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REVIEW ARTICLE

Physiological significance of Fuc and Sialic acid containing glycans in the body

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Abstract Complex biomolecular machinery carrying diverse glycan chains are involved in a wide range of physiological activities including blood group determination, cancer recognition protein stabilization and sperm–egg interaction. Diversity of glycan chains, linked to lipids and proteins is due to isomeric and conformational modifications of various sugar residues, giving rise to unique carbohydrate structures with a wide range of anomeric linkages. This unique and significant structural diversity of naturally occurring oligosaccharide structures make them the best recognition markers for countless physiological activities. This is a challenging task to explore the relationship between biological processes and stereochemical behavior of sugar residues. Current review article is related with the physiological significance of glycans carrying fucose and/or sialic residues in

Abbreviations: Fuc, fucose; Neu, neuraminic acid; Gal, galactose; GalNAc, *N*-acetylgalactosamine; Glc, glucose; GlcNAc, *N*-acetylglucosamine; Cer, ceramide; Man, mannose; Neu5Gc, 5-glycolyl neuraminic acid; LacNAc, *N*-acetyl lactosamine; LacdiNAc, Di-N-acetylated Lactosamine; Lewis^x determinant, Gal(β1-4)[Fuc(α1-3)]GlcNAc(β1-R; Dimeric Lewis^x, Gal(β1-4)[Fuc(α1-3)]GlcNAc(β1-3)Gal(β1-4)[Fuc(α1-3)]GlcNAc(β1-)-R; Trimeric Lewis^x, Gal(β1-4)[Fuc(α1-3)]GlcNAc(β1-3)Gal(β1-4)[Fuc(α1-3)]GlcNAc(β1-3)Gal(β1-4)[Fuc(α1-3)]GlcNAc(β1-)-R; Sialyl-Le^x, Neu5Ac(a2-6)Gal(b1-4)GlcNAc(b1-3)Gal(b1-4)[Fuc(a1-3)]GlcNAc(b1-)-R; GT1c, Galβ(1-3)GalNAcβ(1-4)[Neu5Acα(2-8)Neu5Acα(2-8)Neu5Acα(2-3)]Galβ(1-4)Glcβ(1-1)Cer; GT1, Neu5Acα(2-3)Galβ(1-3)GalNAcβ(1-4)[Neu5Acα(2-8)Neu5Acα(2-3)]Galβ(1-4)Glcβ(1-1)Cer; GQ1, Neu5Acα (2-8)Neu5Acα (2-3)Galβ(1-3)GalNAcβ(1-4)[Neu5Acα (2-8)Neu5Acα (2-3)]Galβ(1-4)Glcβ(1-1)Cer; *N*-glycolyl GM2, GalNAc(b1-4)[Neu5Gc(a2-3)]Gal(b1-4)Glc(b1-1)Cer; N-acetyl GM2, GalNAc(b1-4)[Neu5Ac(a2-3)]Gal(b1-4)Glc(b1-1)Cer]; GD2, [GalNAc(b1-4)[Neu5Ac(a2-8)Neu5Ac(a2-3)]Gal(b1-4)Glc(b1-1)Cer; GD1b, Gal(β1-3)GalNAc(β1-4)[Neu5Ac(α2-8)Neu5Ac(α2-3)]Gal(β1-4)Glc(β1-1)Cer; GT1b, Neu5Ac(α2-3)Gal(β1-3)GalNAc(β1-4)[Neu5Ac(α2-8)Neu5Ac(α2-3)]Gal(β1-4)Glc(β1-1)Cer; GM1, Gal(β1-3)GalNAc(β1-4){Neu5Ac(α2-3)}Gal(β1-4)Glc(β1-1)Cer.

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complex biomolecular assemblies. Both the sugar units have a diverse range of anomery and linkages with the penultimate sugars. The existing literature and databases did not contain comprehensive information regarding structure–function relationship of glycans. Therefore, the current study is scheduled to debate on the structure–function relationship of glycans carrying Fuc and sialic acid in their backbone structures.

Contents

1. Introduction

Today the scientists (biochemists, immunologists, molecular biologists, microbiologists, pathologists and pharmacologists) are putting in tremendous efforts to explore the relationship of sugars with their glycobiology. Glycoproteins and glycolipids are the major constituents of biomembranes, regulating the wide range of cellular functions including cellular differentiation, interaction and communication. These diverse biological functions of glycoconjugates are regulated by complex oligosaccharide structures linked with proteins and lipids in macromolecular assemblies. The diversity in oligosaccharide chains attached with lipids and proteins is specifically linked with the conformational behavior of sugar residues giving rise to unique carbohydrate structures with a wide range of sequence and anomeric linkage.

For example the blood group A determinant is specific with the terminal GalNAc residue having α1-3 anomeric linkage with the penultimate sugar. Similarly, the terminal Fuc α1-2 is linked with blood group H recognition and the Fuc α1-3 core structure is specific for allergic reactions mediated by IgE (Becker and Lowe, 2002), while, sialic acid with α2-3 at the non-reducing end of sugar chain is intrinsically linked with selective adhesion and its extrinsic involvement is associated with various pathogenic bindings (Varki, 2007). Additionally, the specific reactivity of Fl antibody with adult erythrocytes due to the presence of sialic acid at one terminal and Fuc at the other terminal of glycan highlights the physiological vitality of these two sugars (Kannagi et al., 1983).

According to the literature study, the sugars naturally exist in D-form rather than L-isoform (Salam, 1991). But the fucose sugar unlike other sugar monomers exists naturally in L-form rather than D and found covalently linked with the D-Galactose and D-GlcNAc in most of the oligosaccharide chains (by means of α1-2, α1-3 and α1-4 anomeric linkages), while the sialic acid anchors mostly at C-3, C-6 and C-8 of the Gal and GlcNAc residues (Miyoshi et al., 2008, 2010; Fujihashi et al., 2003; Vrionis et al., 1989).

This review article discusses the physiological importance of Fuc and sialic acid residues in complex carbohydrate structures, and then focuses on the physiological specificity of particular stereochemical features (sequence and anomeric linkages) of Fuc and sialic acid in vital cellular phenomena.

2. Physiological efficacy of fucosylated glycans

Glycans having fucose residue at their terminal and subterminal regions are involved in various cancer disorders like hepatic cancer, colon cancer, cervical cancer, bladder carcinoma, prostrate cancer, lung cancer, gastric cancer, thyroid cancer and ovarian cancer (Miyoshi et al., 2008, 2010; Dabelsteen et al., 1988; Fukushi et al., 1984; De-Vries et al., 1993). These fucosylated glycans mediate the ligand adhesion with lectins and can provide a useful basis for the diagnosis of various pathologies. Glycoshingolipids containing different Lewis determinant structures (Le^x, Le^a and Le^y) are accumulated in abundance in various human carcinomas like gastric, lung and colon (Holmes et al., 1987; Nudelman et al., 1986; Sueyoshi et al., 1992; Stroud et al., 1991).

Human milk contains α-3-fucosyltransferase, which causes fucosylation at the C-3 of GlcNAc. This alpha-3-fucosyltransferase mediates the biosynthesis of Lex related (difucosylated and trifucosylated) glycan structures which are associated with cancer recognition and selectin based adhesions (Dabelsteen et al., 1988; De-Vries et al., 1993; Sarkar et al., 1997). The ligand interaction of Lex related carbohydrate structures with selectins can provide a useful tool for the study of metastasis in various carcinomas. The literature study reflects that the Fuc moiety in fucosylated glycans behaves as an attachment or modification point for the addition of fucose and various other sugar residues. For example, the terminal addition of GalNAc with α1-3 at the Fuc of H-antigenic determinant causes the formation of blood

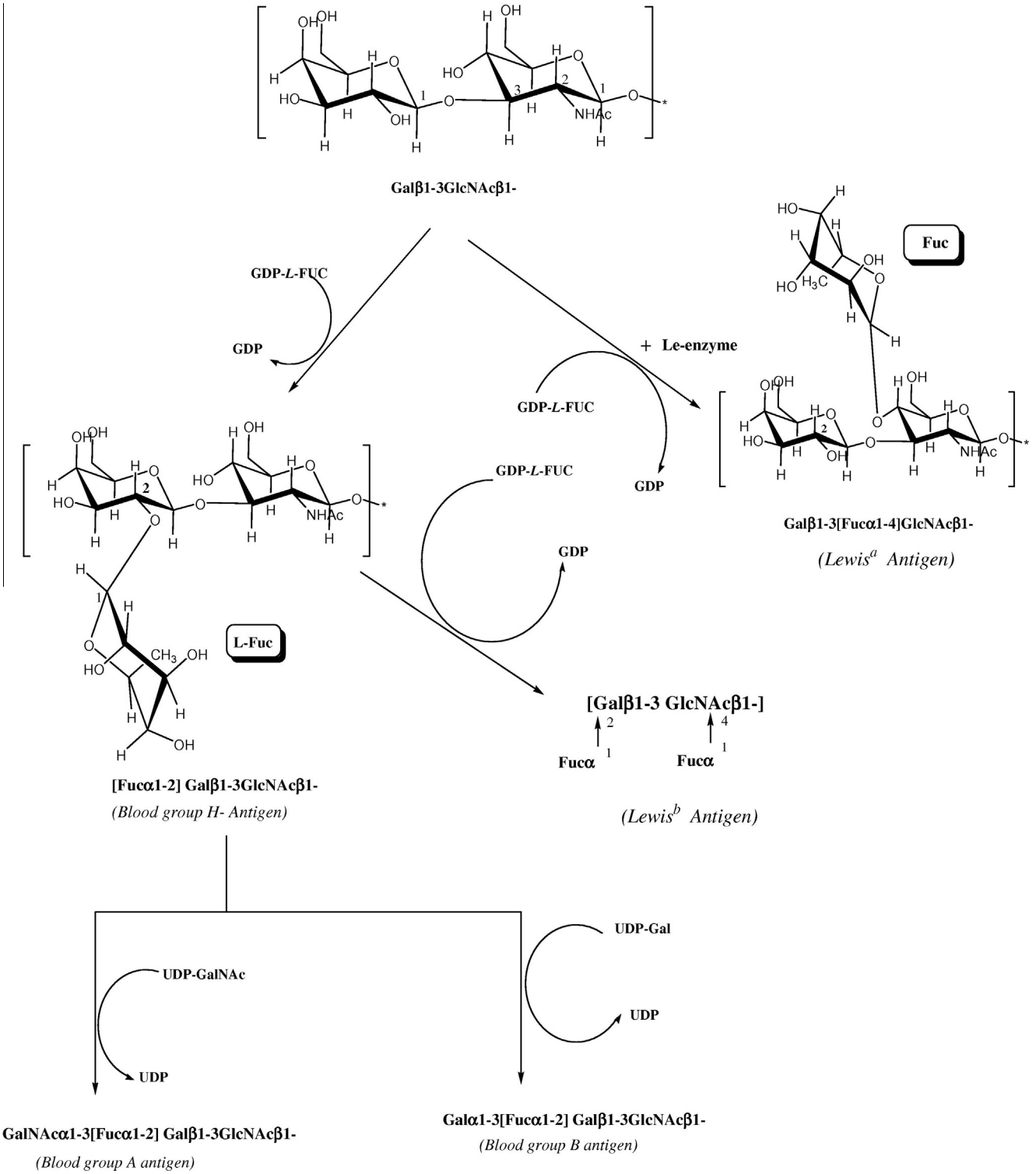

Figure 1 Glycosylation patterns of Galβ1-3GlcNAcβ1- to form the A, B, O and Lewis blood group antigens (Mo et al., 1994).

group A determinant structure. Similarly the addition of Fuc with a particular anomeric linkage (α1-2) at the terminal of Lex determinant structure converts it into Ley antigenic structure and changes the overall physiology of glycan (Kobata, 1992). Hence the physiological strengths of fucosylated glycans are specific with the sequence and anomeric linkage of Fuc sugar within carbohydrate chains.

2.1. Blood group antigens and their cellular physiology

The Lewis and ABO blood group antigens are biologically significant because these glycoepitopes generate the genetical and biochemical specificities on the red blood cells. The experimental study has connected the Fuc moiety with blood group "H (O)" specificity and *N*-acetyl galactosamine residue with blood group

A specificity. The complexity in ABH blood group antigens is due to the diversity in their carrier glycan chains. The literature data elucidate that the blood group H determinant [Fuc α 1-2] Gal β1-3GlcNAcβ1-] acts as a precursor for blood groups A, B and Le^b antigenic structures (Fig. 1) (Kobata, 1992).

The blood group A determinants have different epitopes of lacto-series. The blood group A type 1 structure is highly expressed in goblet and columnar cells of normal fetal mucosa, while the type 2 chains are accumulated in the human colon carcinomas (Dabelsteen et al., 1988). The epitopes of type 1 and 2 chains of blood group A differ only in their anomeric linkages at fucosylated Gal residues and this structural difference causes the basis for their localization in different body tissues. It can also be predicted from this example that the cellular characterization of normal and carcinomal tissues is specifically linked with the anomeric linkages of sugar residues.

Monofucosylated and difucosylated type 2 chains of blood group A are characterized by high concentration in tumor tissues. This high expression of fucosylated type 2 chains in tumor tissues links the alteration in the core structure of carbohydrates with tumor development (Dabelsteen et al., 1988; Fukushi et al., 1984).

According to the reported data, the type 2 chain structures like Le^x, Le^y and sialylated Le^x are also characterized by high concentrations in colonic adenocarcinomas (Nudelman et al., 1986; Laferte et al., 1995). The sequence and anomeric linkages of fucosylated glycans along with their physiological functions are given in Table 1.

2.2. The role of fucoglycans in various cellular pathologies

Fucosylation is one of the main glycosylation patterns observed in cancer tissues. This glycosylation mode is controlled by different fucosyltransferases, which in turn is regulated by several genes in the body. Fucosylated proteins are the well-known cancer markers in the body. Alpha-fetoprotien is one of such proteins involved in different pathological conditions of the liver. It is also observed from the literature that the fucosylated fetoprotein is a renowned hepatocarcinomal marker and a liver cirrhosis determinant. The α1-6 fucosyltransferase has its significant involvement in the regulation of core fucosylation reaction. (Miyoshi et al., 1999, 2010).

Schistosoma mansoni is a significant pathogen which causes schistosomiasis disease in humans. The egg antigens of *S. mansoni* has a receptor binding with the C-type lectin (DC-SIGN) through the α1-3 fucosylated Le^x and LacdiNAc GalNAcb1-4(Fuca1-3)GlcNAc structures (Huang et al., 2001).

Bronchiectasis is an obstructive lung disease, linked with fucolipids for its characterization. According to the documented study, this bronchiectasis disease is associated with different disorders and infections of staphylococcus species. The glycan-aldaltol chains isolated from the respiratory mucins of bronchiectasis patient are Gal(b1-4)[Fuc(a1-3)]GlcNAc(b1-3)Gal(b1-4)[Fuc (a1-3)]GlcNAc(b1-3)Gal(b1-3)GalNAc-ol; Fuc(a1-2)Gal (b1-3) [Fuc(a1-4)]GlcNAc(b1-3)Gal(b1-3)[Gal(b1-4)GlcNAc(b1-6)] GalNAc-ol and Fuc(a1-2)Gal(b1-4)[Fuc(a1-3)]GlcNAc(b1-3) [Gal(b1-4)GlcNAc(b1-6)]Gal(b1-3)GalNAc-ol. These fucosylated glycan chains provide the range of determinant structures for bronchiectasis (Van-Kuik et al., 1991).

Moreover, the Fuc rich glycopeptides and glycoconjugates are also recognized in the urine of fucosidosis patients. Structures obtained from the urine of fucosidosis are Gal(b1-4) [Fuc(a1-3)]GlcNAc(b1-2)Man(a1-6)Man(b1-4)GlcNAc and Gal(b1-4)[Fuc(a1-3)]GlcNAc(b1-2)Man(a1-3)Man(b1-4)GlcNAc. Both the structures have Fuc at the C-3 position of GlcNAc, which is further attached with human through

Table 1 Physiological involvement of glycoepitoes in cellular phenomena.

Glycoepitope ID/ name	Structure	Physiological contexts and references
EP0256/Blood group A Type 1	GalNAc(α1-3)[Fuc(α1-2)]Gal(β1-3)GlcNAc(β1-)-R	Blood group A determinants are potently expressed in columnar cells of normal fetal mucosa (Dabelsteen et al., 1988; Mo et al., 1994)
EP0260/Blood group A Type 1 (Difucosylated glycan)	GalNAc(α1-3)[Fuc(α1-2)]Gal(β1-3)[Fuc(α1-4)]GlcNAc(β1-)-R	Blood group A variants with fucosylated domains are potently expressed in columnar cells of normal fetal mucosa (Dabelsteen et al., 1988)
EP0257/Blood group A Type 2	GalNAc(α1-3)[Fuc(α1-2)]Gal(β1-4)GlcNAc(β1-)-R	Complex carbohydrate structures act as carrier for human carcinomas (Dabelsteen et al., 1988; Fukushi et al., 1984; Clausen et al., 1986)
EP0261/Blood group A Type 2 (Difucosylated glycan)	GalNAc(α1-3)[Fuc(α1-2)]Gal(β1-4)[Fuc(α1-3)]GlcNAc(β1-)-R	Fucosylated structures have their involvement in human normal colon and colon tumor (Dabelsteen et al., 1988; Fukushi et al., 1984; Clausen et al., 1986)
EP0258/Blood group A Type 3	GalNAc(α1-3)[Fuc(α1-2)]Gal(β1-3)GalNAc(α1-)-R	Involvement of blood group epitopes in bladder carcinoma, cervical epidermal carcinoma and colon carcinoma (Dabelsteen et al., 1988; Clausen et al., 1986)
EP0262/Blood group B Type 2	Gal(α1-3)[Fuc(α1-2)]Gal(β1-4)GlcNAc(β1-)-R	Detection of Oncodevelopment changes in rat and human colon cancer cells on the basis of blood group variant (Dabelsteen et al., 1988; Laferte et al., 1995)
EP0093/ $Lewis^x$	Gal(β1-4)[Fuc(α1-3)]GlcNAc(β1-3)Gal(β1-4)[Fuc(α1-3)]GlcNAc(β1-)-R	Recognition of human adrenocarcinomas by Lex expression (De-Vries et al., 1993; Holmes et al., 1987)

β1-2 anomeric linkage (Nishigaki et al., 1978). The structural difference at the anomeric linkages of mannose in both isolated structures reflects that the Fuc moiety may affect the anomeric environment of penultimate sugar residues within glycans.

The experimental study proved that the BR55-2 monoclonal antibody has the potent binding specificity for the Y determinant [Fucα1-2Galβ1-4GlcNAc(Fucα1-3)β1-3Galβ1-4Glcβ1-1Cer] and the Y-related difucosylated determinant structure [Gal α1-3 Gal (Fuc α1-2) β1-4GlcNAc(Fuc α1-3) β 1-3Gal β 1-4Glc β 1-1 Cer], which are identified in human gastric adenocarcinoma cell line KATO III (Blaszczyk-Thurin et al., 1987).

2.3. Involvement of fucose sugar in lectin adhesion

Lectins, the *N*-linked glycoproteins are engaged in regulating several important physiological mechanisms like cell death, immune system homeostasis, and control of tumorigenesis. All lectins having the same nature as that of Iris lectin can be discriminated on the basis of their interactions with detailed carbohydrate structures. For example Lima Bean Lectin (LBL) has strong binding potency for the blood group A trisaccharide structure GalNAc α1-3(Fucα1-2)Gal having Fuc as a side sugar moiety. This agglutination pattern of LBL can be diminished by removing the Fuc sugar from the blood group A variant. Similarly the binding interaction of iris lectin with blood group A is diminished due to the steric hindrance of Fuc residue. The steric hindrance of Fuc residue provides the basis for the failure in blood group A agglutination and can be used as a valuable tool for the characterization and diagnosis of various cellular pathologies (Mo et al., 1994).

Dilochos biflorus agglutinin (DBA) has a strong binding specificity for the Forssmann disaccharide (GalNAcα1-3GalNAc). But this binding interaction is found weaker in the case of blood group A trisaccharide. The poor binding ability of blood group A determinant suggests that the C-2 hydroxyl group of penultimate Gal residue is the vital locus for the lectin binding. The binding capability of DBA is abolished by replacing the C-2 hydroxyl group of Gal with Fuc sugar (Fig. 2) (Hamelryck et al., 1999).

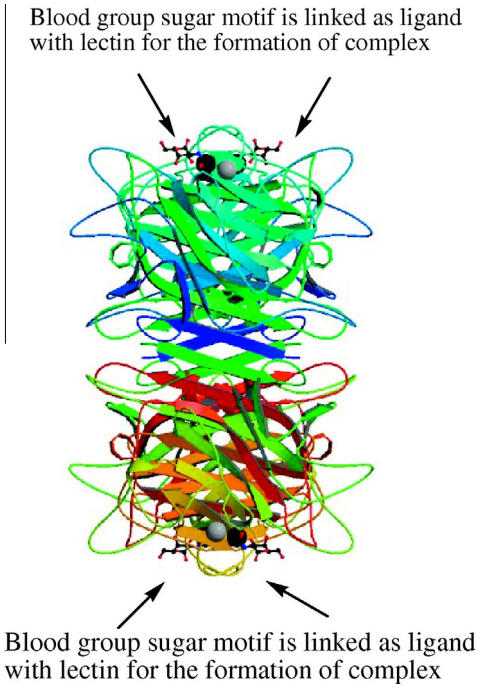

Figure 2 Carbohydrate trisaccharide structure and its ligand complexation with lectin (Hamelryck et al., 1999).

3. Sialic acid chemistry and physiological significance of sialylated glycans

Sialic acid contains backbone structure of 9 carbons including carboxylic acid moiety at the C-1 position. Variations in anomeric linkages and the substitutions at the C-4, C-5, C-7, and C-8 and C-9 positions reflect the diverse nature of sialic acid moiety (Fig. 3). *N*-Acetyl neuraminic acid (Neu5Ac) and *N*-glycolyl neuraminic acid (Neu5Gc) are the two main sialic acid residues found in mammalian glycans. Additional oxygen atom in Neu5Gc distinguishes this sialic acid unit from Neu5Ac and may be the cause of its localization in different species (Neu5Gc is the modified form of Neu5Ac which has been diminished in human species during genetic mutation). In fact, the abnormal occurrence of GM2 gangliosides (*N*-acetyl and *N*-glycolyl species of GM2) is localized in carcinomas by the recognition of *N*-acetyl and *N*-glycolyl groups of sialic acids. The literature study highlights that the Neu5Ac moiety is attached mostly with the Gal and GlcNAc in oligosaccharide chains. Sialic acid causes the increase in the strength of charge density on the whole glycan chain due to the presence of its carboxylic acid moiety. The carboxylic acid moiety, *N*-acetamido group along with the hydroxyl groups are reported in different types of cellular interactions in immunity, homoeostasis and inflammation (Chen and Varki, 2010; Varki, 2007).

Selectins are known as sialic acid binding proteins and engaged in immunity and inflammations related cellular phenomena. The ligand interactions of leukocytes with endothelial-selectin (E-selectin) and platelet selectin (P-selectin) are mediated through sialic acid moieties. So the recognition of all types of selectins is mediated with sialic acid residues (Chen and Varki, 2010; Varki, 1994).

Sialylated Le^x was potently expressed in the malignant tumors of epithelial origin and experimental study demonstrated that the carcinoma having sialyl Le^x could bind with the E-selectin on activated endothelial cells. Sialylated mucins of circulating carcinomas initiate the interactions with platelets and leukocytes by mimicking natural selectin ligands. Hence the existence and distribution of malignant cells in bloodstream are mediated by the platelets and leukocytes. It is also found that the use of heparin as an inhibitor of P- and L-selectin causes the remarkable decrease in metastasis (Varki, 1994; Varki and Varki, 2002).

Siglecs (sialic-acid-recognizing Ig-superfamily lectins) required sialic acid with specific anomeric linkage for their physiological actions. For example, CD22 (Siglec-2) is a known inhibitor of B cell receptor (BCR) signaling due to O-acetylation at C-9 of the sialic acid having α2-6 linkage (Cariappa et al., 2009). Similarly, the CD33rSiglecs are involved in the recognition of pathogens having sialic acid residues. Documented study elucidates that the Siglecs adhesion is mediated by the recognition of carboxylic acid charge density, *N*-acetyl group and the hydroxyl groups of C-4, C-5, C-7, C-8 and C-9 in the sialic acid parent molecule (Cariappa et al., 2009; Vyas et al., 2005; Varki, 2007).

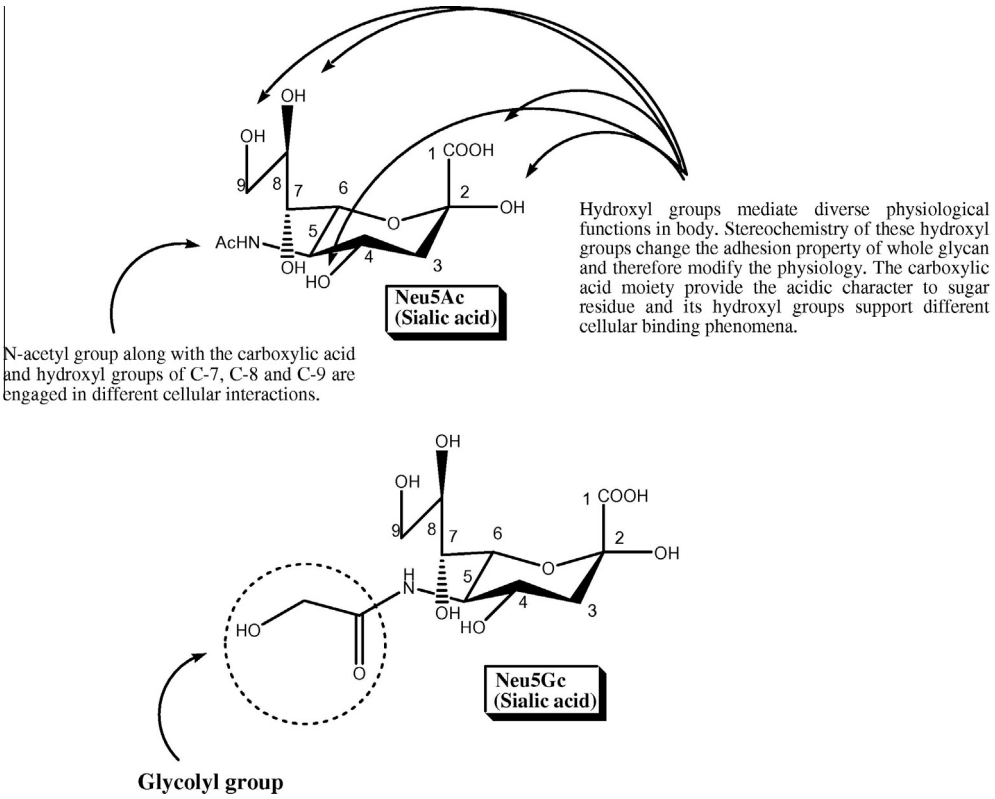

Figure 3 The functional groups are pointed out in stereochemical structure of *N*-acetyl neuraminic acid (NeuAc) and *N*-glycolyl neuraminic acid (NeuGc).

Additionally, the gangliosides are the plasma membrane components having sialic acid sugar residues in their parent chain. The cell signal transduction is regulated by these plasma membrane components of glycolipids. More than 60 gangliosides are known, which have different sequence, anomery and linkage of sialic acid with the vicinal sugars. These gangliosides being part of cell membrane and extracellular matrix mediate different physiological actions like nerve cells interaction, recognition and communication. The GM1, GD1a, GD1b, GT1b, GM2, GM3, GD2, GD3 and GT1c are the common gangliosides present in the central and peripheral nervous system. These gangliosides are homologous to each other but have different number of sialic acid residues in their glycan chain. The GM1, GM2 and GM3 have single sialic acid residue and are known as monosialogangliosides. While the GD1a, GD1b, GD3 and GD2 are disialogangliosides, due to the presence of two sialic acid moities in their glycan structures. Similarly the GT1 contains three and GQ1 contains four neuraminic acid residues. Most of the mono-, di-, and tri-sialogangliosides are biosynthesized by GM3 (Figs. 4 and Fig. 5). The change in the number and sequence of neuraminic acid residues in complex carbohydrate structures may provide the basis for diverse cellular physiologies in different biological systems (Kusunoki et al., 1993; Abregú et al., 2002; Hidari et al., 1993; Vrionis et al., 1989; Kotani et al., 1993; Yamaguchi et al., 1990).

GM1 and GM2 are the valuable markers in the early detection of diabetic complications. During short term diabetes in rats, the change in expressions of GM1 and GM2 is lead by the microscopic hepatocellular modifications (Abregú et al., 2002). It is also observed that the extension in GM2 chain length causes cancer-associated modifications in gastric mucosa. *N*-acetyl- and *N*-glycolyl GM2 antigens are observed in non-seminomatous and seminomatous germ tumors, respectively. The *N*-glycolyl GM2 is linked with the level of differentiation of non-seminomatous germ cell tumors, choriocarcinoma, and teratocarcinoma, which have a positive occurrence of *N*-glycolyl GM2 as compared with the *N*-acetyl GM2 (Miyake et al., 1990). GM2 and GD2 gangliosides are potently expressed on the melanoma, astrocytoma, neuroblastoma, and leukemia cell lines, and the detection of these glycolipids is done by using 3-207 monoclonal antibodies (Miyake et al., 1990; Yamaguchi et al., 1990; Nakamura et al., 1984).

Disialogangliosides, GD3 and GD2 are expressed in large concentrations on the cellular surface of human melanomas. Monoclonal antibodies (Mabs), which have binding potency for the GD3 and GD2, restrict the attachment of melanoma and neuroblastoma with various substrate adhesive proteins like fibronectin, collagen, vitronectin and laminin (Yamaguchi et al., 1990; Longee et al., 1991; Iwamori and Nagai, 1979; Cheresh et al., 1986).

GD1c is an important ganglioside of T cells synthesized by asialo-GM1 [Gal(β1-3)GlcNAc(β1-4)Gal(β1-4)Glc(β1-1)Cer]. The other GM1 derivatives, like GM1b (NeuAc and NeuGc) and GD1a are also detected in large quantity in T cells. The structures containing the GM1 core structure like Gal-LacNAc-GM1, α-Gal-(LacNAc)2-GM1, and sialyl-LacNAc-GM1 are observed in high concentration in B-cells (Iwamori and Nagai, 1979).

GD1b is recognized with the other gangliosides like GQ1b and GM1 in human and rat nervous systems. This glycolipid (GD1b) is characterized on the granular cell bodies surface

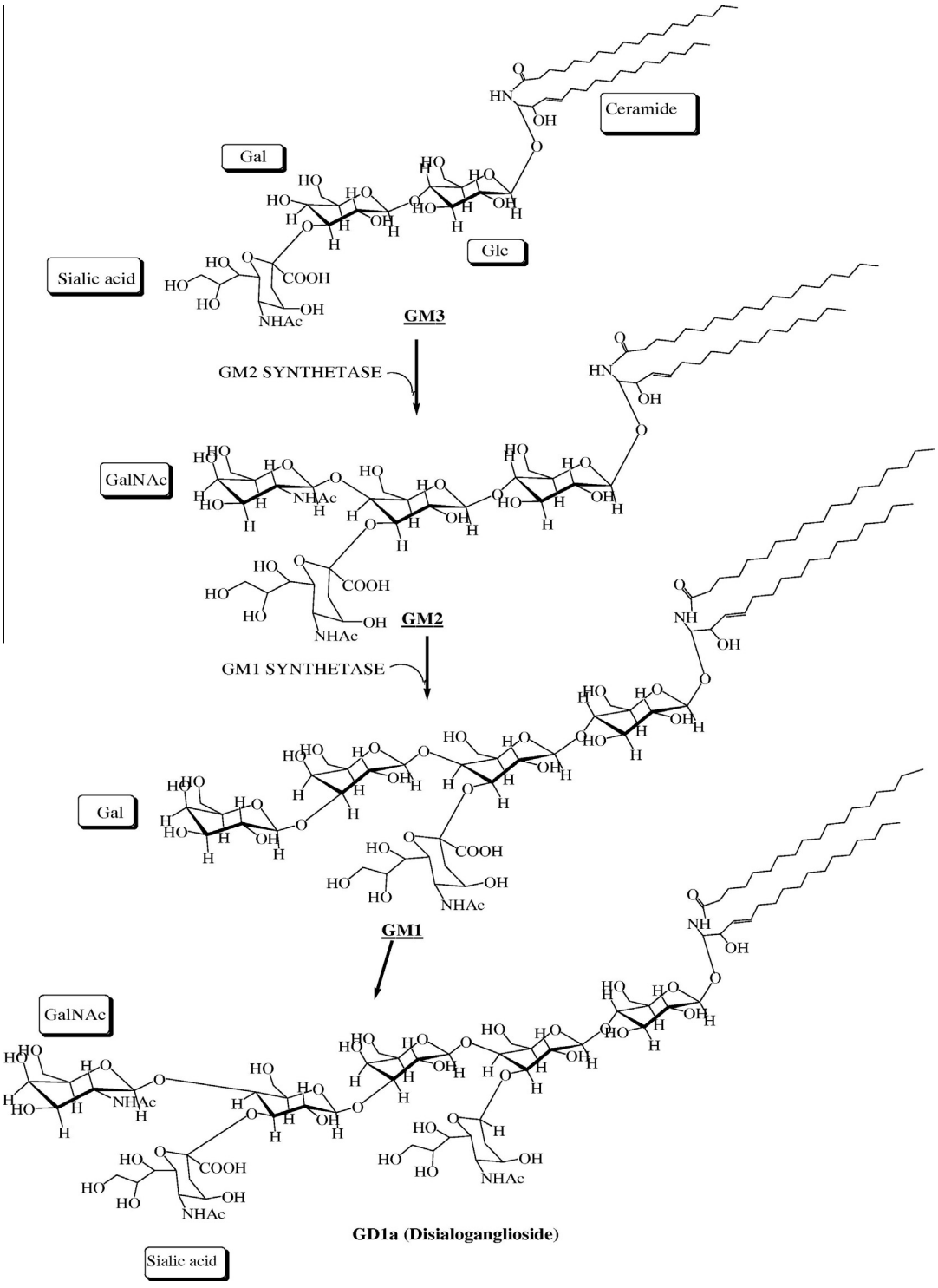

Figure 4 The biosynthesis of different monosialogangliosides (GM1, GM2, GM3 and GD1a).

by means of antibodies. Serum antibodies which have been localized in autoimmune neuropathies can be used for the characterization of GM1 and GD1b in the human peripheral nervous system. GD1b antigen is expressed on neurons and paranodal myelins in the peripheral nervous system while the GM1 is localized with neurons in dorsal root ganglia and sympathetic ganglia (Kusunoki et al., 1993, 1994).

The Immunochemical study of pig cochlea highlights that the glycoconjugates of ganglio-series having GM3, GD3 and GD2 are potently expressed in the neuronal fibers spiral ganglions, and stria vascularis. These structures are completely absent in the tectorial membrane (TM) and Corti's organ of Pig (Hozawa et al., 1993).

Human milk gangliosides contain the GM1 and GM3 structures and block the adhesion of *E. coli* with Caco-2 cells. It is also analyzed from the literature that the bovine milk gangliosides have less blocking tendency for *E.coli* adhesion. The rate of adhesion of *E. coli* in the presence of

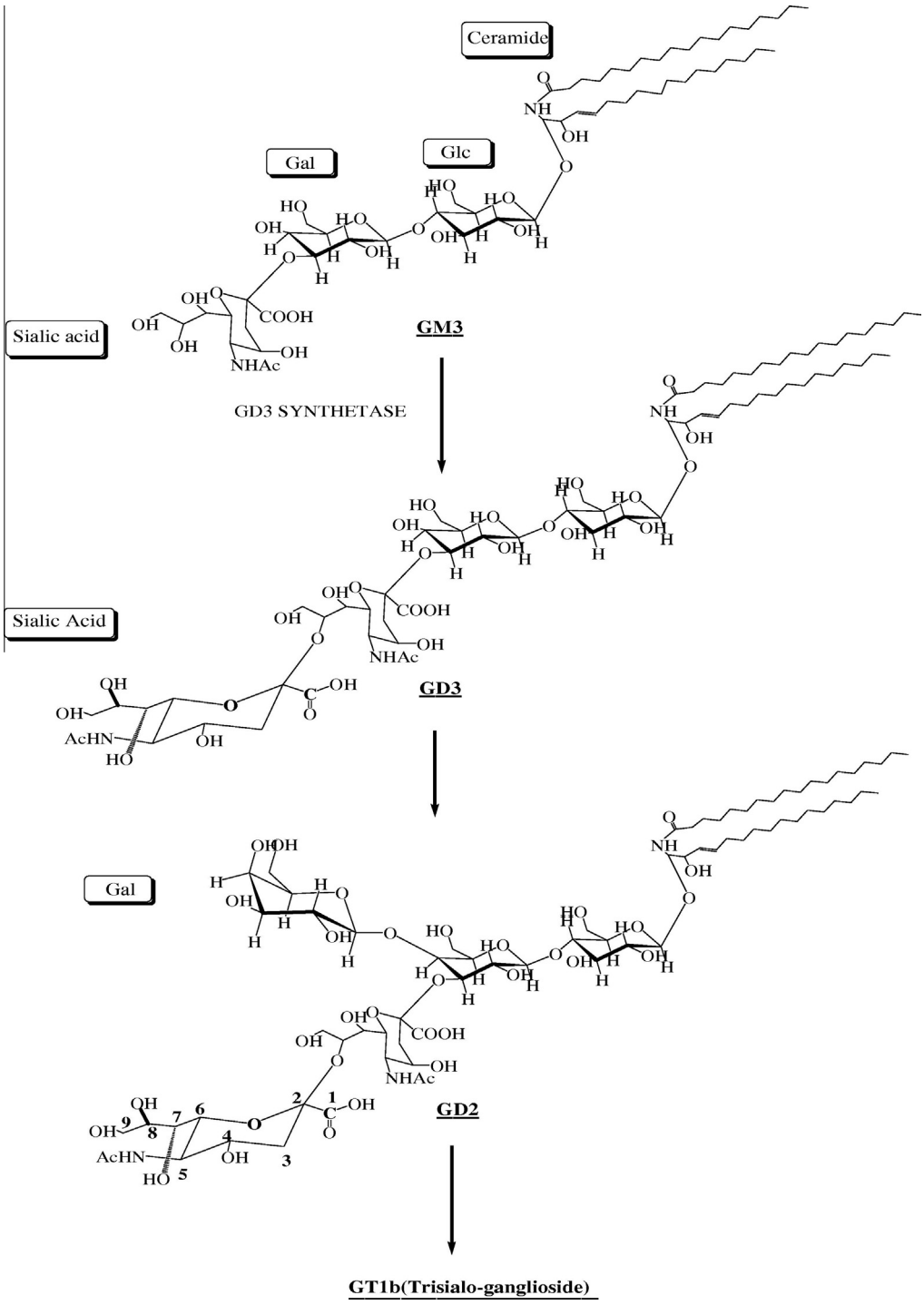

Figure 5 The biosynthesis of different sialogangliosides like GD1, GD2 and GD3. The GM3 ganglioside acts as precursor for the formation of the di and trisalylated gangliosides.

monosialoganglioside 1 (GM1) is found to be less than 20%. The adhesion of *E. coli* is observed to be more than 30% for the monosialoganglioside 3 (GM3). However, the blocking effect of disialoganglioside 3 (GD3) is found to be less than that of GM3 (Nakamura et al., 1984; Idota and Kawakami, 1995).

Similarly, bacterial toxins cause the number of diseases like diarrheal disease due to their recognition by GM1 epitopic domains and its homologs. *Vibrio-cholera* secretes the Cholera-toxin whose B-subunit has strong binding specificity for the GM1 ganglioside. The same preference is found for the GD1b and GT1b [Neu5Ac(α2-3)Gal(β1-3)GalNAc(β1-4)[Neu5Ac(α2-8)Neu5Ac(α2-3)]Gal(β1-4)Glc(β1-1)Cer]. The additional NeuAc causes the reduction in binding affinity due to steric hindrance. It is also shown in the literature that the *N*-acetyl group of neuraminic acid in GM1 is not necessary for its binding with the cholera-toxin B-subunit. The

Table 2 Functional regions of sialylated glycans with their biological efficacy.

Glycan ID/ name	Glycan sequence	Functional region	Function/reference
G00168/ GalNAc-GD1a	GalNAc(b1-4)[Neu5Ac(a2-3)]Gal(b1-3)GalNAc(b1-4)[Neu5Ac(a2-3)]Gal(b1-4)Glc(b1-1)Cer	GalNAc(b1-4)[Neu5Ac(a2-3)]Gal(b1-1	1. Guillain-Barre syndrome (Kusunoki et al., 1994) 2. Brain cancer and related pathophysiology (Idota and Kawakami, 1995; Merritt et al., 1994; Grassi et al., 1990; Yasukawa et al., 1995)
G00109/ GM2	GalNAc(b1-4)[Neu5Ac(a2-3)]Gal(b1-4)Glc(b1-1)Ceramide	GalNAc(b1-4)[Neu5Ac(a2-3)]Gal(b1-4)Glc(b1-1	Human germ cell tumors (Morrison et al., 1991)
EP0052/N-Glycolyl GM2	GalNAc(b1-4)[Neu5Gc(a2-3)]Gal(b1-4)Glc(b1-1)Cer	GalNAc(b1-4)[Neu5Gc(a2-3)]Gal(b1-)	Human germ cell tumors (Morrison et al., 1991)
EP0061/ GD2	GalNAc(β1-4)[Neu5Ac(α2-8)Neu5Ac(α2-3)]Gal(β1-4)Glc(β1-1)Cer	GalNAc(β1-4)[Neu5Ac(α2-8)Neu5Ac(α2-3)]Gal(β1-4)Glc(β1-1)Cer	1. Human neuroectodermal tumor (Eto and Shinoda, 1982) 2. Lung carcinoma (Watarai et al., 1994) 3. Binding interaction of human melanomas and neuroblastomas to extracellular proteins (Svennerholm et al., 1973; Yu et al., 1983)
EP0050/ GM1	Gal(β1-3)GalNAc(β1-4)[Neu5Ac(α2-3)]Gal(β1-4)Glc(β1-1)Cer	Gal(β1-3)GalNAc(β1-4)[Neu5Ac(α2-3)]Gal(β1-4)Glc(β1-1)Cer	1.Recognition of GM1 in small cell lung carcinoma cell lines and tissues (Watarai et al., 1994) 2. Prostate cancer and localization of human peripheral nervous system (Saito et al., 2005; Hidari et al., 1993; Vrionis et al., 1989) 2. Guillain-Barré syndrome (Kusunoki et al., 1994)
G03973	Gal(a1-3)Gal(b1-4)GlcNAc(b1-6)[Neu5Ac(a2-3)Gal(b1-4)Glc(b1-3)]Gal(b1-4)GlcNAc(b1-3)Gal(b1-4)Glc(b1-1)Ceramide	Neu5Ac(a2-3)Gal	Influenza virus A/X-31 (H3N2) binding specificity with sialic acid Gal (Suzuki et al., 1986)

de-*N*-acetyl-neuraminic acid GM1 [Gal(β1-3)GalNAc (β1-4){Neu (α2-3)}Gal(β1-4)Glc(β1-1)Cer] of bovine brain have binding preference for the DM2-1 mouse monoclonal antibody and Cholera-toxin B subunit. So these de-*N*-acetylated gangliosides are bioactive macromolecules having their significant role in the nervous system (Merritt et al., 1994; Grassi et al., 1990; Yasukawa et al., 1995).

GM1 has its involvement in neuronal plasticity and repair mechanisms, and release of neurotrophins in brain. Besides that the GM1 derivatives bind with the T cells resulted in the down regulation of their surface protein CD4, and can reduce human herpesvirus 7 infection (Morrison). The further physiological functions performed by sialic acid containing active domains of glycans are given in Table 2.

4. Databases annotation

Different glycan databases like Glycoepitope, Kegg, Glycosuite, Glycome DB, Complex Carbohydrate Structural Database (CCSD), GlycoMaps, Glycobase and Glycoscience are publicly present to evaluate the implications of sugar anomeric linkages in specific recognition activities. These databases provide the information about glycan structures and their functional diversity, but are still limited about the structure–function relationship of sugar motifs.

The statistical detail of these databases is given below:

Glycoepitope (http://www.glyco.is.ritsumei.ac.jp/epitope/) have 146 glycoepitope entries. Each epitopic ID starts with English Capital letter EP. The information given against each entry contain data like Epitope ID, Sequence, Aliases, History, Molecular weight, Species, compositions and receptor explanation.

Kegg database (http://www.genome.jp/kegg/) contains 10969 glycan entries some of which are methylated, phosphorylated and sulfated. Kegg database gives information about structural ID, Composition, Mass, Structure, Class, biosynthetic pathway, orthology, enzyme details and KCF data of glycan chains. Each Kegg glycan entry starts with the Alphabetical letter G.

Eurocarb bank (www.eurocarbdb.org) consists of 13,457 detailed glycan sequences of which 1 HPLC, 89 Mass Spectrometry, and 0 NMR analyses based glycan structures are present.

Bacterial Carbohydrate Structure Database (BCSDB) encloses 9506 glycan motifs. Each glycan entry contains the information like BCSDB ID, Bibliography, (Sub) structure, Microorganism, NMR signals.

Glycoscience database (http://www.glycosciences.de/sweetdb/) gives details of Structures, Theoretical Mass peaks, NMR Data, Taxonomy etc. This database contains 14857 different sugar structures having *O*-glycans (505), *N*-glycans (3415), and glycolipids (560).

GlycoMaps (http://www.glycosciences.de/modeling/glycomapsdb/) is another database which contains 2585 conformational maps. This database deals with conformational maps of disaccharide motifs. It is linked with other databases like Glycosciences database for further details like pdb files, mass spectra, NMR spectra etc.

Consortium for Functional Glycomics (CFG) (www.functionalglycomics.org) database encloses 7500 entries. Each entry holds structural as well as chemical information.

Glycome DB (http://www.glycome-db.org/showMenu.action?major=database) gives information containing all structures and annotations. It provides details like image of the structure, entries in other databases for the structure, known carbohydrate motifs and encoding of the structure.

5. Conclusion

The structure–function relationship of complex carbohydrates is attracting the attention of scientists working all over the world in the field of science and technology. And it is now clear from the above discussion that the particular stereochemical features of glycans regulate a wide range of physiological functions in the body. It is also observed that a slight change in the structure of the glycan motif can cause a remarkable alteration in their physiological functions. The most prominent example is the involvement of neuramic acid derivatives in cancer progression. The structural difference between the two glycolipids, GalNAc(β1-4)[Neu5Ac(α2-3)]Gal(β1-) and GalNAc(β1-4)[Neu5Gc(α2-3)]Gal(β1-) is provided by the acetyl and glycolyl groups attached with the C-5 of Neuraminic acid in the glycan chain. The glycan structure carrying the acetyl group is linked with hepatic and brain cancers, while the glycolylated glycan structure has its physiological role in brain cancer only (Vrionis et al., 1989).

Similarly, the ligand interaction of blood group variants with lectins is also significantly affected by replacing or adding the fucose sugar with specific anomeric linkage. The accelerated research in glycobiology is corroborating the significance of our study on glycans. This type of study can mediate the basis for the diagnosis of various cellular pathologies. The study can provide the useful tool for the prediction of various diseases and their diagnosis.

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