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REVIEW PAPER

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Glycosylation of immune system proteins and its role in autoimmune diseases and cancer

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ABSTRACT

Introduction. Structural glycans have great biological significance and are involved in signaling and cell communication of the immune system. They are attached to proteins and lipids in an enzymatic process called glycosylation where glycosyltransferase and glycosidases bind sugar residues and lead to the formation of bioconjugates.

Aim. In this paper we describe the importance of glycosylation in the immune system and its changes in diseases.

Material and methods. This review was performed according to systematic literature search of major bibliographic databases.

Results. Proper glycosylation ensures the functioning of the organism, however, defects in structural glycans of immune system changes their properties and can lead to disorders and further to autoimmune diseases. It has been also proven that glycosylation of autoimmune system is changed during cancer. In this paper we described types of structural glycans, significance of glycosylation of selected components of the immune system and its modifications in disorders.

Conclusions. Knowledge about changes in the glycosylation in diseases is the key to understanding the processes of autoimmune diseases and may allow the development of new treatments in the future.

Keywords. Glycosylation, Immunity, Cellular, Humoral, Autoimmune Diseases

Introduction

Glycosides are elementary biomolecules that are involved in many biological processes, both in prokaryotic and eukaryotic cells.[1] Proteins are one of the most commonly glycosylated structures. It is estimated that the structures of the human proteome are at least 40% glycosylated and that glycans can constitute up to 90% of the molecular weight of certain glycoproteins. Changes in glycomes lead to new properties of cells and are often caused by changes in environmental and genetic conditions.[2] However, these modifications can be both positive and negative and can manifest themselves in various diseases.[3]

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Aim

In this paper we describe the importance of glycosylation in the immune system and its changes in diseases. Understanding the mechanisms, modifications and changes occurring in glycan of specific diseases is very important and can help in the development of new diagnostic methods, therapies, and treatments.

Analysis of the literature

Glycosylation is an enzymatic process involving the attachment of carbohydrate groups (sugars, oligosacharids) to proteins, lipids or other oligosacharides by glycosidic bond. In this reaction, important bioconjugates such as glycosphingolipids, glycoproteins, glycosaminoglycans, and proteoglycans are formed. Glycosylated proteins (glycoproteins) of great biological significance are created in the post-translational processing of proteins in endoplasmic reticulum (ER) and Golgi apparatus.[4] Fucose (Fuc) and mannose (Man) residues are attached to many proteins which guarantees them successful folding of the in the ER and provides them with protection against enzymatic degradation - proteolysis in and outside of the cell. Oligosaccharides attached to proteins also have functions in inter-cellular interaction and cell signaling which ensures – among other – that the structure is properly transported to the target organelle.[1,5]

Glycosyltransferases and glycosidases, mostly found in the ER, are crucial for glycosylation process. On the other hand, several enzymes of this type which attach single sugar residues can be found in the cytosol. Glycosyltransferases catalyze the selective transfer of a glycosidic bond using sugar donors. One of the most common are: nuclesides diphosphate (e.g. GDP-Man) but also derivatives of: monophosphate nucleosides (e.g. CMP-NeuAc); lipids phosphates (e.g., dolichol phosphate oligosaccharides); or unsubstituted phosphates. In contrast, glycosidases hydrolyze glycosidic bonds, thereby releasing saccharide molecules.[5,6]

There are two basic types of glycosylation depending on the atom connecting carbohydrate group with protein, forming N- and O-glycans.[7] N-glycans are linked through a glycosidic bond between the amide group of an asparagine residue in the Asn-X-Ser/Thr combination (where: Asn – asparagine; Ser – serine; Thr – threonine; X is any amino acid residue except proline) and Nacetylglucosamine (GlcNAc). Through the function of membrane enzymes – glycosyltransferases and glycosidases – located in the ER and Golgi apparatus, three basic N-glycans are created: oligomannose, hybrid, and complex type. Each of them contains the basic $Man_3GlcNAc_2Asn$ core (Fig. 1A). Oligomannose structures consist of many mannose molecules (Man) but a maximum of nine. Each of them, form α(1,6) and α(1,3) bonds, leading to a branching of the core structure but the terminal Man are connected by α(1,2) bonds. Hybrid N-glycans are formed from the oligomannose type, due to the action of transferases in the Golgi apparatus in which some of Man residues are removed and replaced with GlcNAc, sialic acid (SA), fructose, and galactose (Gal) residues. Subsequently, the structure can be subjected to further reactions which leads to complex structure formation.[2,7,8] O-glycans are linked by a glycosidic bond with the oxygen atom of the hydroxyl group

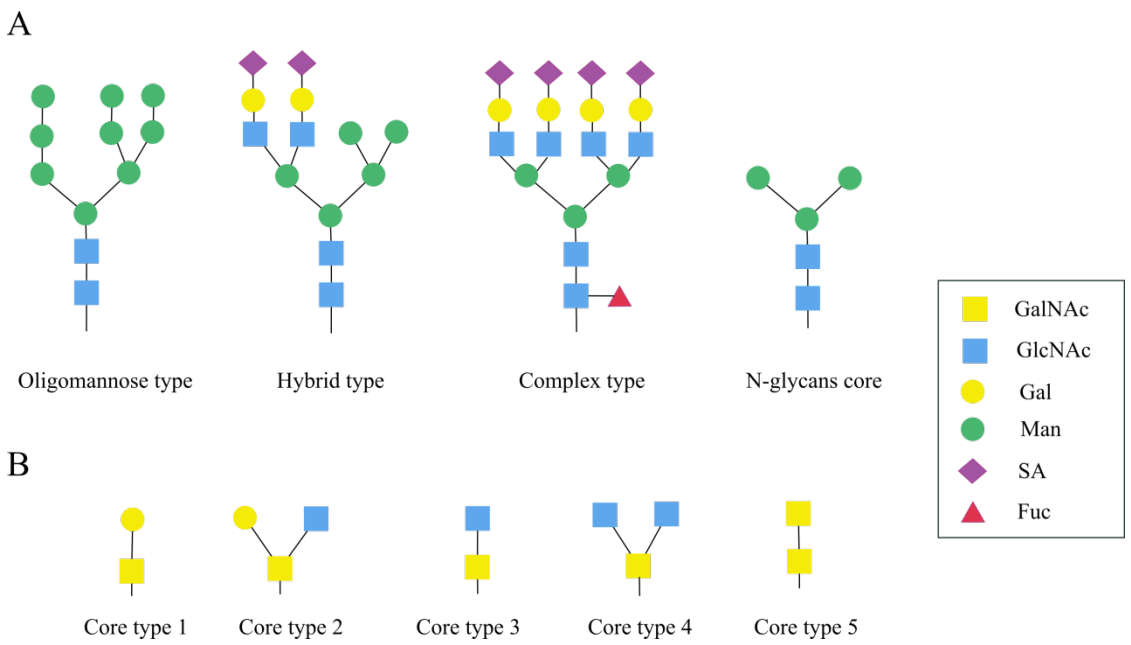

Fig. 1. The basic structures A) N-glycans B) O-glycans. Abbreviations: GalNAc – Nacetylgalactosamine; GlcNAc – N-acetylglucosamine; Gal – galactose; Man – mannose; Fuc – fucose; SA – sialic acid

of a serine or a threonine residue with GalNAc (Nacetylgalactosamine) or GlcNAc. In contrast to N-glycans with one core structure, O-glycans present five core combinations which may additionally differ in configuration and manner of binding of sugar residues. Each of the cores can be further modified and extended by further mono- or oligosaccharides (Fig. 1B).[9] In addition, they can be created even in the cytosol where N-glycosylation does not occur.[4] Furthermore, a common terminal structural element is the LacNAc (N-acetyllactosamine), which can be attached to various protein sites in both O- and N-glycans, leading to the formation of a structure called polylactosamine[2].

As already mentioned, glycosylated biochemical structures are involved in signaling and intercellular communication.[1,5,10] It applies to the immune response which is based on recognizing and responding to the presence of antigens. It is due to the ability to distinguish host cells from others which in turn is possible due to the various glycans present on the surface of both host's immune system and other, foreign cells.[11] The entire range of glycosylated proteins allows for appropriate immune responses that are associated with: leukocyte migration; cell guidance and apoptosis; activation of B and T lymphocyte receptors; antibody functions; antigen presentation by MHC (major histocompatibility complex) as well as differentiation of lymphocyte subpopulation.[12] Below, selected specific types of glycosylation of molecules and cells, responsible for the body's immune responses are presented.

Lymphocytes are an important group of cells involved in cellular and humoral responses. During the formation of T lymphocytes in the thymus, already in the early fetal development, there is an intense production of the T cell receptor protein (TCR), basic for recognizing antigens presented by MHC.[13] It is one of many immune-system proteins that are glycosylated. Heterodimer unit in the form of αβTCR or γδTCR is a membrane protein that contains at least 7 potential Nglycosylation sites.[14,15] β(1,6) glycosylation of GlcNAc and further branching with residues LacNAc, allows binding of galectin 3 (Gal-3) – an endogenous protein capable of binding oligosaccharides – to the TCR receptor which regulates the activity of T lymphocytes.[16] Galectin 3 defines the binding surface of the TCR receptor which reduces the affinity of MHC and blocks its activity by preventing disorders leading to autoimmune diseases.[14,17,18] Another glycosylated protein of immune system is the CD45 membrane protein. Change in the structure of N- and O-glycans of this protein for both, B and T lymphocytes is a determinant of the stage of cell differentiation. For example, naive and memory B cells are characterized by linear structures of N-glycans (poly) LacNAc.[19,20]

Immunoglobulins are proteins secreted at various concentrations by B lymphocytes in the immune response. Five classes of human immunoglobulins are distinguished: IgA, IgD, IgG, IgE, IgM, but the most common is IgG.[21] They all undergo glycosylation which regulates their properties such as conformation and stability, half-life as well as the ability to bind specific antigens and other immune system proteins such as receptors and lectins.[22] These proteins are mainly N-glycosylated, but O-glycosylation of IgA1, IgD, and IgG3 also occurs, however IgA1 is characterized by 3 to 5 glycosylation sites with mucin-type structures which contain terminal GalNAc residues.[23-25]

IgG participates in humoral and innate immune responses. It consists of four polypeptide chains – two heavy and two light chains, forming the characteristic shape of the protein in the form of the letter Y. The antibody has two domains – Fab (antigen binding fragment), responsible for antigen binding and Fc (crystallizable fragment) that binds to receptors.[26,27] Proteins of this subclass have only one Nglycosylation site at Asn^{297} in Fc domain where glycosylation prevents a change in protein conformation, guaranteeing characteristic chain arrangement and receptor binding ability.[28] It has been shown that the crystallizable Fc region undergoes glycosylation changes during disease states, affecting anti-inflammatory properties. In non-pathological conditions, 15-25% of the Fab surface are glycans and it contains more GlcNAc structures, multi-mannose branches, and much more α2,6-sialic acid residues, compared to Fc, which in turn is characterized by increased fucosylation.[29] High fructose content inhibits the cytotoxic cellular response while high content of terminal SA, especially in the α(2,6) configuration, inhibits the inflammatory response.[28,30]

Glycosylation disorders lead to the development of various diseases, including autoimmune diseases and cancers (Table 1).[2,4,11,14,17,31-43] Lack of appropriate sugar residues in receptor proteins interferes with their function, thereby blocking signaling pathways. Dysregulation of the N-glycosylation pattern can lead to the pathological behavior of T cells.[10] For example, defects in the synthesis of Nglycan complexes on T-cell surfaces, results in the enhancement of the TCR receptor signal, resulting in disorders manifested by lower specificity of T lymphocytes of detection to antigens. This phenomenon is observed on autoimmune encephalomyelitis or glomerulonephritis whereas kidney disease occurs in humans as a consequence of type 2 diabetes.[33,44] Glycosylation disorders are very often the outcome of mutations in the genes responsible for enzymes attaching sugar residues. Ohtsubo et al. have shown that glycotransferase disorders transferring GlcNAc on mannose residues in N-glycosylation, lead to glucose transporter receptor (Glut-2) disorders and thereby interfere with insulin secretion, leading to type 2 diabetes.[32] Another example is the lack of the *Mgat5* gene, coding for

Table 1. Summary of glycosylation disorders and their effect on autoimmune and cancer diseases

	Glycosylation disorder	Glycosylation type (N/O)	Outcome of disorder	Diseases	References
1	Disabling GlcNAcT-IVa glycosyltransferase	N	Receptor defect for glucose transporter (Glut-2)	Type 2 diabetes	32
2	Disabling β(13)-N-acetylglucosaminyltranserase action V	N	Reduction of TCR receptor glycosylation	Lower specificity for antigens; increased susceptibility to autoimmune diseases	14
3	Disabling β (1-3) -N-acetylglucosaminyl transferase II	N	Reduction of TCR receptor glycosylation	Lower specificity for antigens; increased susceptibility to autoimmune diseases	33
4	Limiting glycosylation of T lymphocytes	N	Increased T cell response; less specificity for antigens	Autoimmune encephalomyelitis; glomerulonephritis	11,17
5	Molecular chaperone Cosmc glycosyltransferase defect	O	Lack of sugar residues galactose and sialic acid on the Tn antigen	Haemolysis; thrombocytopenia	34,35
6	No sialic acid residues or abnormal binding to CD45 receptor	O	Intercellular signaling disorder by lectin binding disorder	Rheumatoid arthritis; systemic lupus erythematosus	36
7	Lack of sialic acid residues in the Fc domain of IgG antibodies	N	Chronic inflammation	Multiple sclerosis; rheumatoid arthritis; cancer of the prostate, stomach, large intestine and bladder	37-40
8	Tn antigen sialylation	O	Cancer hosting; neoplasia	Cancer	35,41
9	Additional mannose residues in IgG	N	Stimulation of cancer cell growth and survival	Lymphomas	42
10	Sialylation of cancer cell surfaces	-	Disorder of cancer cell recognition by the immune system cells as abnormal	Cancer	31,43

the Nacetylglucosaminyltranserase V (GnT-V) branching enzyme responsible for attaching the GlcNAc β (1-6) residue to the TCR receptor which results in hyperactivity of T lymphocytes.[14] A similar dependence was observed in the mutation of the gene encoding the enzyme attaching the N-acetyllactosamine residues – GnT-II (β(1-3)-Nacetylglucosaminyltransferase).[17] The occurrence of autoimmune diseases is not only associated with changes in the structure of N-glycans, but also in O-glycans disorders of mucin-type proteins. An example is the Tn syndrome characterized by the lack of a developed Tn antigen (galactose and sialic acid defects) on the surface of blood cells which leads to hemolysis and thrombocytopenia (thrombocytopenia). Glycosyltransferase malfunction is responsible for this glycosylation changes and it is caused by the Cosmc molecular chaperone defect of this enzyme, crucial for O-glycosylation of proteins.[34,35]

A compound that plays a large role in the development of human immunity, starting from fetal development, is sialic acid, which affects the activity, half-life and transport of significant proteins such as immunoglobulins.[45] An example of a disorder caused by the loss of free sialic acids in oligosaccharide branches is the undesirable formation of CD45 receptor dimers. Reduced glycosylation of the protein leads to inhibition of signal transduction which results in the arrest of lymphocyte activity, thereby causing autoimmune diseases such as rheumatoid arthritis or systemic lupus erythematosus.[36,47] In addition, sialylated IgG in Fc domain produced by B lymphocytes, have a role in the process of rheumatoid arthritis because they exhibit anti-inflammatory properties. It has already been proven that among people suffering from rheumatoid arthritis, the presence of sialylated IgG is undetectable, but its concentration increases significantly during remission[39]. Similarly, changes in the glycosylation of IgG effected by the decrease in the level of sialylation have been demonstrated in patients with multiple sclerosis in which the presence of pro-inflammatory factors leading to a chronic inflammation in the body is also characteristic.[37,38] It is interesting that the appearance of Tn antigens with sialic acid in the O-glycan structure (Neu5Acα2,6GalNAcα1-Ser/Thr) may be a marker for detecting the early phase of tumor formation.[35,41]

As mentioned above, the manifestation of glycosylation aberrations in cells of the immune system also applies to cancer processes. Glycans are important for the communication of cancer cells during their invasion and metastasis, as well as for fooling and escaping from the immune system, and even for their drug resistance by influencing the mechanism and absorption of the drug.[47,48] Changes in glycosylation have been proven in many cases. Glycosylation aberrations in IgG have been described for prostate, stomach, colorectal and urothelial type bladder cancer. Tanaka et al. showed that in prostate (P) and bladder (U) cancers, the sIgG number significantly decreased in both study groups compared to the healthy controls (C). In addition, Tanaka et al. showed that the

U group had a lower IgG concentration than the others.[40] In different types of lymphomas, Nglycosylation sites in host antibodies are added. They are modified by oligomannose structures bound by Mannose Binding Lectin (MBL) with oligomannose structures, triggering stimulus signals, thereby promoting tumor growth and survival.[42] Compounds on the membranes of cancer cells may also be glycosylated. The high sialylation surface on the cell surface disrupts the recognition pathways of non-host structures and as a result, cells that should be destroyed – are not. In this way, inter alia, are interrupted: signals for CD8+ T cells or ligand for the Fas receptor, favoring the development of the disease.[31,43]

Conclusions

Glycosylation is a very important process that determines the survival of the organism. It is the basis of the immune system, by giving high variability to molecules ensuring its functioning. Its disorders can lead to the development of diseases characterized by autoaggression towards the host organism. The progress of science towards understanding the mechanisms of glycosylation in the immune system is key to understanding the processes of autoimmune diseases. Comprehension the mechanisms that determine the course of immune responses in healthy and sick people will allow us to develop new treatments in the future.

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