**Glycan regulation in cancer, nervous and immune system: A narrative review**

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**ABSTRACT**  
Glycans are carbohydrate components of glycoconjugates, which interact with their receptors; for example, galectins and C-type lectins. The specificity to their receptors makes them the ideal biomarkers that they can be used as a therapeutic target or as a screening tool. We collected and reviewed articles from different databases, which show that glycans play a significant role in several body functions, such as stimulation of the immune system, and can be used in the differentiation among cancer types. They also help in nervous system repair, regeneration, regulation and proliferation. Furthermore, several pathogens like Schistosoma, HIV, Influenza, Candida, and Ebola produce glycoproteins to aid in the invasion via attachment to surface glycoproteins and defend themselves against the host’s immune system.

**Key words:** Glycan, Biomarker Glycoconjugate, Lectins, Immunoglobulin

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**INTRODUCTION**  
As characterized by the IUPAC, the terms glycan and polysaccharide are equivalent and describe a compound containing monosaccharides that are connected glycosidically, or bits of carbohydrate glycoconjugates, such as a glycoprotein, glycolipid, or a proteoglycan¹. Glycans are exclusively comprised of O-glycosidic linkages of monosaccharides. For instance, cellulose is a glycan that is made from β-1, 4-connected D-glucose, and chitin is a glycan that is made from β-1,4-connected N-acetyl-D-glucosaminé²-⁴. Glycans can be homo- or heteropolymers of monosaccharide builds and can be in straight or extended forms. All cells and various macromolecules in nature convey a variety of covalently linked sugars (monosaccharides) or sugar chains (oligosaccharides), which are conventionally alluded to as "glycans"³. Sometimes, these glycans can also be freestanding entities. They perform different functions in multicellular organisms and play the role of mediators between different organisms (e.g., between host and a parasite or a symbiont). In addition, protein-bound glycans are abundant within the nucleus and cytoplasm, where they can serve as regulatory switches¹. During 1960s and 1970s, the initial phase of the molecular biology revolution, investigations of glycans lingered a long way behind those of other major classes of particles. The advancements for studying glycan structures and functions since then opened a novel and new era of molecular biology that was called “glycobiology”. In the late 1980s, this word was first coined to distinguish the molecular biology of glycans and specifically, their conjugates with lipids and proteins¹.  

Various natural bioactive molecules are glycoconjugates and linked to glycans, which can affect the biosynthesis, action, stability, and molecules turnover within intact organisms. For instance, heparin (sulfated mucopolysaccharide) and their derivatives are the utmost generally used drugs globally. Glican biology has turned out to be essential in the current biotechnology because the steps of glycoprotein drug patenting, FDA approval for its usage, and monitoring the overall manufacture require knowledge of the glycan structure. Furthermore, nowadays, glycoproteins are the major products of the biotechnology industry, including monoclonal antibodies, hormones, and enzymes. The diagnostic and/or therapeutic significance of glycans are helpful in several human disease states that are characterized by the changes in glycans biosynthesis⁵.  

There are more glycans than proteins encoded in our entire genome. Defects in genes that control glycan production or glycan chaperone proteins, or defects at the level of Golgi-complex, where their assembly occurs, can cause glycosylation disorders⁶. Glycans have a role in protein modification before it is formed as well as when the protein is mature⁷. Because glycan interaction with their receptors is purely physical, 3D analysis of glycoprotein structure via glyco-
protein crystallography might give better consider-
ate of the contact amongst glycans and their carbo-
hydrate/protein receptors.
Carbohydrates in glycoproteins are attached to their
protein part either via N-linked glycosylation, O-
linked glycosylation or both. N-linked glycans are
made abnormally in cancer cells, which are then
recognized by the CD337 receptor on natural
killer cells. Glycans can change the function of im-
umunoglobulins. Each immunoglobulin (IgG, IgA,
IgM, IgE or IgD) has unique properties based on
the way it is glycosylated. For example, when IgG
CH2-84.4 glycans are sialylated and fucosylated, it will
give that antibody the anti-inflammatory properties,
whereas G0 glycan at CH2-84.4, which lacks galac-
tose and is neither sialylated nor fucosylated, gives
the antibody the pro-inflammatory properties, and
increases the level of what is seen in various auto-
immune diseases. Immune systems have glycan
binding receptors, which are known as lectins. These
can be secreted, such as galectins, or membrane-
bound like siglecs. Regardless of their locations,
al lectins have carbohydrate-recognition domains
(CRDs) that bind to the glycan portion of glycoconju-
gates such as glycoprotein, glycolipid, and proteogly-
can. A macrophage galactose-type lectin (MGL),
which is expressed exclusively on immature den-
dritic cells and macrophages, is an example of specific
lectins.
Glycosylation is an important post-translational
modification, and almost half of all proteins are gly-
cosylated. Glycosylation can act as a key regulatory
mechanism controlling several physiopathological
processes, and different types of glycosylation
can interfere with cell development as well as the
microenvironment, which can then lead to cancer
formation and progression.

GLYCANs REGULATION IN
different systems
Glycosylation Alteration in Cancer
For almost six decades, it has been known that can-
cer cells show alterations in glycosylation, but very
little is acknowledged about their role in cancer pro-
gression and metastasis, or their correlation with the
survival rates. However, with the invention of mon-
oclonal antibody technology, which demonstrated that
glycans were the target of tumor-specific antibodies,
and the recent focus on glycans in the field of cancer
research, significant advancements have been made
giving much more understanding of tumors’ glyco-
proteins and the significance of glycosphingolipid alter-
ations.
Tumor cells show different forms of glycosylation
alterations when compared with their neighboring
healthy cells. Glycosylation of proteins increases di-
versity in their functions while very few changes are
imposed on cell structure. These alterations occur
at specific locations on the protein and in specific
cells. Changes in the specificity of glycosylation in
healthy cells are different from glycosylation in can-
cerous cells, and one or more factors may be involved
in these changes in cancer cells.
Glycosylation can occur through altered expression of
the enzyme (glycosyltransferase) responsible for cata-
yzing the addition of carbohydrates onto the protein
(glycosylation) at the gene level, or through the de-
defects in the Golgi apparatus where this assembly oc-
curs. Chaperone dysfunction can also lead to the
glycosylation changes seen in malignant cells. Most
common glycosylation changes seen in cancer cells
are fucosylation, sialylation, and N- and O-linked
branching glycan. Genetic, epigenetic and several
environmental factors may be responsible for these
changes seen in malignantly transformed cells.

Glycan’s Role in Lung Cancer
Acute phase proteins undergo glycosylation in in-
flammation and cancer. Changes in glycosylation are
correlated with the severity of the disease. A1AT
(α-1-antitrypsin) is an example, whose primary func-
tion is to regulate protease/anti-protease activity. It
also has a role in cancer, as the altered glycosy-
lation of A1AT is seen in lung, liver, breast, and
prostate cancer. A1AT can be used in cancer de-
tection and differentiation: the glycosylated patterns
of A1AT may help in detection of lung cancer as
galactosylated A1AT can distinguish NSCLC (non-
small-cell lung cancer) from benign pulmonary dis-
eases, while fucosylated A1AT can differentiate ADC
(adenocarcinoma) from other types of lung cancers
and A1AT-containing poly-LacNAc is useful in detec-
tion of SCLC. Several NSCLC (non-small-cell lung
cancer)-specific glycoproteins and their N-linked gly-
cosylation sites have been identified, and these can
increase the specificity of thoracic CT scans con-
ducted to detect lung cancers. The pulmonary sur-
factant’s main components, or SP-A (lung surfactant
protein A), interacts with macrophages or monocytes
and is uptaken by macrophages and transported into
secondary lysosomes. This uptake is inhibited by
alpha-D-mannosyl-bovine serum albumin (BSA), but
not by beta-D-galactosyl-BSA. SP-A is a glycoprotein
with N-glycosylated glycans, so it could act as a ligand
for the mannose-specific receptor on macrophages.
As SP-A is a mannose-specific lectin itself, it can bind to mannose residues on cell surface of macrophages. One study showed that cigarette smoking leads to increased expression of the receptor for advanced glycation end-products (RAGE) involved in the activation of NF-κB, which is mediated by Ras, leading to inflammatory lung disease. Protein glycosylation affects protein folding, functionality, and stability. Abnormally glycosylated protein aids in malignant transformation of tumor cells. Lung cancer expresses sialylated or fucosylated glycans on their cell surfaces, including, Globo H, sialyl Lewis x (sLex), sialyl Tn (sTn), Lewis y (Ley) and polysialic acid. EGFR (epidermal growth factor receptor), a glycoprotein, has tyrosine kinase activity. EGFR is over-expressed in cancer cells, which supports cancer cell invasion, metastasis, and angiogenesis. Twelve glycosylation sites are known to exist on EGFR extracellular region and glycosylation may help to regulate some of EGFR functions. CL1-0 and CL1-5 are two distinct cell lines derived from lung cancers, each holding distinct invasive properties with high sialylation and fucosylation of EGFR. Sialylation and fucosylation could modulate EGFR-mediated lung cancer invasiveness. Increased sialylation and fucosylation downregulate EGFR, thus leading to lower lung cancer cell metastasis, while facilitating incorporation of the core fucos via α1,6-fucosyltransferase, which upregulates EGFR, leads to greater cancer metastasis. This may also be the mechanism behind cancer cell resistance to EGFR inhibitors. Beta-glycan, which is also known as Type III TGF-β receptor or RIII, is a proteoglycan. Its expression is controlled by TGF-β1 (transforming growth factor beta). TGF-β1 is an inhibitor of growth even though small cell lung cancer (SCLC) seems to be resistant to its growth inhibiting properties due to lacking the expression of R1, R2 TGF-β receptor proteins. Another study indicates that only the lack of R2 receptors might explain cancer cell resistance to TGF-β.

Haptoglobin is an acute phase protein. It is made in the liver and is regulated by several cytokines. Its two glycoforms, sialylated and fucosylated haptoglobins, can potentially serve as biomarkers for NSCLC. P-selectin, which is a transmembrane adhesion receptor present at Weibel Palade bodies of endothelial-cells and alpha-granules of platelets, binds to the glycans of neutrophils and monocytes containing sialyl-Lewis X antigens. Higher sialylation of the glycoprotein P-selectin has been observed in cancer cells, and P-selectin was suggested to aid in cancer invasion and metastasis. In one experiment, lung metastasis of the colon cancer was prevented by inhibiting sialyltransferase, indicating the role of P-selectin in metastasis.

**Glycans and the Role in Cancer Diagnosis**

Early detection of cancer is the main factor in fighting against this ever-evolving disease. Glycans have the potential to act as noninvasive biomarkers that can detect cancer before it metastasizes, which helps to monitor malignant progression, and accurately predict prognosis. One successful example of a glyco-biomarker is AFP (alpha-fetoprotein), a glycoprotein made during embryo genesis and fetal development that is currently used for the detection of hepatocellular carcinoma (HCC). However, AFP is not very useful in differentiating benign liver disease from HCC. Fucosylated AFP-L3 fraction, on the other hand, appears in the serum of a patient with cirrhosis just before its malignant transformation to cancer, thus making it an ideal glyco-biomarker in diagnosis. Beta-HCG (beta-human chorionic gonadotropin), which is used in gynecological malignancy monitoring; or PSA (prostate-specific antigen) in prostate cancer, and Dx and CEA (carcinoembryonic antigen) in colon cancer monitoring, are all examples of glycol biomarkers that are used today. The EML4 ALK [Echinoderm Microtubule linked protein as 4(EML4), ALK (Anaplastic Lymphoma Kinase)] and KRAS (V-Ki-ras2 Kirsten rat sarcoma homolog viral oncogene) are other examples of glycol biomarkers used for lung cancer detection. Further discovery of more glycol biomarkers that are able to detect cancer in its early stages will contribute greatly to lowering cancer-related deaths, provide more accurate prognosis and diagnosis of cancers, and will facilitate the differentiation of cancer types.

**Glycan and the Role in Cancer Treatment**

Cancers are defined as a diseases group, which involves irregular cell development and the ability to occupy other areas of the body. PTMs (post-translation modifications) such as methylation, N-acetylation, phosphorylation, and glycosylation are involved in the maintenance of proteins functioning in both cancer and normal cells. Most commonly occurring PTMs is glycosylation, and is involved in various biological mechanisms. Glycans are the essential biosynthetic precursors and attached to lipids or proteins to form glycoproteins or glycolipids as structural elements. As an important factor in the understanding of different cancer mechanisms, diagnostic and therapeutic strategies, glycans...
Glycans have important functions in nervous system development, regeneration, and maintenance of its plasticity. Oligodendrocytes express an extracellular glycoprotein tenascin-R, which is only found in the central nervous system of vertebrates, can support axon regeneration and remyelination. Phosphorylation, Aggrecan, Versican, Neurocan, Brevican are the ligands to which tenascin-R attaches, and they play an important role in synaptogenesis, neural cell adhesion and migration. One of the most common posttranslational modifications of proteins is N-Glycosylation, which plays an important role in the central nervous system. For example, it is active in the biosynthesis of ganglioside, which is regulated by glycosyltransferases. Cells can switch between expressing simple and complex gangliosides, or in between simple and complex gangliosides during the development of the brain. However, glycosyltransferases need to be fine-tuned at the subcellular level and stated in a precise way in the biosynthesis of gangliosides in parallel enzymatic pathways.

CNS recovery can be halted if reactive astrocytes produce chondroitin sulfate proteoglycan, which acts to inhibit axonal regeneration. Lectin-glycan interaction was suggested to play an important role in NSC (Neural Stem Cell) regulation and proliferation due to the glycan binding ability of Galectin-1 in the extracellular matrix.

The Role of Glycans in the Nervous System

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The Role of Glycans in the Immune System and Autoimmunity

The immune system of human is presented every day with the challenging task of differentiating the ‘self ‘ from the invaders and the cells that have gone cancerous. The immune system does this via an intricate system; if anything in this system goes wrong, it could lead to autoimmunity. One area in which the immune system must discriminate antigens is with gut microbiota. There are 10 bacterial cells for every human cell, with more than 10,000 species of bacterial cells. Collectively they constitute 1-3% of human body weight, and yet we know very little about how these microorganisms exist in harmony with their host. Recent studies have shown that glycogen conjugates may be behind such host-microbial relationships. For example, if Helicobacter pylori bind to a fucosylated or sialylated glycans, this will prime to the activation of the defense in the immune system. However, Bacteroides, a normal flora of the gut, can attach to fucosylated glycans without activating similar response.
The controlled expressions of glycans on the cell surface through the enzymes glycosyltransferase and glycosidase, both of which modify glycans, are vital in immune cell activation and homeostasis. Galectin, a family of lectins, is expressed by almost all immune cells, either continuously or in inducible forms. It can be upregulated by other immune cells such as activated B and T cells. All galectins have at least one CRD (carbohydrate receptor domain) that binds to glycan. Galectins upregulation has been observed in many tumors. Prostate cancer cells that express a low level of the glycosyltransferase GCNT1, are resistant to apoptosis mediated by galectin 1, but they express a high enough level of glycosyltransferase GCNT1 to eliminate effector T cells. Changes in the tri- and tetra-antennary glycan structures, sialyl Lewis X epitopes and galactosylated bi-antennary glycans, are observed in cancer patients, and many of these changes in chronic inflammatory diseases have also been observed.

Systemic lupus erythematosus (SLE), rheumatoid arthritis, Crohn’s disease, and other autoimmune diseases are known to have altered patterns of glycosylation of glycoprotein IgG. Decreased galactosylation and sialylation of the Fc region have also been observed in autoimmune diseases. In fact, IgG can be switched between its anti-inflammatory and pro-inflammatory properties depending on the degree of its sialylation. Streptococcus pyogenes has an EndoS (endoglycosidase) that hydrolyzes asparagine-linked glycan on IgG, which acts to render IgG inactivity so that it can no longer bind to FcγR on white blood cells and trigger an immune response.

The influenza virus that killed over 50 million people in just one year in the ‘90s also attached to its host via a glycan with an sialic acid on its end by using a glycoprotein known as Hemagglutinin (HA). This interaction of HA and glycan was critical in the infectivity and transmission of the influenza virus. Its specificity depends on the fucosylation, sulfation, and sialylation of the host receptors, as well as the type of linkage possessed by sialic acid. The human influenza virus binds to α 2-6 linked sialic acid located on the respiratory tract epithelium making it different from the avian influenza virus binding site, which binds to α 2-3 linked sialic acid located on the epithelium of intestinal tract. Though H5N1 virus binds to α 2-3 sialylated glycan, some mutant strains have been observed binding to α 2-6 sialylated glycan, which can lead to human adaptation of this strain.

HIV interaction with its human host is also dependent on a glycoprotein, gp120, which is a viral protein used by HIV to bind to the host's CD4+ve T-cells. There are contrary data on whether carbohydrates play a role in this interaction. Glycans' role in escaping the host's defense system is not limited to HIV; other viruses and parasites also use them in to fight against the host defense system. HIV and Ebola viruses bind to DC-SIGN(R) (dendritic cell-specific ICAM-3 grabbing nonintegrin)(receptor) on host cell surfaces via glycoproteins present on their envelope. Candida albicans also produce glycans that recognize DC-SIGN(R) via α-Man. Our immune system can use the same glycans to recognize foreign invaders. For example, Schistosoma and other helminths produce glycans that can trigger an immune response.

CONCLUSION

There is an increasing need to study glycan and its interaction with receptors as they are involved in many functions in the human body. Thus, it is impossible to ignore its future role in medicine. Recent advancements in deciphering the information about glycan receptor interactions have led to an understanding that glycan binding receptors (galectins, siglecs) and their interaction with glycan play a significant role in immunity, autoimmune, homeostasis, and cancers. Researchers only have the faintest glimmer of knowledge concerning the possible role of glycan in disease development and progression. Future measures are needed to take what is known about protein-saccharide interaction to develop effective treatments for diseases for which there are currently no cures. These include various autoimmune diseases, cancer, and chronic inflammation. The impressive progress over the recent years in understanding glycans as promising biomarkers in cancers has contributed to the discovery of glycans and their importance to clinical applications as potential targets for personalized and individualized medicine.

ABBREVIATIONS
NSCLC: Non-small cell lung cancer
A1AT: α-1-antitrypsin
SCLC: small cell lung-cancer
ADC: adenocarcinoma
PSA: prostate-specific antigen,
AFP: alpha-fetoprotein,
HCC: Hepatocellular carcinoma
NSC: Neural Stem Cell
EndoS: endoglycosidase
EGFR: epidermal growth factor receptor
DC-SIGN(R): dendritic cell-specific ICAM (intercellular adhesion molecule)-grabbing nonintegrin
TGF-β1: transforming growth factor beta
HIV: Human immunodeficiency virus
AUTHORS’ CONTRIBUTIONS
All authors equally contributed to this review.

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