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Minireview

Recent advances in the glycosylation of sphingosines and ceramides

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Abstract—Glycosphingolipids (GSLs) are ubiquitous components of eukaryotic cell membranes. They are highly bioactive and are involved in many aspects of cell signalling like cell–cell interaction, cell–substratum interaction and cell–pathogen interaction. GSLs also are involved in the modulation of signal transduction, resulting in regulation of cell proliferation and differentiation. The biological importance and complexity of these compounds afford many opportunities to prepare synthetic analogues for studies of their metabolism in intra- and intercellular processes. This review focuses on recent contributions in the synthesis of GSLs, highlighting improvements in glycosylation reactions leading to α and β glycosyl sphingosines and ceramides and related compounds. Literature from 2000 to the present is covered. The glycosylation reactions leading to the synthesis of GSLs are classified in function of the configuration of the created glycosidic bond (α or β) and of the acceptor used, either azido-sphingosine or ceramide.

Keywords: Carbohydrate; Glycosphingolipids; Glycosylation; Ceramides; Sphingosine; Phytosphintgosine

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1. Introduction

Biological membranes[1] are described as a 'mosaic of lipid domains' where glycosphingolipids (GSLs) are building blocks of the plasma membrane and where their hydrophilic portions are exposed towards the cell

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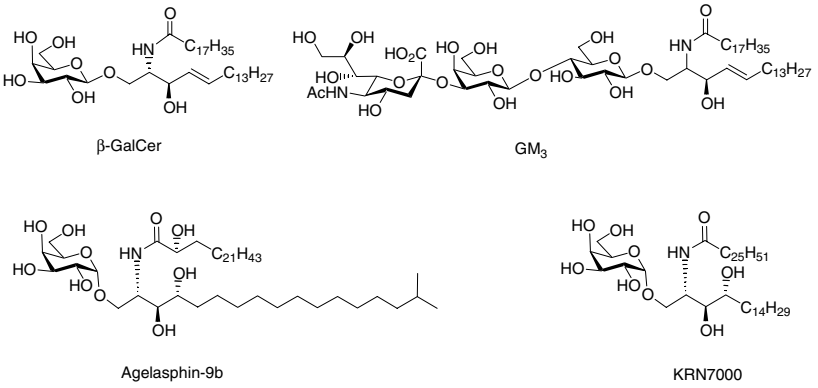

Figure 1.

surface and the hydrophobic moieties are inserted into the membrane layer. GSLs are involved in cellular trafficking, signalling functions,[2] interactions with external agents,[3] proliferation, differentiation, apoptosis and cellular embryogenesis.[4] The majority of GSLs are composed of a hydrophobic base, ceramide. Attached to this base is a hydrophilic group of core monosaccharides. Ceramide is composed of a long chain amino alcohol linked to a fatty acid, most commonly with a long chain, which is sometimes hydroxylated. The most frequently occurring long chains contain a C4–C5 double bond in the *trans*-D-*erythro* configuration (see β-GalCer and GM_3, Fig. 1). Less frequent are sphinganines, which lack the double bond, and phytosphingosine, which carries an additional hydroxyl group on C4, for example, as in Agelasphin-9b and α-galactosyl-ceramide (α-GalCer, KRN7000) (Fig. 1).[5] The carbohydrate moiety contains one or more monosacharides, and is linked to ceramide via a glycosidic bond. GSLs are classified as: (a) cerebrosides (containing a sugar residue), (b) sulfatides (containing a sugar residue with a sulfate group), (c) neutral glycosphingolipids (containing oligosaccharides with two or more sugar residues) and (d) gangliosides (containing neuraminic acid residues). The saccharide units present in GSLs are glucose, galactose, *N*-acetylglucosamine, *N*-acetylgalactosamine, fucose, sialic acid and glucuronic acid.[6]

GSLs have been the subject of interesting studies as the molecular[7] basis of raft–pathogen interactions and the effect of such interactions.[8] However, in the past few years, the field of GSLs research has been addressed as a strategy for preventing different diseases: microbial infections (HIV),[9,10] cancer,[11] diabetes,[12,13] Alzheimer's[14,15] and Parkinson's.[16] To increase these activities, two alternatives have been developed. The first approach consists of anchoring the oligosaccharide units on a chemical matrix to obtain a multivalent neoglycoconjugate.[17,18] The other approach is to modify the structure of the hydrophobic part of GSLs, with the goal of obtaining water-soluble analogues[19] in which the conformation of the binding domain of the analogue is similar to GSLs.

There are three components of the immune systems in mammals. Two types of cells associated with these systems are necessary for the recognition of antigens. One family is B cells and the second is T cells. The third component involve CD1 (Cluster of differentiation 1) molecules.[20] At the molecular level, glycolipids have been shown to act as a connecting ligand presented by the CD1d molecule of antigen-presenting cells to the mouse Vα14 receptor and the human Vα24 receptor of natural killer T (NKT) cells. Upon recognition of the galactosylceramide in the context of CD1d, the NKT cell then is stimulated to produce interferon-γ (IFN-γ), interleukin-4 (IL-4) and interleukin-2 (IL-2).[21] The release of proinflamatory cytokines is believed to be responsible for the antitumour, antiviral, antibacterial effects of GSLs. Since the discovery of galactosyl-ceramides from marine sponges in 1993,[22] the potent immunostimulant activity of this family of molecules has been studied. Preliminary structure–activity studies suggested that structural variations in the lipid chains result in relatively small changes in IFN-γ and IL-4.[23] The immunostimulatory activities of GSLs analogues have led to the development of anticancer chemotherapeutics that are currently in clinical trials.[24]

In this context, significant work has been recently devoted to the preparation of natural GSLs and analogues, with the goals of improving these properties and understanding the interactions responsible for biological activity. A key step in the synthesis of GSLs is the formation of the glycosidic bond between carbohydrate and ceramide or sphingosine.[5] To accomplish this key synthetic step, a variety of glycosyl donors have been utilized including glycosyl trichloroacetamidates, fluorides, phosphates and sulfides.[25] Regardless, the glycosylation reaction is still one of the main determining factors in the synthesis, because glycosylations of ceramides are generally plagued by low yields.[26] This problem has been attributed to the low nucleophilicity of