Research Progress and Plan of Glycomics in China: A Review

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Abstract

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Abstract

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Keywords: Glycan, Glycomics, Glycosylation, China

Introduction

Related research at home and abroad has carried out in-depth exploration of genomics, proteomics and metabolomics. As a basic macromolecule that constitutes life with lipids, proteins and nucleic acids, carbohydrates can also be defined as glycomics[1]. Glycomics is a new research field after genomics and proteomics. Glycome refers to all sugar chains (including sugar complexes) in cells. Glycomics is a science that studies the expression, regulation and physiological functions of sugar chains. It mainly focuses on the structural analysis of glycoproteins and all glycoproteins involving individual individuals, and determines the mechanism of gene encoding glycoproteins and protein glycosylation[2]. Its basic research part is also called glycobiology[3]. Nucleotide-constituent genes and amino acid-constituent proteins are connected by linear and single combinations. Monosaccharides are always polymerized into glycans, which are connected by multi-site and multi-spatial orientation, resulting in a variety of polymers including linear and branched structures. As a single glucose, it can be polymerized into two completely different structures of amylose and liver glycogen. In addition to storing and providing energy for organisms, there is also a large class of polysaccharides (such as N-glycans or O-glycans) aggregated by a variety of monosaccharides modified on molecules such as nucleic acids, proteins or lipids[4]. Among them, the sugar chains present on the cell surface are covalently linked to cell membrane lipids and proteins, forming a rich dynamic structure on the cell surface. In life activities, glycans cooperate with other three types of biological macromolecules and participate in various physiological and pathological processes of organisms[5].

Polysaccharides constitute an important part of biodiversity due to their complexity and variability. There are about 30,000 to 60,000 genes in the human genome[6]. The human proteome contains more than 1 million proteins ; more than half of the proteins are modified by different glycans, which can produce numerous changes. The blood group H antigen determinant on the surface of red blood cells determines the different ABO blood groups by whether it has terminal N-acetylgalactosamine (GalNAc) or galactose (Gal) residues. The species of various organisms depends on the information-genome of biological systems. Various proteins formed by gene coding constitute the cornerstone of biological functions, and glycans, like buildings built on them, show the diversity of life, regulate and affect physiological and pathological processes. During fertilization, glycans regulate sperm capacitation and sperm-egg recognition[7]; tumor development can be promoted by N-glycan branching structure[4]; glycans and glycan binding proteins can not only regulate immune function, but also mediate the interaction between pathogens and hosts[8]. Because of the special status of glycans and their structural diversity and plasticity, they have become a key factor in biological functional diversity and disease development. The importance and complexity of the role of glycans in life activities have attracted a large number of domestic and foreign scientists to carry out in-depth research, and gradually formed a new discipline-glycomics[9].

Due to the important physiological functions of sugar chains, countries around the world have attached great importance to the related research of glycobiology and invested a lot of manpower and material resources for research[10]. Although glycomics research has attracted much attention in the early years, it has been continuously broken through in recent years due to the development of related technologies[11]. It is worth noting that the development of glycomics in China is very rapid and has gradually led the trend of international research.

Development and status of glycomics

Glycosylation is one of the most common post-translational modifications of proteins. Glycans on proteins play a role in many important biological processes such as cell adhesion, protein folding, molecular transport and clearance, receptor activation and signal transduction[12]. Glycosylation refers to the process of con-

necting sugar chains with proteins or lipids as substrates under the action of enzymes. As one of the most important protein modification methods in vivo, glycosylation has been studied by more and more teams. Glycosylation modification can regulate the location, diverse functions, activities and lifespan of proteins in cells [13]. Various studies have shown that glycosylation modification can occur on 50% -70% of proteins in cells, and they are involved in various important life activities including cell recognition, cell differentiation, development, signal transduction, and immune response. Abnormal protein glycosylation occurs in many diseases, such as cancer, neurodegenerative diseases, cardiovascular diseases, metabolic diseases, immune diseases and infectious diseases[14, 15]. As a major post-translational modification, glycosylation has a crucial effect on protein function. At present, based on the characteristics of glycosylated proteins, human glycoproteins have been successfully expressed in yeast through glycosylation engineering. Because the glycans of the modified target protein also have the characteristics of uniform structure, large-scale production of glycosylated protein drugs has become possible.

Protein glycosylation is one of the most common post-translational modifications of proteins. It is the process of transferring sugars to proteins under the action of glycosyltransferases and forming glycosidic bonds with special amino acid residues on proteins[16]. According to the differences in binding sites and structures, the sugar chains are divided into the following types:

1. N-linked glycans (also known as N-glycosylation) attached to amide nitrogen of asparagine (Asn) residues.
2. O-linked glycans (also known as O-glycosylation) linked to hydroxyl oxygen of serine (Ser) and threonine (Thr) residues.
3. Sugar chain linked to phosphoric acid on serine phosphate.
4. C-linked glycans (also known as C-glycosylation, rare) attached to the carbon of Tryptophan (Trp) residues.
5. Glycosylphosphatidylinositol.

Among the five types of glycans, N-glycosylation is widespread in eukaryotes and is also the most in-depth study of glycosylation.

2.1 The development history and current situation of O-GlcNAc in China

O-glycoprotein mainly exists in mucus and immunoglobulin. The O-glycosylation process of forming O-glycoprotein is carried out in the Golgi apparatus. The sugar chain is covalently linked to the free OH group of serine or threonine. Usually, the first connected sugar unit is N-acetylgalactose, and then the sugar residue is successively transferred to form an oligosaccharide chain, and there is also a case where only monosaccharides are connected[17]. Sugar donors are also nucleoside sugars, such as UDP-galactose. The O-glycosylation site has no conserved sequence, and the sugar chain has no fixed core structure. Its composition can be either a monosaccharide or a huge sulfonated polysaccharide. The glycan formed by O-glycosylation has no sugar group, and there is one or no branch on the carbon skeleton. Since no specific glycosylation sequence has been found, the analysis of O-glycosylation is more complicated than other glycosylation.

2.2 The development history and current situation of N-GlcNAc in China

N-glycosylation occurs on the amide nitrogen of the asparagine side chain, and the sugar chain is covalently linked to the free NH2 group of the aspartic acid of the protein. The synthesis of N-linked sugar chains starts in the endoplasmic reticulum (ER) and completes in the Golgi apparatus. The first step in the synthesis of N-glycans is to add a 14-glycan core oligosaccharide to the asparagine residue of the newly formed polypeptide chain with the characteristic sequence of Asn-Xaa-Ser/ Thr/Cys (Xaa can be any amino acid other than proline), asparagine acts as a sugar chain receptor. The core oligosaccharide is composed of 2 molecules of N-acetylglucosamine, 9 molecules of mannose and 3 molecules of glucose. The first N-acetylglucosamine binds to the phosphate group of the phosphopolyterpene alcohol on the ER bilayer membrane. When a new polypeptide is synthesized on the ER membrane, the entire sugar chain is transferred together. After transferring the oligosaccharide to the nascent peptide, it is further processed in the ER, and 3 molecules of glucose and 1 molecule of mannose are removed in turn. The glycoprotein formed by ER has similar sugar

chains. After entering the Golgi apparatus from the Cis surface, most of the mannose on the original sugar chain is removed during the transport between the membrane vesicles, but a variety of glycosyltransferases are added in turn. Different types of sugar molecules form oligosaccharide chains with different structures. The glycan formed by N-glycosylation has only one glycosyl group, but has multiple branches. Proteins in body fluids such as plasma are mostly N-glycosylated, so N-glycoprotein is also known as plasma glycoprotein. Almost all such glycosylation modifications in animal cells are N-acetylglucosamine GlcNAc, and all are β-configuration[18].

2.3 History and current status of C-GlcNAc and other glycosylation in China

C-glycosylation refers to the process by which a molecule of mannose group is connected to the C-2 position of the tryptophan indole ring through a C-C bond to modify the protein. This glycosylation mostly occurs on the first tryptophan residue of the W-X-X-W-W-X-X-C or W-X-X-F sequence[19]. This glycosylation is rare in living organisms.

Glycosylphosphatidylinositol, the fifth type of sugar chain, is the only way for proteins to bind to the cell membrane. Unlike general lipid modification components, its structure is extremely complex. Many cell receptors, differentiation antigens and some biologically active proteins have been shown to bind to cell membranes through glycosylphosphatidylinositol (GPI) structure. The core structure of GPI is composed of ethanolamine phosphate, three mannosides, glucosamine, and cellolipids. The C-terminus of the anchoring protein is bridged to the core glycan by ethanolamine phosphate, which is highly conserved. At the same time, another phospholipid structure connects the GPI anchor to the cell membrane. The core glycan formed by C-glycosylation can be modified by a variety of side chains, such as ethanolamine anchored groups, mannose, galactose, sialic acid or other sugar groups.

2.4 Progress in research methods of Chinese unique glycomics

2.4.1 Research on glycoproteins

Protein is the executor of life activities. During the study of proteins, researchers found that proteins have many modifications. Among these modifications, glycosylation is very common, and more than 50% of the proteins found so far have glycosylation. Glycans are the sugar components of glycoproteins, including sugar groups and various types of branching structures, composed of various sugars, such as glucose, galactose, mannose and rhamnose. Polysaccharides complete the glycosylation modification of proteins by connecting oxygen on specific amino acid residues to proteins. One way to study glycomics is to analyze glycoproteins.

For glycoproteins, there are the following research methods:

1. Glycosyl capture: Lectin can specifically recognize one sugar or a variety of sugars to agglutinate glycoproteins, which can be used to obtain crude glycoproteins[20].
2. Fluorescent dyes: Fluorescent dyes are usually used in combination with high-throughput two-dimensional gel electrophoresis for protein discovery and identification[21].
3. Liquid chromatography: Separation of glycoproteins by SEC-HILIC-CapLC workflow and other techniques can be used to construct a three-dimensional liquid phase glycan profile to obtain glycan structure information[22].
4. Mass spectrometry: Mass spectrometry is used to analyze the cleavage rules of protein skeleton and sugar skeleton, which can be used for glycosylation site analysis[23-25].
5. Magnetic resonance: Through the change of atomic energy transition, accurate calculation of composition, ring size and abnormal carbon conformation can be used to accurately confirm the structure of sugar chain[26].

2.4.2 Bioinformatics research of Chinese glycomics

In addition to structural analysis techniques, glycoinformatics and microarray technology of glycans/lectins also play an important role in glycomics. The newly reported glycoinformatics method SPRINT-Gly has been superior to many existing algorithms and performs well in analyzing glycomic data. On the other hand,

glycan/ lectin arrays are now powerful glycomics tools that can be used to identify glycan recognition patterns of certain pathogenic bacteria. Sugar chip technology is widely used to reveal glycan-protein interactions in animal, plant and microbial food matrices. At present, the glycomics method is developing towards more general and accurate analysis.

Significance of Chinese glycomics research

3.1 Glycomics research reveals emerging targets for disease diagnosis and treatment

Glycomics is mainly a new subject to study the structure and function of the body's glycans. In recent years, the correlation between glycan changes and various diseases has been increasing. Diabetes is a chronic disease with a high incidence worldwide. Diabetic patients generally have a variety of pathophysiological changes and metabolic disorders, especially glucose metabolism disorders. At present, many studies have reported that diabetes is associated with changes in the sugar group. The number, structure and immunoglobulin G N-glycans in the serum of diabetic patients have changed, and N-glycans may be used as diabetes biomarkers. The number and structure of glycans on glycoproteins are closely related to the body's blood glucose levels and diabetes progression[27-30]. Therefore, glycomics has potential application value in the diagnosis, prediction and prognosis of diabetes and other diseases. There have been many reports on its related research, mainly focusing on the changes of N-glycans in the occurrence and development of diabetes and its correlation with diabetic kidney disease, cardiovascular disease and other complications[31].

3.1.1 Research progress of O-Glycomics and heart disease

O-GlcNAcylation is a special sugar modification after protein transcription and translation, which is related to a variety of pathophysiological processes in cells[32]. The total level of O-GlcNAcylation is determined by the regulation of mitochondrial energy metabolism. The two key enzymes involved in this regulation process are O-GlcNAc transferase (OGT) and O-GlcNAc hydrolase (OGA)[33].

Some researchers have found that in infarcted heart failure, the specific loss of OGT in cardiomyocytes will lead to a decrease in O-GlcNAc glycosylation, increase apoptosis and fibrosis, thereby aggravating cardiac remodeling and ultimately aggravating cardiac dysfunction and mortality, which indicates that elevated O-GlcNAc glycosylation may improve heart failure[34]. In addition, in patients with diabetes or hyperglycemia and myocardial dysfunction, studies have also found that the level of O-GlcNAc glycosylation is increased, and OGT inhibitors can improve pathological myocardial hypertrophy[35].

However, some studies have found that intracellular O-GlcNAcylation is significantly increased in heart failure. This seems to mean that O-GlcNAc glycosylation is harmful. Although increased O-GlcNAcylation is currently one of the hallmarks of heart failure, it is not clear whether excessive O-GlcNAcylation causes or promotes heart failure and cardiomyopathy[36]. Excessive O-GlcNAcylation can lead to cardiomyopathy, which may be due to the blockage of mitochondrial energy metabolism, while increasing OGA activity and reducing O-GlcNAcylation levels may alleviate heart failure and cardiomyopathy[37].

Increased O-GlcNAcylation in myocardium is associated with a variety of cardiovascular and metabolic diseases, such as aortic stenosis, hypertension, ischemia and diabetes[33, 34]. The research team led by Mark Anderson and Priya Umapathi of Johns Hopkins University in the United States published important research results in the top journal Circulation in the cardiovascular field, providing a transgenic mouse model that can independently control the level of O-GlcNAcylation in the myocardium to clarify that O-GlcNAcylation in the myocardium may not depend on pathological stress response. Elevated levels of O-GlcNAcylation in the myocardium can cause dilated cardiomyopathy and premature death, while overexpression of OGA in the myocardium can reduce the level of O-GlcNAcylation and specifically protect pathological cardiac hypertrophy[38].

This suggests that reducing excessive O-GlcNAcylation in myocardium may contribute to the treatment of heart failure, and O-GlcNAcylation is expected to become a new target for the treatment of cardiomyopathy, which is of great significance for clinical application. Related fields have been further explored with the efforts of Chinese scientists. Professor Zhang Zhenlu's team found that glycosylation is an inevitable influencing

factor for all NT-proBNP tests. The glycosylation ratio of proBNP is as high as 70% in chronic heart failure, which makes the detection value of NT-proBNP abnormally low, resulting in false negatives[39]. In addition, more than 30% of patients with chronic heart failure are clinically complicated with renal insufficiency. It should be noted that renal insufficiency can lead to abnormal elevation of NT-proBNP, causing false positives and interfering with clinical judgment[33]. For these patients, BNP detection should be preferred to obtain accurate and reliable test results (Figure 1).

3.1.2 Research progress of N-Glycomics in diabetic patients

Type 1 diabetes mellitus (T1DM): Bermingham et al. retrospectively selected 818 T1DM patients with a large annual loss of glomerular filtration rate, and analyzed the relationship between the relative abundance of 39 serum N-glycans and diabetes-related clinical indicators. It was found that with the increase of glycated hemoglobin A1c (HbA1c), the relative abundance of simple diantennary N-glycan (NA2) gradually decreased. The relative abundance of complex multi-branched, galactosylated and sialylated N-glycans gradually increased, and the corresponding N-glycan levels also changed significantly with the decrease of blood glucose levels after treatment, and returned to healthy controls[40-42]. Another study found that multi-branched N-glycans are closely related to the occurrence of autoimmune diseases, which may be related to the pathogenesis of T1DM[43, 44]. Rudman et al. analyzed the serum N-glycans of 1917 children and adolescents with T1DM from DanDiabKids (Denmark), and found that the relative abundance of galactosylated N-glycans in serum decreased significantly, and the proportion of bisecting N-acetyl-D-(+)-glucosamine (GlcNAc) and high mannose structure increased significantly. A logistic regression model was established using serum N-glycans to identify children with T1DM. The area under the receiver operating characteristic curve (AUC) was 0.915. The model is helpful to identify high-risk individuals of T1DM at an early stage, and then prevent the progression of T1DM through timely intervention, which has certain clinical practical value[45, 46].

In addition, studies have found that a variety of sugar synthesis-related genes are associated with the pathogenesis of T1DM.For example, the fucosyltransferase 2 gene has been identified as a T1DM pathogenic gene[47]. Different levels of gene expression lead to the differentiation of glycan synthesis process, which is manifested as the change of glycan structure or quantity. It can be seen that the change of N-glycan is closely related to the occurrence of T1DM, and the purpose of early warning or auxiliary diagnosis of T1DM can be achieved by detecting the change of serum N-glycan profile. It is expected that more and more in-depth research in the future can explore the potential clinical application value of N-glycan profile in diabetes.

Type 2 diabetes mellitus (T2DM): Dotz et al. analyzed the serum N-glycan profiles of 1583 T2DM patients and 728 healthy controls, and found that 18 N-glycans and derived traits were closely related to T2DM, among which the change of sialylation modification was the most prominent. The degree of overall sialic acid modification in the T2DM group was higher than that in the control group. The double-antenna α2,6-linked sialic acid-modified N-glycan increased, while the three-antenna α2,3-linked sialic acid-modified N-glycan decreased.

In addition, the proportion of fucosylation and flat typing in dual-antenna N-glycans also decreased. Keser et al. conducted a glycomics study on a 10-year follow-up cohort (FinRisk cohort) from Finland, and found that individuals with T2DM had a decrease in low-branched N-glycans, an increase in multi-branched N-glycans, and an increase in galactose and sialylated N-glycans. The overall performance is an increase in the structural complexity of N-glycans. Similar trends were observed in T2DM high-risk populations and populations with elevated HbA1c, indicating that the increased complexity of N-glycans is closely related to the development of T2DM and poor blood glucose control[48-50].

Testa et al. found that the relative abundance of α1,6/3-linked monogalactosylated core fucosylated double-antenna N-glycans in the T2DM group was significantly lower than that in the healthy control group, while digalactosylated NA2 was significantly increased. The changes of α1,3-linked monogalactosylated core fucosylated double-antenna N-glycans and NA2 were more significant in T2DM patients with complications. The former was considered to be closely related to diabetic macroangiopathy[41-43]. Similar to the results of T1DM-related studies, the changes of N-glycans in the serum of T2DM patients are generally characterized

by increased branching and modification[51], but the changes of NA2 are more complex[52]. The proportion of fucosylation modification is reduced, and the proportion of modified N-glycans such as galactose and sialic acid is also quite different. In summary, serum N-glycans in patients with T2DM have changed to a certain extent, and N-glycans may become biomarkers for early diagnosis of T2DM and complications[53], but further research is still needed.

3.1.3 Study on the relationship between the distribution of serum N-glycan group and age (aging) and gender

3.1.3.1 Serum N-glycan profile has potential as a biomarker of aging

It has been previously reported that the serum N-glycan profile of Belgians and Italians has changed during aging, and its potential as a biomarker for aging has been proposed[54]. The 12 most significant N-glycan structures were analyzed by exoglycosidase digestion[55]. Finally, it was found that the relative abundance of the three main N-glycan structures (NGA2F, NGA2FB and NA2F) changed significantly with age, and had the same variation trend in both sexes, which made the serum N-glycan profile have the potential as a biomarker of aging.

3.1.3.2 The changes of N-glycan profile were different between genders.

During aging, the total core-α-1,6-fucose level of males remained unchanged. In contrast, the incidence in the youngest age group of women began to be higher, but then gradually decreased with age, reaching a similar level[56]. The results showed that serum glycans were also closely related to age and gender[57]. Serum N-glycan levels changed significantly with age. Polysaccharides with the same variation trend in both sexes are more useful as age-related markers. The different trends between men and women suggest that gender should be considered in the development of serum glycomic markers. N-glycan profiling should be studied more extensively, such as long-term longitudinal studies. The serum glycan profile is easy to derive, and it can be developed as an accurate biomarker that can indicate physiological age[58, 59]. These results may help to establish a specific blood monitoring technique based on accurate markers of gender and age-related diseases in men and women.

3.1.4 Research progress of IgG N-glycomics in patients with breast hyperplasia

Mammary gland hyperplasia (MGH) is very common in young and middle-aged women. Immunoglobulin G (IgG) is a glycosylated molecule that accounts for about 75% of serum immunoglobulin and plays an important role in the regulation of inflammatory response. The association between IgG N-glycosylation and MGH has been reported[60]. The serum levels of the five initial characteristics and seven derivative characteristics of glycans between MGH and healthy individuals are different. Although the sensitivity and specificity of the current predictive association are not up to the diagnostic level of conventional clinical use, this finding shows the prospect of glycomics. The difference in IgG N-glycans between people and their combination with multiple sets of student biomarker strategies provides a promising way to identify MGH risk populations and diagnose MGH (Figure 2).

3.2 Glycomics research and tumor markers

The serum N-and O-glycan profiles of patients with different types of non-small cell lung cancer (NSCLC) at different stages and healthy controls were measured by lectin microarray analysis[61]. To compare the changes of serum glycosylation in patients with non-small cell lung cancer and the control group, and to evaluate the stage-related changes of serum glycosylation. The results showed that compared with the control group, 18 lectins in the lung adenocarcinoma group could significantly change the serum glucose type. Among them, 16 lectins showed significant serum glycoform changes in the squamous cell carcinoma (SCC) group.

Although fucosylation is essential for normal biological functions, changes in fucosylation are closely related to the development and progression of tumors[62]. The core fucosylation serum level of stage I/II adenocarcinoma is significantly increased, so core fucosylation may be a potential diagnostic biomarker for early

detection of lung adenocarcinoma[63]. It can be further inferred that other lectins that cause significant changes in serum glycotypes can also be used to diagnose different types and stages of non-small cell lung cancer and serve as a standard for the diagnosis of such diseases[64, 65].

3.3 Application of glycomics research in traditional Chinese medicine(TCM)

3.3.1 Application of glycomics research method in TCM disease state

The normal spatial structure and normal functional status of the sugar group is one of the important conditions for maintaining the normal life activities of the human body. The physiological characteristics of the sugar group are reflected in the normal physiological characteristics of the human body, which are the microscopic parameters of the disease-free state in the state of traditional Chinese medicine. When people respond to the relatively mild stimulation of external factors, they can control the state in the state of disease or disease-free state without changing to the state of disease by virtue of their own regulatory mechanism of "yin and yang harmony". When the degree of external stimulation exceeds the scope of the human body's self-regulation ability, the human state will enter the disease state.

Under the stimulation of external pathogenic factors, the sugar group in the human body will undergo corresponding abnormal structure, resulting in changes in the spatial structure and function of the sugar group, eventually leading to the occurrence of diseases and changes in the state of the human body. In the process of disease development, the change of glycome plays an important role. The change of glycosylation is often related to the occurrence of disease. Glycomics can provide microscopic parameters for the state of traditional Chinese medicine. Modern research shows that[66], in the process of disease development, especially cancer, due to changes in the activity of oligosaccharide chain metabolic enzymes, can cause abnormal glycan structure, which leads to the dysfunction of glycoproteins and their cells, and even malignant phenotypes, such as malignant tumors. Therefore, the study of glycomics can enrich the microscopic parameters of TCM state, provide some reference for the microscopic identification of state, and provide reference data for the establishment of TCM microscopic identification database.

3.4.2 Glycomics analysis of traditional Chinese medicine efficacy

Ka-Man Yip et al. used multiple chromatography and mass spectrometry techniques, combined with multivariate statistical analysis, combined metabolomics and glycomics to study the changes of secondary metabolites and glycomics in Moringa (MOR) in different growth years and different tissues[25]. The principal component analysis showed that the secondary metabolites and saccharides between raw products and processed products changed significantly, which provided a chemical basis for the application of different types of Codonopsis pieces, and provided clues and tips for further study of the chemical mechanism during processing.

3.4.3 The situation of glycomics in TCM research

At present, the application of glycomics in the study of TCM state is still in its infancy, and there are still many problems to be solved.

1. Because the research of glycomics requires high-throughput detection, the research cost is high, and the equipment cost is high, it is difficult for scientific research units to have sufficient funds to introduce related equipment for research.
2. At present, in the study of TCM state, the application of glycomics is not much, and the data scale is not large, so it is difficult to form a complete database.
3. The data sample size of glycomics is small, and the conclusion is not comprehensive, so it is difficult to interpret the material basis of TCM state as a whole.
4. At present, there are few literatures on the study of TCM state through glycomics, and a large number of physiological state studies are needed as the background to establish the data model.**4.Problems and prospects of Chinese glycomics research**Studies on the structure-activity relationship of glycans have shown that glycans often exhibit functional and structural overlap, that is, glycans of a certain structure may have many different functions due to different synthesis sites or binding substrates

; or conversely, several different polysaccharides with similar structures may produce the same function. Therefore, from the perspective of disease diagnosis, therapeutic drug and reagent development, the bottleneck hindering the transformation of glycan-based clinical applications mainly exists in the description framework of synthesis methods, analytical methods and biological functions. At the same time, the integration of the above three research methods is particularly important for elucidating the structure-activity relationship of glycans and developing innovative drugs and diagnostic reagents.**4.1 Chinese glycan research needs more mature synthesis methods.**At present, some progress has been made in the study of the function of glycosides by different means. However, unlike nucleic acids and proteins, sugar chains do not have synthetic templates. In organisms, the synthesis of glycans is produced by the synergy of biological synthetases, without the assistance or replication of templates, which is completely different from the synthesis of genes and proteins. Therefore, complex glycans cannot be synthesized by a simple amplification strategy. The existing glycan synthesis methods can only use chemical synthesis, enzyme catalytic cooperation and microbial synthesis. These methods have their own advantages, but they all have certain limitations. To carry out large-scale research on the efficacy of glycans, new low-cost and efficient synthesis techniques must be developed to easily obtain glycans for research.**4.2 Chinese glycan research needs more perfect analytical methods.**The diversity and complexity of the structural units, chemical bonds and spatial composition of glycans make it very challenging to analyze the composition and structure of glycans in vivo and in vitro. At present, mass spectrometry (imaging), high performance liquid chromatography, capillary electrophoresis (CE), chip, MR and orthogonal labeling are used to coordinate each other and take their own advantages to carry out comprehensive analysis of glycans, but they still often encounter the dilemma of blind people. For example, the study of N-glycosylation of a certain locus has proved to be difficult. Because two N-glycan sequences are located adjacent to each other and are separated by only one arginine residue. At different sites, trypsin decomposition produces peptide chains of different sizes and lengths, which cannot be effectively fragmented and detected in mass spectrometry. Because of its complexity, it also poses a serious challenge to software-based detection. In addition to techniques such as instrumental detection, bioinformatics algorithms and techniques for genomics and proteomics cannot be directly used in glycomics due to the complexity of glycan structure. Therefore, it is necessary to develop more perfect analytical methods under more disciplinary exchanges and teamwork, and to obtain the functional and structural relationships of glycans through innovative technologies and automated workflows[67].**4.3 The elucidation of the biological function of glycans requires a new description framework.**In organisms, glycans mainly function at the multicellular level and are mostly carried out in a multivalent interaction manner. If we use the classic in vitro cell model of the pharmaceutical industry, the screening method of small molecule lead compounds, and the screening method of polysaccharide binding agents with a stoichiometric ratio of 1:1, it is possible to ignore the crucial information of the role of complex polysaccharides in the study of specific biological processes. For example, in the design of compounds that inhibit leukocyte homing and extravasation, it is necessary to consider both multivalence and structural complexity. Therefore, a new description framework for the biological function of glycans is another challenge to apply the results of glycan research to drug development.**4.4 The study of Chinese glycans requires more in-depth international exchanges and cooperation**Glycomics is a newly born discipline, and its development is still in its infancy. Basic research is not perfect, and research methods are relatively few. Up to now, there are only a few network tools and databases for glycomics, and the relevant data of each database cannot be shared due to the lack of consistent algorithms. These factors seriously limit the development of glycomics. Sugar chains have important biological functions and have shown attractive prospects in the prevention and treatment of tumors, AIDS and other stubborn diseases. The study of sugar chains will be related to the healthy development of all mankind, but its mechanism of action for these diseases is still unclear. The synergy of carbohydrates, such as the interaction between carbohydrates and proteins, carbohydrates and carbohydrates, is involved in many physiological and pathological processes. The adhesion between cells and the interaction between molecules involved in carbohydrates can be blocked by using the corresponding carbohydrate molecules, so that some physiological and patholog-

ical processes cannot occur. In-depth study of the role of sugar chains remains to be further explored from the level of molecular biology, which requires a lot of capital and talent investment. Only by different countries to jointly study and explore glycomics and continue to exchange cooperation and data sharing, can the mystery of glycomics be uncovered as soon as possible to achieve the health and safety of all mankind. It is believed that with the in-depth development of glycomics, the innovation of glycan analysis technology and the development of related instruments, there will be new breakthroughs and progress in glycomics research. In-depth study of glycoprotein or glycan structure and its mechanism of action is of great significance for revealing complex life phenomena, preventing and treating diseases.

Abbreviations

GalNAc: N-acetylgalactosamine, Gal: Galactose, Asn: Asparagine, Ser: Serine,Thr: Threonine, Trp: Tryptophan, ER: Endoplasmic Reticulum, GPI: Glycosylphosphstidylinositol, OGT: O-GlcNAc Transferase, OGA: O-GlcNAc hydrolase, T1DM: Type 1 Diabetes Mellitus, HbA1c: Glycated Hemoglobin A1c, NA2: Diantennary N-glycan, GlcNAc: N-acetyl-D-(+)-glucosamine, AUC: Area Under Receiver Operating Characteristic Curve, T2DM: Type 2 Diabetes Mellitus, MGH: Mammary Gland Hyperplasia, IgG: Immunoglobulin G, NSCLC: Non-Small Cell Lung Cancer, SCC: Squamous Cell Carcinoma, TCM: Traditional Chinese Medicine.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

RYZ, PFL, LZ, ZGR and XYJ conceived the study and drafted the manuscript. JHY, ZLJ and YL prepared the figures. All authors read and approved the final manuscript.

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Consent for publication

Not applicable.

Data Availability Statements

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

References

[1] A.V. Everest-Dass, E.S.X. Moh, C. Ashwood, A.M.M. Shathili, N.H. Packer, Human disease glycomics: technology advances enabling protein glycosylation analysis - part 2, Expert review of proteomics, 15 (2018) 341-352.

[2] K. Yamada, K. Kakehi, Recent advances in the analysis of carbohydrates for biomedical use, Journal of pharmaceutical and biomedical analysis, 55 (2011) 702-727. [3] in: A. Varki, R.D. Cummings, J.D. Esko, P. Stanley, G.W. Hart, M. Aebi, D. Mohnen, T. Kinoshita, N.H. Packer, J.H. Prestegard, R.L. Schnaar, P.H. Seeberger (Eds.) Essentials of Glycobiology, Cold Spring Harbor Laboratory Press Copyright © 2022 by the Consortium of Glycobiology Editors, La Jolla, California. Published by Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York. All rights reserved., Cold Spring Harbor (NY), 2022. [4] L. Oliveira-Ferrer, K. Legler, K. Milde-Langosch, Role of protein glycosylation in cancer metastasis, Seminars in cancer biology, 44 (2017) 141-152. [5] M. Pucci, N. Malagolini, F. Dall'Olio, Glycobiology of the Epithelial to Mesenchymal Transition, Biomedicines, 9 (2021). [6] K. Li, X. Liu, X. Zhang, Z. Liu, Y. Yu, J. Zhao, L. Wang, Y. Kong, M. Chen, Identification microbial glycans substructure associate with disease and species, Carbohydrate polymers, 273 (2021) 118595. [7] F. Rosati, A. Capone, C.D. Giovampaola, C. Brettoni, R.

Focarelli, Sperm-egg interaction at fertilization: glycans as recognition signals, The International journal of developmental biology, 44 (2000) 609-618. [8] M. Gómez-Gaviria, A.P. Vargas-Macías, L.C. García-Carnero, I. Martínez-Duncker, H.M. Mora-Montes, Role of Protein Glycosylation in Interactions of Medically Relevant Fungi with the Host, Journal of fungi (Basel, Switzerland), 7 (2021). [9] T. Feizi, B. Mulloy, Carbohydrates and glycoconjugates. Glycomics: the new era of carbohydrate biology, Current opinion in structural biology, 13 (2003) 602-604. [10] T.W. Rademacher, R.B. Parekh, R.A. Dwek, Glycobiology, Annual review of biochemistry, 57 (1988) 785-838. [11] S. Hemmerich, Glycomics: coming of age across the globe, Drug discovery today, 10 (2005) 307-309. [12] E. Adua, A. Russell, P. Roberts, Y. Wang, M. Song, W. Wang, Innovation Analysis on Postgenomic Biomarkers: Glycomics for Chronic Diseases, Omics : a journal of integrative biology, 21 (2017) 183-196. [13] A.J. Parodi, Reglucosylation of glycoproteins and quality control of glycoprotein folding in the endoplasmic reticulum of yeast cells, Biochimica et biophysica acta, 1426 (1999) 287-295. [14] J.N. Arnold, M.R. Wormald, R.B. Sim, P.M. Rudd, R.A. Dwek, The impact of glycosylation on the biological function and structure of human immunoglobulins, Annual review of immunology, 25 (2007) 21-50. [15] P. Hossler, Protein glycosylation control in mammalian cell culture: past precedents and contemporary prospects, Advances in biochemical engineering/biotechnology, 127 (2012) 187-219. [16] W. Wang, Glycomics Research in China: The Current State of the Art, Omics : a journal of integrative biology, 23 (2019) 601-602. [17] H. Nie, H. Ju, J. Fan, X. Shi, Y. Cheng, X. Cang, Z. Zheng, X. Duan, W. Yi, O-GlcNAcylation of PGK1 coordinates glycolysis and TCA cycle to promote tumor growth, Nature communications, 11 (2020) 36. [18] C. Huang, Y. Harada, A. Hosomi, Y. Masahara-Negishi, J. Seino, H. Fujihira, Y. Funakoshi, T. Suzuki, N. Dohmae, T. Suzuki, Endo-β-N-acetylglucosaminidase forms N-GlcNAc protein aggregates during ER-associated degradation in Ngly1-defective cells, Proceedings of the National Academy of Sciences of the United States of America, 112 (2015) 1398-1403. [19] J. Hofsteenge, D.R. Müller, T. de Beer, A. Löffler, W.J. Richter, J.F. Vliegenthart, New type of linkage between a carbohydrate and a protein: C-glycosylation of a specific tryptophan residue in human RNase Us, Biochemistry, 33 (1994) 13524-13530. [20] F. Turroni, C. Milani, S. Duranti, J. Mahony, D. van Sinderen, M. Ventura, Glycan Utilization and Cross-Feeding Activities by Bifidobacteria, Trends in microbiology, 26 (2018) 339-350. [21] L.C. McDermott, J.A. Freel, A.P. West, P.J. Bjorkman, M.W. Kennedy, Zn-alpha2-glycoprotein, an MHC class I-related glycoprotein regulator of adipose tissues: modification or abrogation of ligand binding by site-directed mutagenesis, Biochemistry, 45 (2006) 2035-2041. [22] M.P. Winters, Z. Sui, M. Wall, Y. Wang, J. Gunnet, J. Leonard, H. Hua, W. Yan, A. Suckow, A. Bell, W. Clapper, C. Jenkinson, P. Haug, T. Koudriakova, N. Huebert, W.V. Murray, Discovery of N-arylpyrroles as agonists of GPR120 for the treatment of type II diabetes, Bioorganic & medicinal chemistry letters, 28 (2018) 841-846. [23] L. Shao, Y. Luo, D.J. Moloney, R. Haltiwanger, O-glycosylation of EGF repeats: identification and initial characterization of a UDP-glucose: protein O-glucosyltransferase, Glycobiology, 12 (2002) 763-770. [24] S.S. Zhou, J. Xu, C.K. Tsang, K.M. Yip, W.P. Yeung, Z.Z. Zhao, S. Zhu, H. Fushimi, H.Y. Chang, H.B. Chen, Comprehensive quality evaluation and comparison of Angelica sinensis radix and Angelica acutiloba radix by integrated metabolomics and glycomics, Journal of food and drug analysis, 26 (2018) 1122-1137. [25] K.M. Yip, J. Xu, S.S. Zhou, Y.M. Lau, Q.L. Chen, Y.C. Tang, Z.J. Yang, Z.P. Yao, P. Ding, H.B. Chen, Z.Z. Zhao, Characterization of Chemical Component Variations in Different Growth Years and Tissues of Morindae Officinalis Radix by Integrating Metabolomics and Glycomics, Journal of agricultural and food chemistry, 67 (2019) 7304-7314. [26] S.A. Priola, V.A. Lawson, Glycosylation influences cross-species formation of protease-resistant prion protein, The EMBO journal, 20 (2001) 6692-6699. [27] G. Thanabalasingham, J.E. Huffman, J.J. Kattla, M. Novokmet, I. Rudan, A.L. Gloyn, C. Hayward, B. Adamczyk, R.M. Reynolds, A. Muzinic, N. Hassanali, M. Pucic, A.J. Bennett, A. Essafi, O. Polasek, S.A. Mughal, I. Redzic, D. Primorac, L. Zgaga, I. Kolcic, T. Hansen, D. Gasperikova, E. Tjora, M.W. Strachan, T. Nielsen, J. Stanik, I. Klimes, O.B. Pedersen, P.R. Njølstad, S.H. Wild, U. Gyllensten, O. Gornik, J.F. Wilson, N.D. Hastie, H. Campbell, M.I. McCarthy, P.M. Rudd, K.R. Owen, G. Lauc, A.F. Wright, Mutations in HNF1A result in marked alterations of plasma glycan profile, Diabetes, 62 (2013) 1329-1337. [28] M. Tijardović, T. Štambuk, A. Juszczak, T. Keser, D. Gasperikova, M. Novokmet, E. Tjora, E. Pape Medvidović, J. Stanik, P. Rasmus Njølstad, G. Lauc, K.R. Owen, O. Gornik, Fucosylated AGP glycopeptides as biomarkers of HNF1A-Maturity onset diabetes of the young, Diabetes research and clinical practice, 185 (2022) 109226. [29] A.T. Sage, L.A. Walter, Y. Shi, M.I. Khan, H. Kaneto, A. Capretta, G.H. Werstuck,

Hexosamine biosynthesis pathway flux promotes endoplasmic reticulum stress, lipid accumulation, and inflammatory gene expression in hepatic cells, American journal of physiology. Endocrinology and metabolism, 298 (2010) E499-511. [30] K. Sasai, Y. Ikeda, T. Fujii, T. Tsuda, N. Taniguchi, UDP-GlcNAc concentration is an important factor in the biosynthesis of beta1,6-branched oligosaccharides: regulation based on the kinetic properties of N-acetylglucosaminyltransferase V, Glycobiology, 12 (2002) 119-127. [31] J. Gu, Development of glycoscience in China, Glycoconjugate journal, 29 (2012) 239-240. [32] I.G. Lunde, J.M. Aronsen, H. Kvaløy, E. Qvigstad, I. Sjaastad, T. Tønnessen, G. Christensen, L.M. Grønning-Wang, C.R. Carlson, Cardiac O-GlcNAc signaling is increased in hypertrophy and heart failure, Physiological genomics, 44 (2012) 162-172. [33] P. Umapathi, O.O. Mesubi, P.S. Banerjee, N. Abrol, Q. Wang, E.D. Luczak, Y. Wu, J.M. Granger, A.C. Wei, O.E. Reyes Gaido, L. Florea, C.C. Talbot, Jr., G.W. Hart, N.E. Zachara, M.E. Anderson, Excessive O-GlcNAcylation Causes Heart Failure and Sudden Death, Circulation, 143 (2021) 1687-1703. [34] J.N. Wright, H.E. Collins, A.R. Wende, J.C. Chatham, O-GlcNAcylation and cardiovascular disease, Biochemical Society transactions, 45 (2017) 545-553. [35] R.V. Jensen, I. Andreadou, D.J. Hausenloy, H.E. Bøtker, The Role of O-GlcNAcylation for Protection against Ischemia-Reperfusion Injury, International journal of molecular sciences, 20 (2019). [36] L.J. Watson, H.T. Facundo, G.A. Ngoh, M. Ameen, R.E. Brainard, K.M. Lemma, B.W. Long, S.D. Prabhu, Y.T. Xuan, S.P. Jones, O-linked β-N-acetylglucosamine transferase is indispensable in the failing heart, Proceedings of the National Academy of Sciences of the United States of America, 107 (2010) 17797-17802. [37] R. Gélinas, F. Mailleux, J. Dontaine, L. Bultot, B. Demeulder, A. Ginion, E.P. Daskalopoulos, H. Esfahani, E. Dubois-Deruy, B. Lauzier, C. Gauthier, A.K. Olson, B. Bouchard, C. Des Rosiers, B. Viollet, K. Sakamoto, J.L. Balligand, J.L. Vanoverschelde, C. Beauloye, S. Horman, L. Bertrand, AMPK activation counteracts cardiac hypertrophy by reducing O-GlcNAcylation, Nature communications, 9 (2018) 374. [38] H. Zhao, H. Yang, C. Geng, Y. Chen, J. Pang, T. Shu, M. Zhao, Y. Tang, Z. Li, B. Li, C. Hou, X. Song, A. Wu, X. Guo, S. Chen, B. Liu, C. Yan, J. Wang, Role of IgE-FcεR1 in Pathological Cardiac Remodeling and Dysfunction, Circulation, 143 (2021) 1014-1030. [39] P.S. Banerjee, J. Ma, G.W. Hart, Diabetes-associated dysregulation of O-GlcNAcylation in rat cardiac mitochondria, Proceedings of the National Academy of Sciences of the United States of America, 112 (2015) 6050-6055. [40] E. Memarian, L.M. t Hart, R.C. Slieker, R.F.L. Lemmers, A.A. van der Heijden, F. Rutters, G. Nijpels, E. Schoep, A.G. Lieverse, E.J.G. Sijbrands, M. Wuhrer, M. van Hoek, V. Dotz, Plasma protein N-glycosylation is associated with cardiovascular disease, nephropathy, and retinopathy in type 2 diabetes, BMJ open diabetes research & care, 9 (2021). [41] S.S. Singh, R. Heijmans, C.K.E. Meulen, A.G. Lieverse, O. Gornik, E.J.G. Sijbrands, G. Lauc, M. van Hoek, Association of the IgG N-glycome with the course of kidney function in type 2 diabetes, BMJ open diabetes research & care, 8 (2020). [42] X. Meng, M. Song, M. Vilaj, J. Štambuk, M. Dolikun, J. Zhang, D. Liu, H. Wang, X. Zhang, J. Zhang, W. Cao, A. Momčilović, I. Trbojević-Akmačić, X. Li, D. Zheng, L. Wu, X. Guo, Y. Wang, G. Lauc, W. Wang, Glycosylation of IgG Associates with Hypertension and Type 2 Diabetes Mellitus Comorbidity in the Chinese Muslim Ethnic Minorities and the Han Chinese, Journal of personalized medicine, 11 (2021). [43] A. Sarrats, R. Saldova, E. Pla, E. Fort, D.J. Harvey, W.B. Struwe, R. de Llorens, P.M. Rudd, R. Peracaula, Glycosylation of liver acute-phase proteins in pancreatic cancer and chronic pancreatitis, Proteomics. Clinical applications, 4 (2010) 432-448. [44] K.R. Reiding, G.C.M. Vreeker, A. Bondt, M.R. Bladergroen, J.M.W. Hazes, Y.E.M. van der Burgt, M. Wuhrer, R. Dolhain, Serum Protein N-Glycosylation Changes with Rheumatoid Arthritis Disease Activity during and after Pregnancy, Frontiers in medicine, 4 (2017) 241. [45] M. Nikolac Perkovic, M. Pucic Bakovic, J. Kristic, M. Novokmet, J.E. Huffman, V. Vitart, C. Hayward, I. Rudan, J.F. Wilson, H. Campbell, O. Polasek, G. Lauc, N. Pivac, The association between galactosylation of immunoglobulin G and body mass index, Progress in neuro-psychopharmacology & biological psychiatry, 48 (2014) 20-25. [46] J. Krištić, F. Vučković, C. Menni, L. Klarić, T. Keser, I. Beceheli, M. Pučić-Baković, M. Novokmet, M. Mangino, K. Thaqi, P. Rudan, N. Novokmet, J. Sarac, S. Missoni, I. Kolčić, O. Polašek, I. Rudan, H. Campbell, C. Hayward, Y. Aulchenko, A. Valdes, J.F. Wilson, O. Gornik, D. Primorac, V. Zoldoš, T. Spector, G. Lauc, Glycans are a novel biomarker of chronological and biological ages, The journals of gerontology. Series A, Biological sciences and medical sciences, 69 (2014) 779-789. [47] K. Ihara, C. Fukano, T. Ayabe, M. Fukami, T. Ogata, T. Kawamura, T. Urakami, N. Kikuchi, I. Yokota, K. Takemoto, T. Mukai, A. Nishii, T. Kikuchi, T. Mori, N. Shimura, G. Sasaki, R. Kizu, N. Takubo, S. Soneda, T. Fujisawa, R. Takaya, Z. Kizaki, S. Kanzaki, K. Hanaki, N.

Matsuura, Y. Kasahara, K. Kosaka, T. Takahashi, K. Minamitani, S. Matsuo, H. Mochizuki, K. Kobayashi, A. Koike, R. Horikawa, S. Teno, K. Tsubouchi, T. Mochizuki, Y. Igarashi, S. Amemiya, S. Sugihara, FUT2 non-secretor status is associated with Type 1 diabetes susceptibility in Japanese children, Diabetic medicine : a journal of the British Diabetic Association, 34 (2017) 586-589. [48] R.F.H. Lemmers, M. Vilaj, D. Urda, F. Agakov, M. Šimurina, L. Klaric, I. Rudan, H. Campbell, C. Hayward, J.F. Wilson, A.G. Lieverse, O. Gornik, E.J.G. Sijbrands, G. Lauc, M. van Hoek, IgG glycan patterns are associated with type 2 diabetes in independent European populations, Biochimica et biophysica acta. General subjects, 1861 (2017) 2240-2249. [49] Z. Wu, H. Li, D. Liu, L. Tao, J. Zhang, B. Liang, X. Liu, X. Wang, X. Li, Y. Wang, W. Wang, X. Guo, IgG Glycosylation Profile and the Glycan Score Are Associated with Type 2 Diabetes in Independent Chinese Populations: A Case-Control Study, Journal of diabetes research, 2020 (2020) 5041346. [50] E.E. Irons, J.T.Y. Lau, Systemic ST6Gal-1 Is a Pro-survival Factor for Murine Transitional B Cells, Frontiers in immunology, 9 (2018) 2150. [51] E. Lontchi-Yimagou, E. Sobngwi, T.E. Matsha, A.P. Kengne, Diabetes mellitus and inflammation, Current diabetes reports, 13 (2013) 435-444. [52] M.C. Calle, M.L. Fernandez, Inflammation and type 2 diabetes, Diabetes & metabolism, 38 (2012) 183-191. [53] J.T. Smilowitz, S.M. Totten, J. Huang, D. Grapov, H.A. Durham, C.J. Lammi-Keefe, C. Lebrilla, J.B. German, Human milk secretory immunoglobulin a and lactoferrin N-glycans are altered in women with gestational diabetes mellitus, The Journal of nutrition, 143 (2013) 1906-1912. [54] V. Vanhooren, W. Laroy, C. Libert, C. Chen, N-glycan profiling in the study of human aging, Biogerontology, 9 (2008) 351-356. [55] X.E. Liu, L. Desmyter, C.F. Gao, W. Laroy, S. Dewaele, V. Vanhooren, L. Wang, H. Zhuang, N. Callewaert, C. Libert, R. Contreras, C. Chen, N-glycomic changes in hepatocellular carcinoma patients with liver cirrhosis induced by hepatitis B virus, Hepatology (Baltimore, Md.), 46 (2007) 1426-1435. [56] E. Staudacher, F. Altmann, I.B. Wilson, L. März, Fucose in N-glycans: from plant to man, Biochimica et biophysica acta, 1473 (1999) 216-236. [57] N. Ding, H. Nie, X. Sun, W. Sun, Y. Qu, X. Liu, Y. Yao, X. Liang, C.C. Chen, Y. Li, Human serum N-glycan profiles are age and sex dependent, Age and ageing, 40 (2011) 568-575. [58] W.E. Naugler, T. Sakurai, S. Kim, S. Maeda, K. Kim, A.M. Elsharkawy, M. Karin, Gender disparity in liver cancer due to sex differences in MyD88-dependent IL-6 production, Science (New York, N.Y.), 317 (2007) 121-124. [59] F.X. Bosch, J. Ribes, M. Díaz, R. Cléries, Primary liver cancer: worldwide incidence and trends, Gastroenterology, 127 (2004) S5-s16. [60] Z. Meng, C. Li, G. Ding, W. Cao, X. Xu, Y. Heng, Y. Deng, Y. Li, X. Zhang, D. Li, W. Wang, Y. Wang, W. Xing, H. Hou, Glycomics: Immunoglobulin G N-Glycosylation Associated with Mammary Gland Hyperplasia in Women, Omics : a journal of integrative biology, 24 (2020) 551-558. [61] Y. Liang, P. Han, T. Wang, H. Ren, L. Gao, P. Shi, S. Zhang, A. Yang, Z. Li, M. Chen, Stage-associated differences in the serum N- and O-glycan profiles of patients with non-small cell lung cancer, Clinical proteomics, 16 (2019) 20. [62] Z. Kyselova, Y. Mechref, P. Kang, J.A. Goetz, L.E. Dobrolecki, G.W. Sledge, L. Schnaper, R.J. Hickey, L.H. Malkas, M.V. Novotny, Breast cancer diagnosis and prognosis through quantitative measurements of serum glycan profiles, Clinical chemistry, 54 (2008) 1166-1175. [63] M.N. Christiansen, J. Chik, L. Lee, M. Anugraham, J.L. Abrahams, N.H. Packer, Cell surface protein glycosylation in cancer, Proteomics, 14 (2014) 525-546. [64] J. Wu, X. Xie, S. Nie, R.J. Buckanovich, D.M. Lubman, Altered expression of sialylated glycoproteins in ovarian cancer sera using lectin-based ELISA assay and quantitative glycoproteomics analysis, Journal of proteome research, 12 (2013) 3342-3352. [65] J.H. Rho, J.J. Ladd, C.I. Li, J.D. Potter, Y. Zhang, D. Shelley, D. Shibata, D. Coppola, H. Yamada, H. Toyoda, T. Tada, T. Kumada, D.E. Brenner, S.M. Hanash, P.D. Lampe, Protein and glycomic plasma markers for early detection of adenoma and colon cancer, Gut, 67 (2018) 473-484. [66] Y. Wang, J.J. Zhang, Z.X. Wang, F. Cui, Q.N. Zhang, P.P. Song, B. Li, Z.S. Tang, F.D. Hu, X.F. Shi, Characterization of chemical composition variations in raw and processed Codonopsis Radix by integrating metabolomics and glycomics based on multiple chromatography-mass spectrometry technology, Journal of separation science, 45 (2022) 2375-2393. [67] L. Liu, H. Qin, M. Ye, [Recent advances in glycopeptide enrichment and mass spectrometry data interpretation approaches for glycoproteomics analyses], Se pu = Chinese journal of chromatography, 39 (2021) 1045-1054.

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