functions of Membrane Glycolipids

Membrane glycolipids perform a number of functions in biological system. Glycolipids have roles in response to cell contact, as receptor components, as anchors for proteins and as markers for tumor progression and cell differentiation [18].

Glycolipids as signal transducers

Glycolipids have been known to be modulators of signal transduction. Glycosphingolipids and sphingomyelin in animal cells are clustered and organized as membrane microdomains closely associated with various signal transducer molecules such as cSrc, Src family

kinases, small G-proteins (e.g. RhoA, Ras), and focal adhesion kinase. Glycosphingolipid clustering in such microdomain causes adhesion to complementary glycosphingolipids on the surface of counterpart cells through carbohydrate-carbohydrate interaction. Glycosphingolipids dependent cell adhesion in microdomain causes activation of the signal transducers, leading to cell phenotypic changes [19,20]

Glycosphingolipid microdomains mediate signal response either by associating with GPI-anchored proteins or Immuno and growth factor receptors. Kasahara et al. [20] reported that GPI anchored proteins and acylated proteins like src-family tyrosine kinases and trimeric-G proteins are known to associate with glycosphingolipid microdomains. GPI-anchored proteins having saturated acyl chains were likely to insert preferentially into glycosphingolipid microdomains. They observed that antibody (or ligand)-mediated crosslinking of GPI-anchored proteins induces activation of src-family kinases and transient increase in tyrosine phosphorylation of several substrates. Reports showed that enzymatic removal of the carbohydrate moiety from cell-surface glycosphingolipids impairs the activation of the src-family kinase by antibody-mediated crosslinking of GPI-anchored protein.

Glycosphingolipid microdomains are also involved in signaling by immunoreceptors and growth factor receptors [21]. Efficient T-cell activation requires one signal from a T-cell antigen receptor and a second signal from the co-stimulatory molecule. The co-stimulation leads to the recruitment of glycosphingolipid microdomains to the site of cell-cell contact between the T cell and antigen-presenting cell.

Iwabuchi et al. [22] reported that adhesion process is based essentially on a glycosphingolipid-enriched microdomain (GEM) at the B16 cell surface. More than 90% of GM3 present in the original cells were found in GEM. GEM is also enriched in several signal transducer molecules, e.g. c-Src, Ras, Rho, and focal adhesion kinase.

The general function of glycosphingolipid microdomains in signal transduction may be to concentrate receptors and effectors on both sides of the membrane, thus speeding up binding during signaling and preventing inappropriate crosstalk between pathways.

Glycolipids as receptors of bacteria and bacterial toxins

Binding of pathogenic bacteria and bacterial toxins to host cell surfaces is an essential step in establishing infection in tissues and producing toxic effect. Glycolipids on cell surfaces are receptors for binding to cells. Many pathogenic bacteria bind to glycolipids of host cell surface for colonization and infection.

Rodighiero et al. [23] reported that many bacterial toxins bind to gangliosides as the receptors on cell surface and invade host cells. The best known of these is the cholera toxin, an enterotoxin produced by *Vibrio cholerae,* and its specific cell surface receptor was identified as ganglioside GM1. The entry of cholera toxin into target epithelial cells and the induction of toxicity depend on the cholera toxin binding to ligand-based receptor GM1 and association with the glycosphingolipid microdomain [24]. Cholera toxin consists of a pentameric B subunit that binds to GM1 and an A subunit with direct toxic activity. The binding of B subunit to membrane GM1 induces a conformational change in the toxin, resulting in the entry of the A subunit into the cell. Wolf et al. [25] observed that to induce toxicity cholera toxin must bind ganglioside GM1 at plasma membrane, enter the cell by endocytosis and then retrograde into endoplasmic reticulum. They proposed that GM1provides the sorting motif necessary to retrograde trafficking into biosynthetic, secreatory pathway of host cells. The entry of cholera toxin into target epithelial cells and the inductions of toxicity depend on cholera toxin binding to the lipid-based receptor ganglioside GM1 and association with detergent-insoluble membrane microdomains. Cholera toxin action depends on the stable formation of the cholera toxin B-subunit- GM1 complex.

Bock et al. [26] studied that enterohaemorrhagic *E. coli* bind to neutral glycosphingolipids having an alpha-1,4 galabiose moieties in the sugar chain, such as galabioside (Ga2Cer) and ceramide trihexoside (Gb3Cer).They suggested that *E. coli* bind to glycosphingolipid by recognizing not only the terminal sequence but also the internal sequence of the sugar chain. *Propionibacterium*, which causes skin disease, recognizes the lactosyl moiety of glycosphingolipids as a binding epitope. These bacteria bind strongly to lactosylceramide and also bind to isoreceptors such as asialo GM1 (GA1) and asialo GM2 (GA2). This bacterium could not bind to any glycosphingolipids composed of a dihydroxy base and nonhydroxy fatty acid in ceramide, even though they contain a lactosylmoiety.

Glycolipids in modulation of cell proliferation

Several observations underline the role of the glycolipids in regulation of cell growth by interacting through growth factor receptors [22]. Auge et al. [27] observed that intracellularly produced ceramide, Lac Cer stimulated DNA synthesis in endothelial smooth muscle cells. They also potentiated the mitogenesis induced by various growth factors including platelet-derived growth factor. The lactosylceramide (LacCer, Galβ4Glcβ1Cer) activates NADPH oxidase to modulate the intercellular adhesion molecule-1 expression on human umbilical vein endothelial cells and to induce the proliferation of human aortic smooth muscle cells. Reports showed that decrease in ceramide content via increased activity of ceramidase, sphingomyelin synthase or GlcCer synthase correlated with proliferative response of smooth muscle cells.

Sphingolipid breakdown products, sphingosine and lysosphingolipids, inhibit protein kinase C, an important enzyme in cell regulation and signal transduction. Sphingolipids and lysosphingolipids affect significant cellular responses and exhibit antitumor promoter activities in various mammalian cells. These molecules may function as endogenous modulators of cell function and possibly as second messengers [28]. Ceramides in turn activate the serine-theronine protein phosphatases PP1 and PP2A. Ceramide activated protein phosphates leads either to cell cycle arrest or to apoptosis [18]

Some gangliosides are apoptotic inducers. Ceramide is a mediator of programmed cell death signaling in lymphoid cells. GD3 is potent mediator of cell death. De Maria [29] reported that the apoptotic signal triggered by CD 95 in lymphoid and myeloid tumor cells increases the ceramide levels, which is followed by an increase in ganglioside GD3 synthesis. Addition to cells in culture damaged mitochondria with consequent dissipation of mitochondrial transmembrane potential and caused DNA fragmentation in HuT78 cell. Glycosphingolipids are abundant components of external leaflet of the plasma membrane of cancer cells. Addition of anti-ganglioside GD2 monoclonal antibodies into cell medium results in apoptosis in GD2 expressing human lung cancer cells.

Glycolipids as biosurfactant

Biosurfactants are amphiphilic compounds containing hydrophobic and hydrophilic moieties that reduce surface tension and interfacial tensions between individual molecules at the cell surface and interface respectively. Glycolipids are the most common types of biosurfactants. The polar moiety is a carbohydrate and the nonpolar moiety is a long carbon chain fatty acid. Mannosylethritol lipids (MELs) are microbial

extracellular glycolipids composed of mannosylethritol and fatty acids as hydrophilic and lipophilic moieties, respectively. They are produced by *Schizonella melanograma, Candida antarctica* T-34 [30] and *Ustilago maydis* [31]. MEL glycolipids produced by *Candida antarctica* T-34 showed excellent surface and interfacial tension lowering actions and exhibited antimicrobial activity particularly against Gram-positive bacteria, thereby suggesting a strong potential for their industrial use. The excellent surface tension reducing and emulsifying characteristics of MELs glycolipids and its stability over a wide range of temperature and pHs, made MELs important for commercial application. MELs glycolipids were potent inducers of apoptosis and differentiation in mouse melanoma cells.

Role of glycolipids in calcium homeostasis

The association of calcium ions with glycolipids especially gangliosides were involved in neuronal function. Gangliosides micelles bind calcium ions with high affinity. This may have some significance in the process of synaptic transmission. Levade et al. [31] reported that sphingosine and ceramide mediated a profound release of calcium ions from intracellular stores. Gangliosides function in calcium homeostasis and signaling. He observed that gangliosides induced changes in cellular calcium, which was accomplished through modulation of calcium influx channels, calcium exchange proteins and various calcium dependent enzymes that were altered through the association with the gangliosides. Lloyd-Evans et al. [32] demonstrated that elevation of intracellular glucosylceramide (GlcCer) levels results in increased functional Ca^{2+} stores in cultured rat neurons. Surface glycolipid galactocerebroside participate in the opening of the Ca^{2+} channels in oligodendrocytes cells.

Conclusion

Overall, it can be stated that glycolipids in the cell membranes play an important role in recognition and signaling events in a variety of biological phenomena, are potent inducers of apoptosis and differtiation in melanoma cells, regulating cell growth by interacting through growth factor receptors, concentrated receptors and effectors on both sides of the membrane, thus speeding up binding during signaling and preventing inappropriate crosstalk between pathways.

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