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Glycosylation as an intricate post-translational modification process takes part in glycoproteins related immunity

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Abstract

Protein glycosylation, the most ubiquitous and diverse type of post-translational modification in eukaryotic cells, proteins are input into endoplasmic reticulum and Golgi apparatus for sorting and modification with intricate quality control, are then output for diverse functional glycoproteins that are utilized by cells to precisely regulate various biological processes. In order to maintain the precise spatial structure of glycoprotein, misfolded and unfolded glycoproteins are recognized, segregated and degraded to ensure the fidelity of protein folding and maturation. This review enumerates the role of five immune-related glycoproteins and reveals the relevance of glycosylation to their antigen presentation, immune effector function, immune recognition, receptor binding and activation, and cell adhesion and migration. With the knowledgement of glycoproteins in immune responses and etiologies, we propose several relevant therapeutic strategies on targeting glycosylation process for immunotherapy.

Keywords Glycosylation, Glycans, Quality control, Glycoprotein, Immune response, Immunotherapy

Introduction

Glycosylation as an enzymatic process is likely as ancient as life itself that may produce glycosidic linkages between saccharides and other saccharides, proteins or lipids, which work out abundant repertoire of glycans to regulate critical cellular processes [1]. In the present review, protein glycosylation as intricate protein post-translational modification (PPTM) pathway was further discussed. Endoplasmic reticulum (ER) and Golgi apparatus as predominant location that intricate glycosylation modification processes are occurred, in where native glycosyltransferases and glycosidases attach different glycans to proteins using active nucleotide sugars as substrates, then transport from ER to Golgi apparatus and cell membrane to yield various functional glycoproteins [2, 3, 4]. As a conserved PPTM, protein glycosylation makes indispensable contributions to abundant repertoire of glycoproteins while ensuring their stability through rigorous quality control for folding and degradation.

Glycoproteins, formed by the combination of glycans and proteins, represent crucial biomacromolecules with distinct structural properties and a diverse array of biological functions that are involved in various physiological processes as well as disease mechanisms [5]. Nearly

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all essential molecules that participate in innate and adaptive immune responses may rely on the involvement of glycoproteins [6]. The process of protein glycosylation allows glycoproteins to fold correctly and mature to maintain their precise spatial structure and quality control, forming a wide variety of glycoproteins with different immunological roles, which provide immune-related substrates for subsequent immune responses such as antigen presentation, immune effector functions, immune recognition, receptor binding and activation, as well as cell adhesion and migration. Given the variety and intricacy of glycoprotein structures and corresponding functions, we cannot summarize all immune-related glycoproteins here, but instead focus on a few illustrative examples, which include major histocompatibility complex (MHC) proteins, immunoglobulin (Ig), complement, immune cell receptors, and cell adhesion molecules (CAMs).

This review discusses the occurrence of protein glycosylation process and its biological significance, focusing on five types of glycoproteins that are vital to the immune system. Moreover, since the significant roles of glycoproteins in medicine which are associated with various human diseases, as cancer [7], several relevant therapeutic strategies to target glycosylation are also introduced.

Background of protein glycosylation

While the amino acid sequences of most proteins are determined by the genetic codes encrypted in DNA sequences, many undergo various PPTM, including phosphorylation, sulphation, lipidation, acylation, alkylation and glycosylation [8]. Among them, glycosylation stands out as one of the most common and intricate forms that significantly influences protein spatial structure, and is crucial for the biosynthesis and biological activity of glycoproteins involved in numerous biological recognition events [5, 9]. Of note, the synthesis of glycans occurs without a template, and a massive of factors involved in this cellular glycosylation machinery, collectively of which make the complex repertoire of glycogens found on glycoproteins. As the most intricate PPTM, glycosylation brings diversity and heterogeneity of glycoprotein spatial structure to suit the desired function within the cell [9]. Generally speaking, protein glycosylation reflects both the repertoire of glycosyltransferases and the capacity for glycosylation within producing cells. However, some individual proteins may not undergo efficient glycosylation, leading to cause diseases, and specific characteristics of glycosylation are directed towards particular proteins rather than being universally found. Furthermore, various cellular and environmental factors that affect glycosylation efficiency influence both the secretory pathway and glycosylation machinery.

Requirements for glycosylation

Protein glycosylation is the most ubiquitous and intricate PPTM that occurs primarily in ER and Golgi apparatus [10, 11]. The inherent structural variations of glycans makes this process an effective way to generate protein diversity and regulate its properties [12]. This process not only requires a highly efficient and well-coordinated system to ensure accuracy and quality control during the processing of sugar chains, but also necessitates precise allocation of various mechanisms including glycosyltransferases (that add sugars), glycosidases (that remove sugars), nucleotide sugars transporters (that provide sugar substrates) and nascent polypeptide (that connect with glycans) (Fig. 1A) [12]. These activated nucleotide sugars mainly include uridine diphosphate N-acetylglucosamine (UDP-GlcNAc), uridine diphosphate N-acetylgalactosamine (UDP-GalNAc), uridine diphosphate galactose (UDP-gal), uridine diphosphate glucose (UDP-glc), uridine diphosphate xylose (UDP-xyl), uridine diphosphate glucuronic acid (UDP-GlcA), guanosine diphosphate mannose (GDP-man), guanosine diphosphate fucose (GDP-fuc), and cytidine monophosphate N-acetyl neuraminic acid (CMP-Neu5Ac) (Fig. 1B and C) [13, 14, 15]. They are primarily produced in cytoplasm and nucleus, then transported into ER and Golgi apparatus by nucleotide sugar transporters (NSTs) located within their membranes since nucleotide sugars are unable to cross the organellular membranes [16, 17].

Primary sites where glycosylation occurs

The glycosylation of proteins mainly accomplished by the collaboration between ER and Golgi apparatus [18, 19]. There are many covalent modifications of transporters between these two organelles, including glycosylation, selective proteolysis, sulfation, phosphorylation, and fatty acid addition, which can be biochemical markers of this process. Among them, the most in-depth research is glycosylation [20]. About one-third of the cellular proteins are directed to ER lumen for proper folding and initial modification before being transported to Golgi apparatus for further PPTM like glycosylation, since they contains a series of native components assisting glycoprotein synthesis and maturation, such as chaperones, folding enzymes, glucosidases, and carbohydrate transferases [21, 22, 23, 24]. Between ER and Golgi apparatus, proteins also must be sorted into coated vesicles in order to flow [25]. The COPII transports properly folded glycoproteins from ER to Golgi apparatus via a complex involving ERGIC53 and oxidoreductase ERp44, and then being sorted for delivery to their final destinations [26]. However, If native components that assist in glycoprotein production in the ER is accidentally reached to Golgi apparatus, the COPI recognize and transport it back to the ER (Fig. 1A) [27]. On the whole, except that

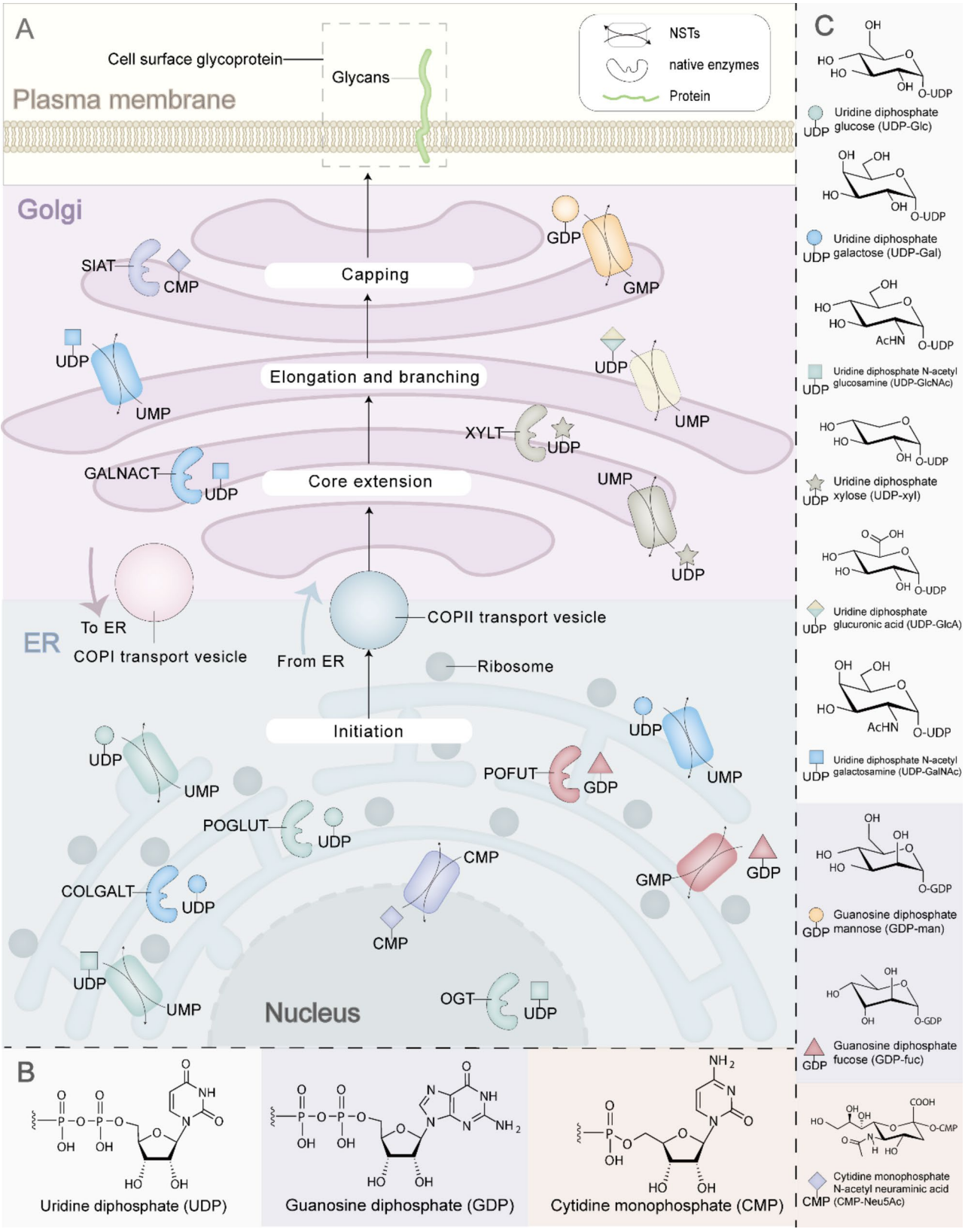

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Fig. 1 Subcellular organelles of protein glycosylation. **A|** Glycosylation occurs within ER and Golgi apparatus, which contain diverse native glycosyltransferases and glycosidases that use nucleotide sugars as substrates to form glycoproteins by attaching different glycans to proteins in the presence of enzymes. Since nucleotide sugars cannot cross organellular membranes, NST are required to introduce them into ER and Golgi apparatus. With the exception of O-GlcNAcylation in cytosol and nucleus, most protein glycosylation initiation steps occur in the ER and subsequent processes (core extension, elongation, and capping) occur in Golgi apparatus. Meanwhile, between ER and Golgi apparatus, substances need to be sorted into coated vesicles in order to flow. **B|** Mammalian glycans consist of nine monosaccharides that undergo activated through UDP, GDP and CMP to form activated nucleotide sugars, which serve as substrates for the glycosylation, and then glycosyltransferases use these activated nucleotide sugar donors to transfer the monosaccharides onto developing glycan chains. In this figure we also draw the chemical structure of three nucleotides. **C|** The figure reflects the chemical structure of nine nucleotide sugars. UDP, uridine diphosphate; GDP, guanosine diphosphate; CMP, cytidine monophosphate; GMP, guanosine monophosphate; UMP, uridine monophosphate; OGT, O-GlcNAc transferase; COLGALT, collagen O-Gal transferase; POGLUT, protein O-Glc transferase; POFUT, protein O-fucosyltransferase; GALNACT, polypeptide GalNAc-transferase; XYLT, protein O-Xyl transferase; SIAT, sialyltransferases. (All figures are designed by ourselves with Adobe Illustrator 2024)

mucin-type O-glycosylation starts from the Golgi apparatus, most of the rest takes place primarily within ER and ends in Golgi apparatus [28, 29].

Main types of glycosylation

Glycosylation refers to the template-free and continuous process of attaching glycans to proteins, and the variety of glycans attached immensely increases the complexity of the resulting protein structure. Within ER and Golgi apparatus, protein glycosylation primarily includes N-glycosylation, O-glycosylation, C-mannosylation, and the formation of glycosylphosphatidylinositol (GPI) -anchored proteins, of which N- and O-glycosylation are two most prevalent types [29, 30]. Newly synthesized proteins undergo proper folding, as well as initial N- and O-glycosylation within the ER before being transported to the Golgi apparatus for further processing, maturation of glycans, trafficking, and sorting [31].

Many proteins undergo N-glycosylation initiating in ER and maturing in Golgi apparatus, in which GlcNAc forms a covalent bond with nitrogen atom of Asn side chain through an N-glucosidic linkage within consensus sequence Asn-X-Ser/Thr, where X represents any amino acid except proline [19, 32, 33]. Based on their side chain branches, N-glycans can be categorized into three major subtypes like high mannose N-glycans (characterized by elongated by mannose residues), complex N-glycans (which undergo further chain elongation with the addition of GlcNAc to Golgi apparatus), and hybrid N-glycans (incorporating galactose or fucose residues alongside mannose in Golgi apparatus) [34]. The entire process of protein N-glycosylation occurs in the ER and Golgi apparatus through four stages. First, the precursor molecule containing 14 sugar molecules (Glc3Man-9GlcNAc2) is synthesized within the ER membrane, then the glycan is attached to its substrate. Subsequently, the glycoprotein undergoes initial processing within the ER lumen, followed by further maturation of the glycan in the Golgi apparatus. [35].

O-glycosylation refers to adding glycans to serine or threonine in Golgi apparatus and involves initially linking several monosaccharides including Gal, Man, Fuc, and GalNAc, which occurs during the post-translational stage of the Golgi apparatus [36, 37]. Unlike N-glycosylation, O-glycosylation lacks specific consensus sequence. Its synthesis involves the progressive addition of individual monosaccharides along the exocytic pathway [38]. In higher eukaryotic cells, two primary types of O-glycans synthesized in Golgi apparatus: shorter mucin-type glycans and longer glycosaminoglycan chains found on proteoglycans [10]. Reversible O-glycosylation is prevalent modification observed in various proteins including transcription factors, cytoskeletal proteins, oncogenes and kinases [29].

Compared with N/O-glycosylation, the extent of PPTM in C-mannosylation is significantly lower, which is referred to as C-glycosylation due to the attachment of α-mannopyranose monosaccharide to a tryptophan residue within the polypeptide sequence Trp-X-X-Trp, where X represents any amino acid, through carbon-carbon bonds [32]. And formation of GPI-anchored protein is the use of glycans as linker to connect proteins to phosphatidylinositol anchors in the membrane, also known as glypiation [10].

The biological significance of protein glycosylation

Protein glycosylation plays a crucial role in connecting intricate metabolic pathways to different proteoforms, refining protein structures, and performing biological functions [2]. The modification involves the addition of complex oligosaccharides, known as glycans, which have diverse effects on overall structure and function [39]. Moreover, glycans play a direct role in numerous biological processes, including intracellular trafficking, interactions between cells and extracellular matrix, signalling pathways, development, host-pathogen interactions, and immune responses [5]. One significant role of glycosylation is promoting protein folding and subsequent trafficking, in addition to modulate interactions with receptors and ligands, and influencing innate and adaptive immune responses [40]. Generally, accurate protein glycosylation affects almost every aspect relevant to cellular processes that control protein stability [41], assist in protein folding [12], promote protein secretion

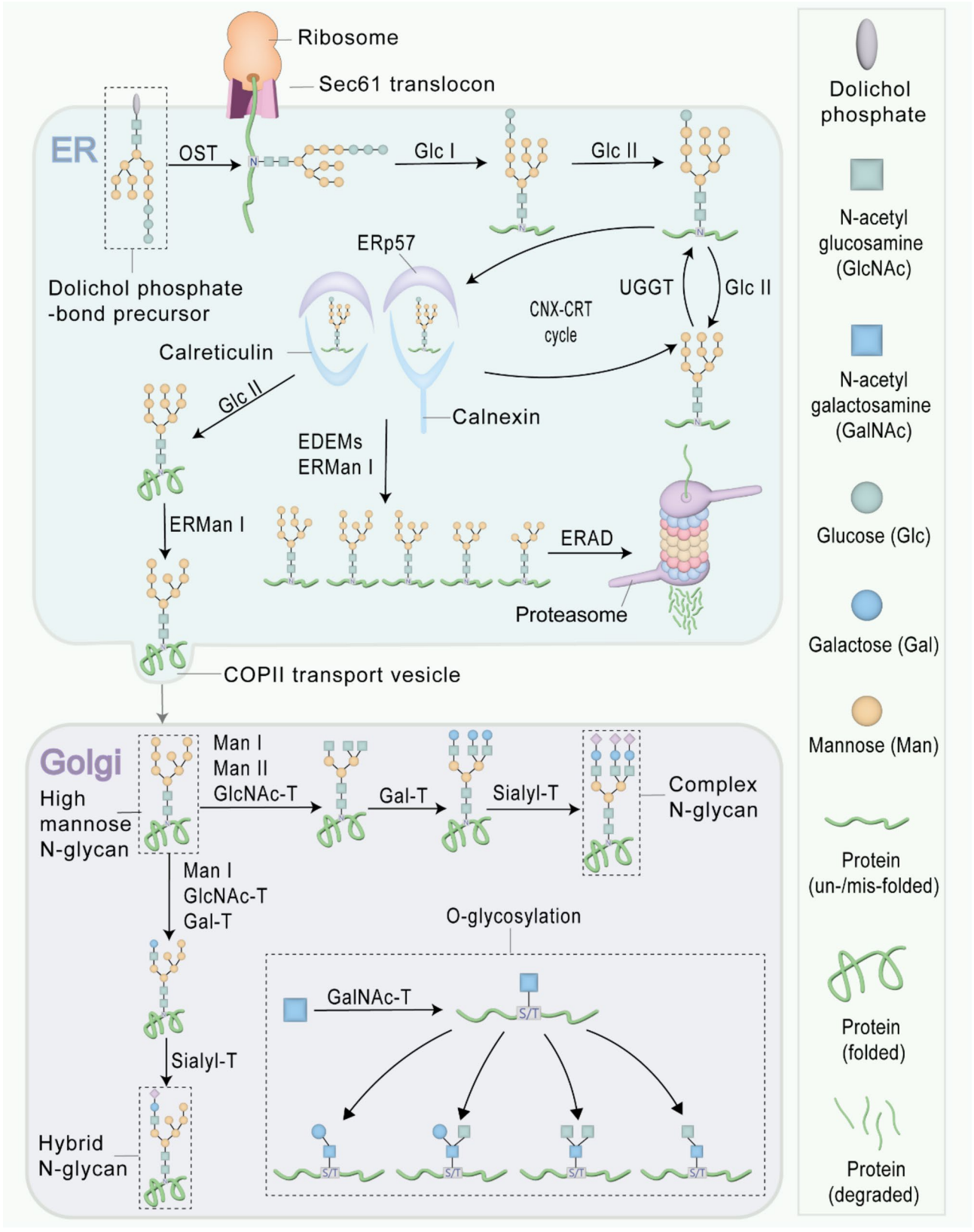

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Fig. 2 Protein N- and O-glycosylation in quality control of protein folding and degradation. Glycosylation of protein mainly accomplished through the synergistic action of ER and Golgi apparatus. N-glycosylation involves adding glycans to amide group of Asn(N) residues within ER and Golgi apparatus, whereas O-glycosylation refers to attaching a single glycan to hydroxyl oxygens of Ser (S) or Thr(T) residues in Golgi apparatus. Based on their side chain branches, N-glycans can be categorized into three main types like high mannose, complex and hybrid N-glycans, whereas O-glycans are synthesized by first attaching GalNAc to the Ser/Thr side chain, and then extending them with additional sugars such as Gal, GlcNAc, sialic acid, and Fuc resulting in either linear or branched glycan. However, due to variability in O-glycosylation and an absence of consensus sequences, only four core types are shown in the figure. During glycoprotein synthesis, nascent polypeptides are translated and subsequently translocated through Sect. 61 pore while OST transfers $Glc_3Man_9GlcNAc_2$ from dolichol phosphate onto unfold proteins. Then, native folded glycoproteins are then generated with the help of various glycosyltransferases, glycosidases, molecular chaperones and lectins. At this point, properly folded glycoproteins proceed to Golgi apparatus for further modifications via COPII, meanwhile, un/misfolded proteins will be degraded through ERAD pathway. ER, endoplasmic reticulum; OST, oligosaccharyltransferase; ERMan I, ER mannosidase I; Man I/II, mannosidase I/II; Glc I, glucosidases I; Glc II, glucosidases II; Gal-T, galactosyltransferases; GalNAc-T, GalNAc-transferase; Sialyl-T, sialyltransferase; GlcNAc-T, GlcNAc-transferase; ERp57, Endoplasmic Reticulum Protein57

and trafficking [42], and protect protein from degradation [43], facilitate recognition between cells and extracellular matrix [44]. All of these participates in immune responses [4]. Studies have confirmed that abnormal glycosylation is either cause or result of various diseases such as autoimmune diseases, diabetes, cancer, cardiovascular, and cystic fibrosis [19, 31]. For the process of protein glycosylation, inputs the form of given post-translational protein enter ER and Golgi apparatus for sorting and modification with intricate glycosylation, are then output diverse functional glycoproteins, which is utilized by cells to precisely regulate critical cellular immune responses.

Role of glycosylation in the quality control of glycoprotein folding and degradation

Glycoproteins are essential in regulating various immune responses. If not correctly folded and matured within ER and Golgi apparatus, misfolded and unfolded dysfunctional glycoproteins are expressed on cell surface or extracellular spaces, resulting in disruptions in signaling pathways that respond to the function of immune cells [45]. In mammalian systems, the toxic accumulation of abnormal proteins necessitates sophisticated quality control mechanisms to identify, isolate and degrade these misfolded proteins, thereby ensuring proper protein folding and maturation [46, 47]. Among them, a key part of ER protein quality control is glycosylation, which facilitates the delivery of properly folded glycoproteins. Glycan structures present on newly synthesized glycoproteins play a crucial role in their secretion by affecting protein folding, assisting in quality control monitoring within ER and enable transport along the secretion pathway with selective targeting [48, 49]. The glycoprotein quality control system efficiently also employs many chaperone enzymes and lectins, including UDP-glucose: glycoprotein glucosyltransferase (UGGT), calnexin (CNX), calreticulin (CRT), protein disulfide bond isomerase (ERp57 or PDIs), and glucosidases to convert nascent glycopolypeptides into properly folded native forms [50]. These intricate glycosylation processes of proteins may exert a repertoire of biological function in glycoprotein maturation and accurate folding to maintain their precise spatial structure on surveillance of quality control for subsequent immunological recognition, antigen presentation, immune effector functions, immune checkpoint, cell adhesion and migration, and receptor binding and activation.

Glycosylation influences glycoprotein spatial structure through protein folding processes

It is well established that glycans can profoundly influence the conformation of short glycopeptides [51]. The majority of protein molecules need to adopt specific three-dimensional structures in order to acquire function properly, therefore it is necessary to ensure protein folding properly [52]. When proteins are in the translocon complex, glycans are added to unfolded proteins to aid protein folding [12, 49, 51]. In addition, newly synthesized proteins encounter several chaperones or folding enzymes that work together to help correct protein fold before being released from the ER [22]. Chaperones identify immature, abnormal, or easily aggregated proteins through exposed hydrophobic fragments, assisting in the maturation of non-glycosylated proteins or unmodified domains on glycosylated proteins [53].

In the process of N-glycosylation (Fig. 2), after the eukaryotes transfer $Glc_3Man_9GlcNAc_2$ glycans to the new polypeptide chains, the two Glu residues are pruned to form the $GlcMan_9GlcNAc_2$ structure, which serves as a ligand for CNX and CRT [14, 48]. When glucosidases I and II trim these two glucoses from N-linked core glycans to form $GlcMan_9GlcNAc_2$ structure, nascent glycoproteins associate with CNX and/or CRT. In this way, this interaction introduces another folding factor, ERp57 that thiol oxidoreductase that associates with CNX and CRT. If cysteine is present in the glycoprotein, it forms disulfide bonds with ERp57, thereby stabilizing the spatial structure of the peptide chain [5, 49]. Once glucosidases II remove third glucose residue to yield $Man_9GlcNAc_2$, these complexes separate. If glycoprotein remains improperly folded, UGGT will re-glycosylate oligosaccharides by recognizing exposed hydrophobic regions on its surface through its unique multiple domains,

which allows misfolded glycoproteins to be identified and rebound to lectins. This cycle continues until either proper folding occurs or quality control mechanisms break it [46, 54].

Once folded correctly, glycoproteins are no longer recognized by glucosyltransferase, meanwhile, they can exit ER successfully, and most of glycoproteins will enter the Golgi apparatus by various membrane-bound lectins, namely VIPL, VIP36 or ERGIC53 [8, 51, 55]. In this organelle, enzymes like glycosyltransferase and glycosidase facilitate O-glycosylation while converting high mannose-type glycans into mature acidic sialyloligosaccharides along with additional O-glycosylation [50]. Generally speaking, interactions among calnexin, calreticulin, ERp57, and UGGT will slow down protein folding rates but increase overall efficiency [56].

Glycoprotein degradation

The function of chaperones, folding catalysts and protein-modifying enzymes in ER lumen are responsible for identifying and binding misfolded proteins, facilitate refolding until they form the correct conformation for exiting ER [57]. After protein reaches its native structure, modified glycan will act as a signal that directs its transport to various cellular compartments such as endosomes, lysosomes, or defaults to secretion at plasma membrane [34]. However, due to environmental factors and inherent complexities, protein folding is one of error prone processes during gene expression [58]. If protein fails to fold correctly, it will be degraded by the ER-associated degradation (ERAD) pathway (Fig. 2) [21]. ERAD is a rather complex and ordered process in which misfolded proteins are recognized by resident factors within ER in protein secretion pathway and directed by transport mechanisms to reverse shuttle into the cytoplasm, where they undergo ubiquitination before being degraded by proteasomes via the ubiquitin-proteasome system [56, 59]. Glycans also have a significant role in ERAD of proteins [51]. If protein folded incorrectly, ER degradation-enhancing α-mannosidase-like proteins (EDEM) begins removing mannose residues from their core glycans, resulting in substrate demannosidation, which will be dislocated into the cytoplasm and degraded by ERAD [60, 61, 62]. Once in the cytoplasm, these substrates are immediately ubiquitinated and then degraded by 26 S proteasomes [56]. In addition, EDEM is upregulated upon unfolded protein responses (UPR) activation, which allows directly targeting of substrate glycoproteins to ERAD without needing prior mannose trimming, thereby expediting reduction of excess protein load within the ER [63]. Soluble ER-resident proteins specifically identify trimmed oligosaccharide generated by ERManI/EDEM by mannose-6-phosphate receptor homologous domain [61]. In certain organisms, cytoplasmic peptide-N-glycanase can remove N-glycans from ubiquitinated misfolded proteins destined for proteasomal degradation [59]. When glycosylation processes are inhibited, one commonly observed outcome is an accumulation of aggregated misfolded proteins that do not reach functional states [49, 51]. Misfolding or mistargeting proteins in early secretory pathways pose significant risk to cells [64].

Disruption of ER-associated functions, such as dysregulation of glycoprotein quality control, leads to occurrence of UPR by activating intricate cytoplasmic and nuclear signaling pathways [21]. The UPR initiates an adaptive response aimed at restoring homeostasis within the ER by reducing protein expression levels while increasing molecular chaperone production to manage excess misfolded proteins. It also promotes the degradation of ER-associated proteins to eliminate misfolded entities, but if stress conditions persist or worsen, the UPR may ultimately lead to apoptosis as a means to resolve ongoing issues [65].

Glycosylation modification maintain glycoprotein stability

The presence of bulky oligosaccharide groups hinders interaction formation in unfolded state, forcing polypeptide chain to adopt more extended conformations that enhance protein stability [12, 46]. Research on soybean agglutinin, a glycoprotein, indicates that its non-glycosylated monomeric is less stable than glycosylated counterpart at both normal and higher temperatures. This increased stability in glycosylated proteins is due to non-covalent interactions between proteins and carbohydrate components [66]. CNX-CRT cycle facilitates proper folding, prevents the aggregation of intermediates and premature oligomerization. Meanwhile, the ERAD pathway removes aberrant proteins from ER through degradation that relies on ubiquitin-proteasome system. Together, they maintain glycoprotein stability and provide quality control via blocking incomplete folded glycoprotein from entering Golgi apparatus [49]. In general, glycosylation processes within this quality control system monitor maturation fidelity, through regulating the accurate temporal and spatial folding, maintaining the stability of glycoprotein to respond to internal and external cues and retaining misfolded proteins within the ER for efficient targeting towards degradation [22].

The role of glycoproteins in immune responses

Cell-surface glycoproteins are essential for immune responses. These immune related glycoproteins are very dynamic and diversity, which allow the cell to adapt to over-changing environment [67]. The diversity of protein glycosylation generates the complex spatial structures of glycoproteins that have profound effects on immune responses. As the most fundamental modification

conjugate of macromolecular components, glycans located on the cell membrane can delicately shield or exposure large areas of protein surfaces, which may interfere the lateral protein-protein interactions and influence the orientation of binding sites on attached proteins. Moreover, the specific spatial configuration of individual glycoprotein may anchor one typical molecular pathway to govern some extent immune processes. Based on the diversified glycogen pool as they conjugate to specific substrates and receptors, a diverse and abundant repertoire of glycoprotein are produced. This intricate glycosylation modification precisely manipulate the processes of immunological recognition, antigen presentation, immune effector functions, cell adhesion and migration, along with receptor binding and activation.

Major histocompatibility complex (MHC) in antigen presentation

MHC class I and II are glycoproteins that display endogenous and exogenous antigens on cell surface, facilitating the recognition and activation of circulating T lymphocytes [68]. The oligosaccharides linked to glycoproteins at the junction of T cell and antigen-presenting cells (APCs) assist in orienting the binding surface, offering protection from proteases, and limiting nonspecific lateral protein-protein interactions [6]. In adaptive immunity, glycans play a role in organizing immunological synapses, and are involved in producing and loading of MHC I antigenic peptides, as well as presenting of MHC II antigens [69, 70].

Mature MHC I consists of three subunits: a transmembrane heavy chain glycoprotein; the small soluble non-glycosylated β_2-microglobulin (β_2M) protein that forms the heterodimer essential for presenting antigenic peptides; and antigenic peptides that are necessary for transporting MHC I to the cell membrane [68, 71]. For MHC I, after the core $Glc_3Man_9GlcNAc_2$ structure is attached to Asn86, it undergoes rapid processing by glucosidases I and II, leading to the formation of monoglucosylated $Glc_1Man_9GlcNAc_2$. This modification enables interaction with CNX and CRT. Together with additional accessory molecules, these chaperones play a role in the ER to ensure proper folding of the heavy chain, association with β_2M, and loading of antigenic peptides into the binding groove (Fig. 3) [72, 73]. Blocking MHC I N-glycosylation may cause the failure of β_2M and antigenic peptides to bind, leading to an increase in intracellular misfolded proteins and a reduction in cell surface expression [74].

Unlike MHC I, which utilizes different peptide pools derived from endogenous sources, MHC II processes exogenous proteins internalized through endocytosis. These proteins are subsequently degraded by resident proteases within endosomes or lysosomes into specific peptides ranging from 10 to 25 residues in length before being loaded onto MHC II complexes [68, 75]. MHC II has two highly conserved N-glycosylation acceptor sites at approximately Asn78 on the alpha chain and at Asn19 on the beta chain, but these are variable between different species, which may be related to separate functional roles of MHC II allotypes [68]. N-glycans are thought to guide the MHC II molecules to the Golgi and then to endocytic compartments, protecting them from premature proteolysis in non-acidic vesicles to ensure that the MHC II groove is accessible for antigenic peptide binding [76, 77]. In addition, the elimination of N-glycans on MHC II reduces glycoantigen presentation in live APCs, virtually eliminates their binding to recombinant MHC II in vitro, and significantly limits glycoantigen-mediated T cell recognition and activation in vitro and in vivo, resulting in dysregulation of intestinal immune homeostasis [78, 79]. However, the basic binding properties of MHC to peptides and TCR to MHC-peptide complexes are largely unaffected by the presence or absence of complex N-glycan [78].

In brief, MHC molecules are glycoproteins that display antigenic peptides on the cell surface to recognize and activate circulating T lymphocytes [75]. The presence of glycans is imperative for the functionality of the immune system. For example, tumor cells exhibit epitopes derived from the Mucin 1 core domain with truncated glycosylation, in conjunction with MHC-I molecules, resulting in natural MHC-restricted recognition of 'hypoglycation' epitopes [80]. Alterations in N-glycan branching may influence the capacity of MHCII to present glycoantigens and stimulate anti-inflammatory T cells [78]. Also, the evasion of pathogens through MHC glycan modification has been shown to effectively prevent antigen presentation to CD8 + T cells. MHC glycan modification makes tumor cells less efficient in presenting antigenic peptides, thus escaping cytotoxic T-lymphocytes lysis and promoting metastasis [81].

Immune effector functions of Immunoglobulins

Immunoglobulins are an important type of glycoproteins whose glycans are associated particularly with the Fc domain influencing their immune effector functions. The Fc fragments links various sugar moieties, including fuc, gal, and sialic acid [82, 83].

Human IgG is categorized into four subclasses with 36 potential glycoforms, resulting in up to 144 functional states, making the regulation of antibody effects more complex and precise [84]. Among them, the bi-antennary complex N-glycan is typical sugar linked to asparagine 297 in the Fc of IgG antibodies (Fig. 4). The glycans attached to IgG are crucial for preserving structural integrity, enabling interactions with Fc receptors, and triggering subsequent immune responses [85]. Afucosylation of IgG enhances the affinity of Fc for type I FcγRIIIa

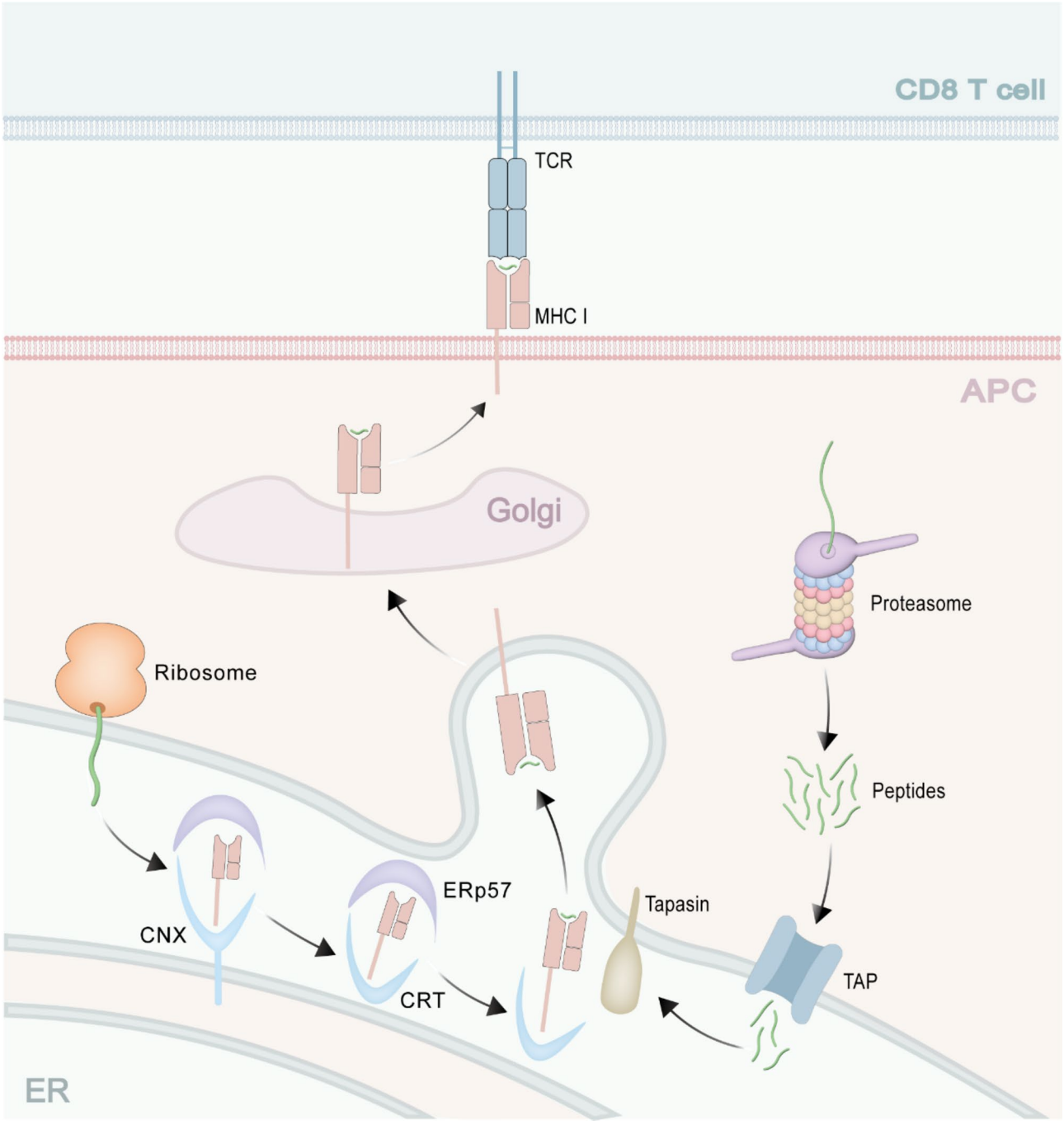

Fig. 3 The protein folding and peptide loading of MHC I manipulates MHC-I/TCR interactions. >Glycosylation of MHC I is crucial for protein folding, transport to cell surface and peptide loading. In the ER, MHC I is formed with the help of CNX, CRT, and ERp57 while peptides are generated by proteolysis of cytoplasmic proteins by proteasome and subsequently translocated from the cytosol to ER via TAP heterodimers for incorporation into newly synthesized MHC I. Tapasin provides a bridge connecting the MHC I and the TAP heterodimer in order to bind these specific peptides with matching sequences to MHC I. Then, the complex is transported to cell surface to engage with TCR on $CD8^+$ T cell

through interaction between the carbohydrate moieties on FcγRIIIa and IgG1 Fc and increases antibody-dependent cellular cytotoxicity (ADCC) by NK cells [82, 86, 87, 88]. Terminal galactosylation increases C1q binding, enhancing the classical complement pathway [89, 90]. Hypo-galactosylation (G0 glycans) is associated with inflammatory conditions like rheumatoid arthritis [91, 92]. Fucosylation and sialylation are two major Fc modifications that affect the recruitment of inflammatory effector cell responses via FcγRIIb and DC-SIGN [82, 93]. Sialylation of IgG (α2,6-linked sialic acid) promotes binding to DC-SIGN on dendritic cells, leading

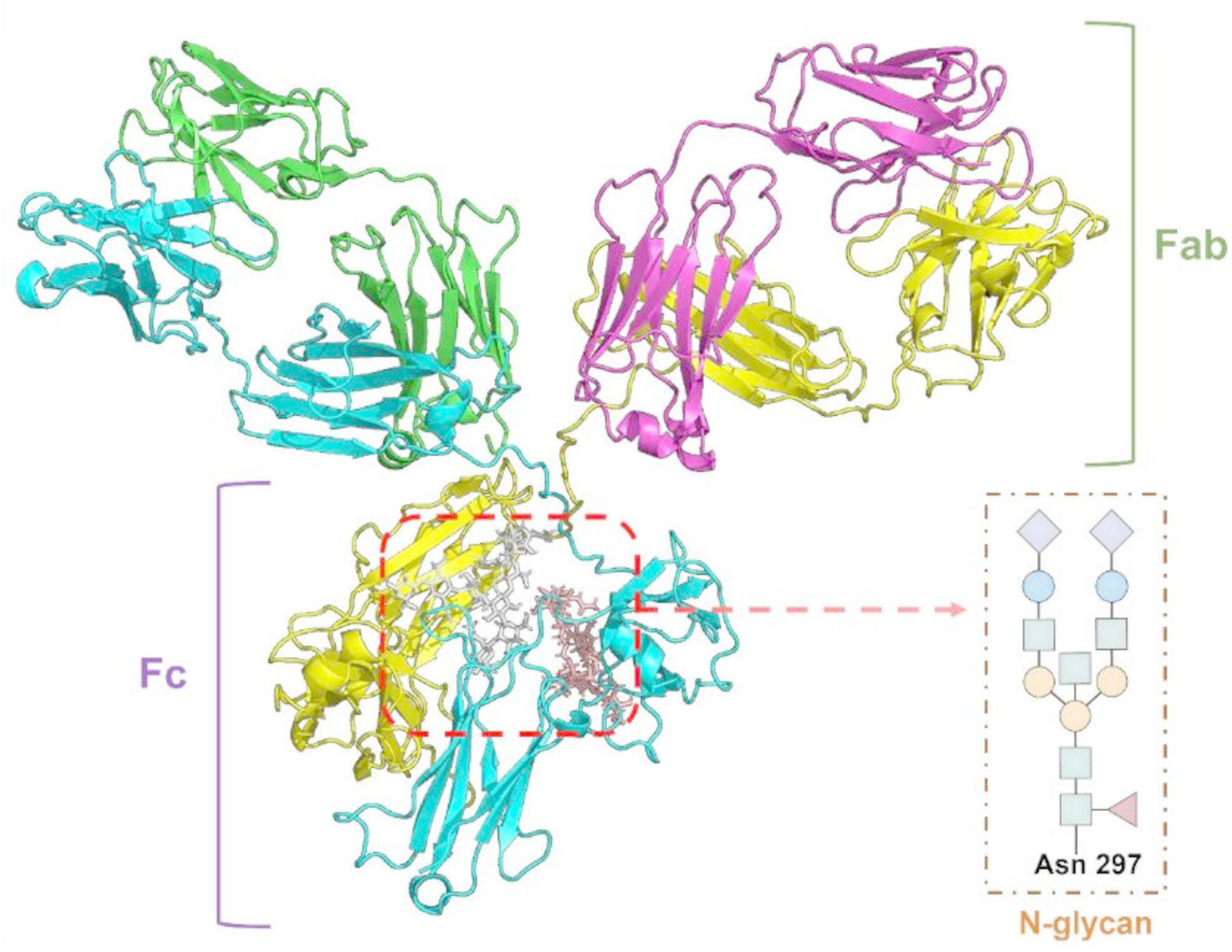

Fig. 4 Antibody and its glycan structure. IgG antibodies consist of two functional domains: the Fab and the Fc. There is a glycan attached to asparagine-297 within Fc domain, which can include up to 13 monomers of N-acetylglucosaminoglucose (GlcNAc, green squares), fucose (red triangle), mannose (yellow circles), galactose (blue circles), and sialic acid (purple diamods). PDB access code 1IGY

to immunosuppressive effects [94]. IVIG (intravenous immunoglobulin) relies on sialylated IgG for its anti-inflammatory function [95, 96]. Furthermore, altered IgG glycosylation patterns are linked to autoimmune diseases [97, 98, 99].

IgE glycans play critical roles in modulating immune responses, particularly in allergic reactions and parasite defensewith multiple N-glycosylation sites [100]. It binds to FcεRI on mast cells and basophils, triggering degranulation and histamine release. Glycosylation of IgE Fc enhances its affinity for FcεRI, prolonging mast cell sensitization [101]. Removing or altering glycans reduces FcεRI binding and weakens IgE-mediated allergic responses [102]. IgE also interacts with CD23 (FcεRII) on B cells and dendritic cells. Data show that non-N-glycosylated CD23 has higher affinity for IgE than glycosylated CD23 [103]. Glycans influence IgE homeostasis, antigen presentation, and B cell regulation. Certain glycan modifications affect FcεRI signaling and the extent of mast cell activation. Glycosylation may influence IgE's ability to recruit eosinophils and macrophages for parasite clearance [104, 105].

In addition, IgA glycans also play essential roles in shaping immune responses, like modulating FcαR affinity, thus affecting inflammation or immune suppression [106, 107]. IgM glycans induce internalisation of IgM by T cells, which in turn cause severe inhibition of T cell responses [108]. IgD glycans are related to the stage of immune response and cell maturity [109].

The glycoproteins of complement system may participate in pathogens phagocytosis

The complement system composed of a repertoire of glycoproteins acts major roles in innate immune system and serves as one of the initial defenses encountered by pathogens during infection [110]. The glycoproteins involved in this system can trigger immune responses that result in cell lysis and mark pathogens by forming the membrane

attack complex for phagocytosis. Almost all complement components are primarily produced in the liver with varying degrees of glycosylation [111]. C1q, which initiates the classical pathway, consists of six trimers each containing one N-glycan located within its globular head domain. These N-glycans are oriented to maximize binding between globular heads and targets while minimizing nonspecific interaction (Fig. 5) [9, 110]. C3, a complement component necessary to initiate the terminal pathway, contains two N-glycan sites on both its α/β-chain, and both chains are modified with high-mannose glycans [112]. CD59, a GPI-anchored glycoprotein found on cell surfaces that contributes to protecting host cells from complement-induced lysis by preventing membrane attack complex formation [111, 113]. Factor B, a component of the alternative pathway of complement, whose N-glycans and Asp254 are typically involved in shielding C3b binding sites, thereby regulating complement activation through alternative pathway [114]. Changes in the glycosylation of factor H, a serum glycoprotein, can improve the affinity for the factor H receptor, thereby increasing the efficacy of factor H in regulating pathogen-related complement activation [115,

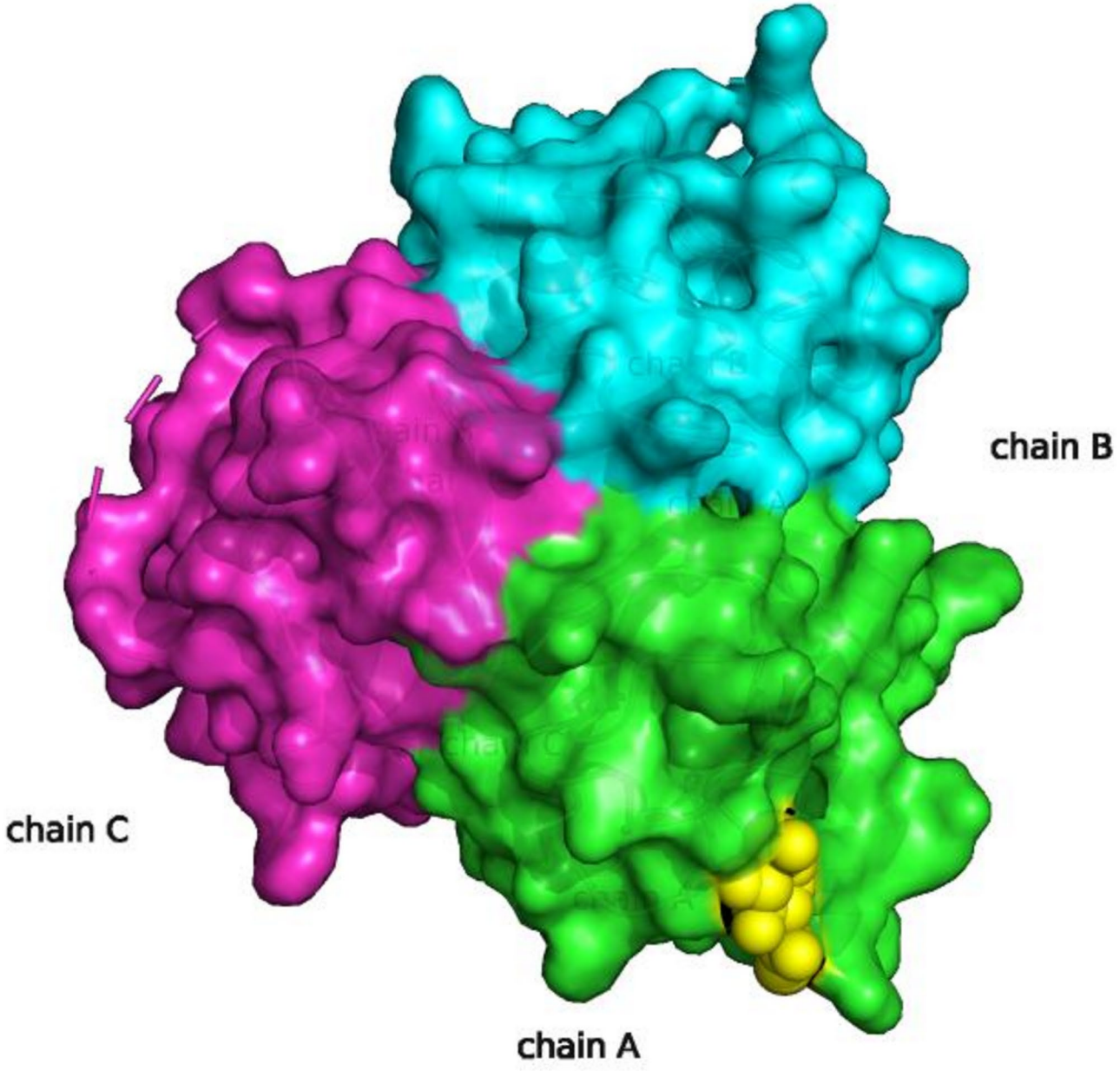

Fig. 5 The model structure of C1q. Complement Component 1q (C1q) is composed of six trimers and featured one N-glycan per trimer that situated within spherical head structural domain. The trimer is colored separately for clarity and the glycan modeled is N-acetylglucosamine (NAG), shown in yellow in the figure. PDB access code 5H49

116]. In addition, C6, C7, C8 and C9 have been reported to be characterized by C-mannosylation. It is hypothesized that these mannoses can bind mannose receptors, with the result that properdin and MAC proteins can recruit macrophages or locate mannose-binding pathogens [117, 118, 119]. Although almost all proteins in this system undergo glycosylation processes, only a limited number have been thoroughly characterized functionally [110].

Glycosylation regulates the process of immune cell receptors binding and activation

A wide range of membrane receptors derived from glycoproteins are involved in modulating immune responses. Numerous immune cell receptors are either positively or negatively regulated by N-glycosylation processes for their binding and activation. After translation, the antigen receptors on T/B cell undergo modifications involving N- and O-glycan chains, thus T cell receptor (TCR) and B cell receptor (BCR) are highly glycosylated multisubunit complex [35]. The selective deletion of conserved N-glycosylation sites in constant regions of both α and β-chains of TCR resulted in enhanced multimerization and reduced TCR-MHC dissociation, which ultimately improving recognition of tumour cell carrying target antigens (Fig. 6) [120, 121]. During the deficiency of Mgat5, which is responsible for the initiation of GlcNAc-β-(1,6)-branching on N-glycans, and therefore the reduction of N-acetyllactosamine, lowers the threshold of T cell activation in vitro by enhancing TCR clustering [122]. Alterations in the distribution of deglycosylated BCR in the plasma membrane may affect its binding to other membrane proteins, potentially hindering signalling and involvement in downstream oncogenic pathways [123]. For example, inhibition of BCR glycosylation reduces BCR clustering and internalization, while promoting its binding to CD22, thereby weakening the activation of PI3 kinase and NF-κB [124].

CD28, a glycoprotein located on T cell surface, functions as an immune receptor that modulates immune responses by interacting with CD80/CD86 (B7-1/B7-2) present on APCs to transmit secondary signals of T cell activation. Removing of N-glycosylation on CD28 significantly increases its binding affinity to CD80 and amplifies downstream signaling, suggesting that N-glycosylation negatively regulates the function of CD28 (Fig. 6) [125]. NKp30, a natural cytotoxicity receptor found on NK cell, is responsible for clearing cancerous cells is activated upon stimulation by tumour-expressed B7-H6. It has been shown that B7-H6 binds more effectively to glycosylated NKp30 compared to de-glycosylated mutants [126], moreover, N-glycosylation is required for the oligomerization of NKp30 which triggers receptor activation

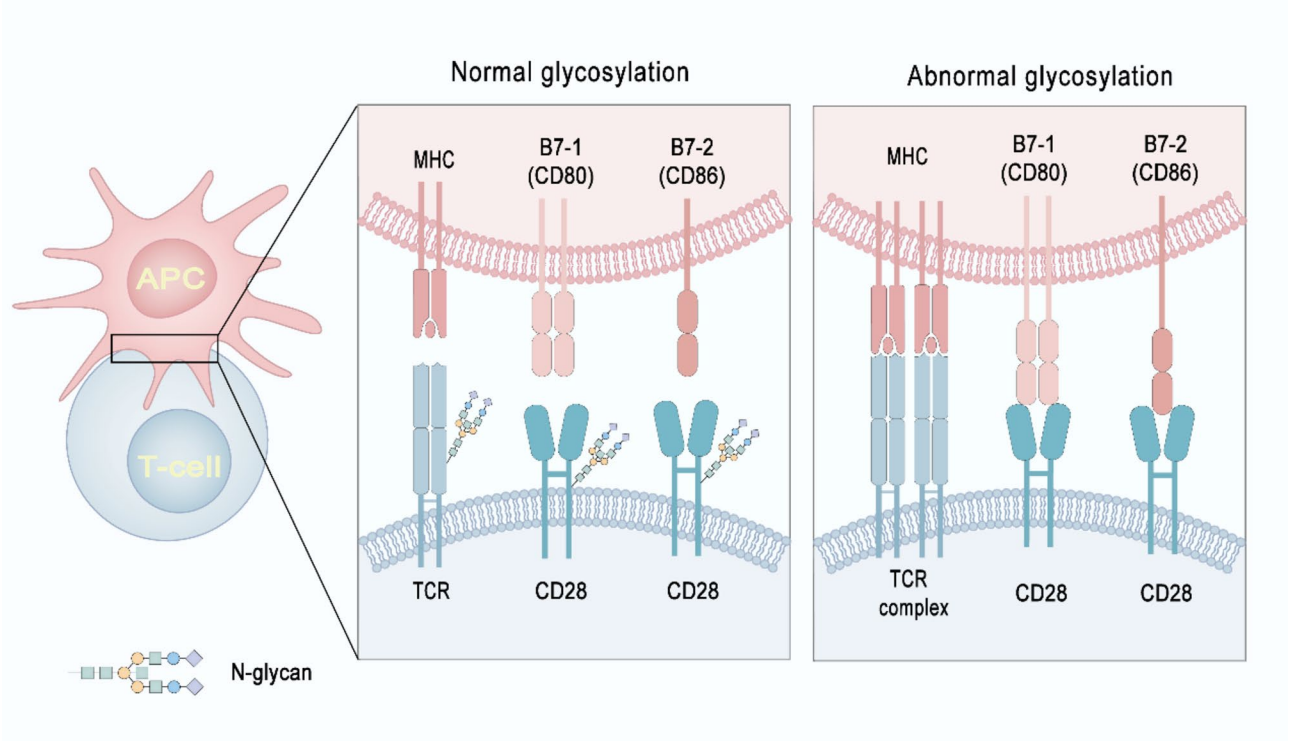

Fig. 6 Immune receptors on T cell surface are regulated by N-glycosylation. Depicted are common ligand-receptor interactions on T cell surfaces that are regulated by glycosylation. Selective removal of N-glycosylation from TCR enhances TCR multimerization, reduces TCR-MHC dissociation, and improves recognition of tumour cell that expresses target antigen. Removal of N-glycosylation on CD28 significantly increases its binding affinity for CD80 and CD86

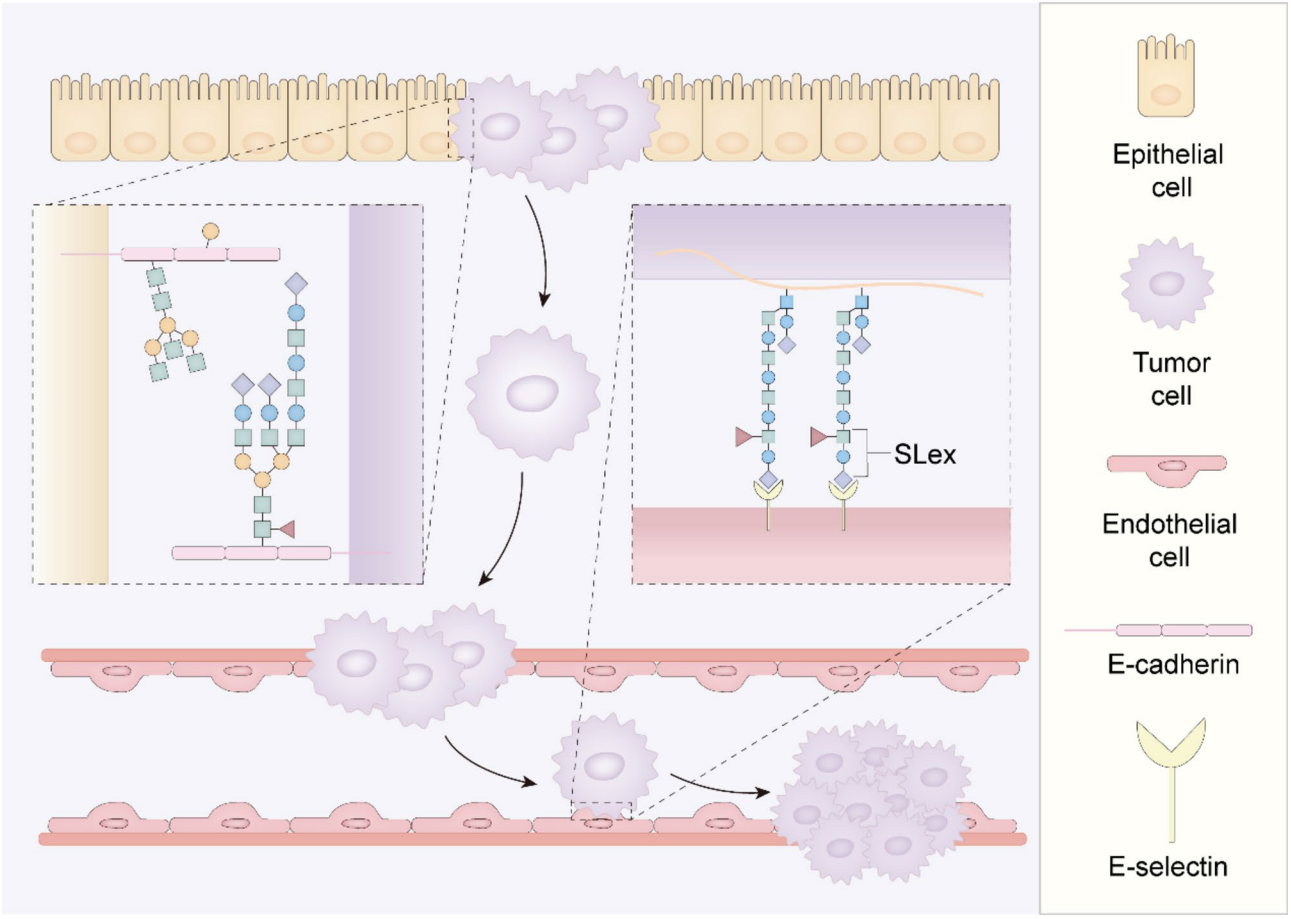

Fig. 7 The role of glycosylation acts on E-cadherin and E-selectin for tumour cell adhesion and invasion. Glycans interfere with intercellular adhesion during the dissociation and invasion of tumour cell. Increased N-glycan branching along with α2,6-sialylated terminal structure on epithelial calreticulin (E-cadherin) weakens cell adhesion and facilitates tumour cells invasion. The adhesion receptors like E-selectin found on endothelial cell can interact with their ligands sialyl Lewis x (SLex), a tumour-associated carbohydrate determinant, thereby enhancing tumour cell adhesion and metastasis

[127]. In addition, mammals have evolved phyloglycomic recognition system to identify glycans from lower organisms as part of non-self recognition mechanisms leading to immune activation [45].

Cell adhesion molecules are involved in immune cells adhesion and migration

The glycosylation modification governed protein folding processes make glycoproteins with delicate spatial structures, which enlarge the chances of protein-glycan interactions, and furtherly conduct the immune response of cells to communicate with each other [85]. Most cell adhesion molecules (CAMs) are glycoproteins, including families such as selectins, integrins, cadherins and immunoglobulin superfamily, which can mediate binds to other cells and extracellular matrix within microenvironment, contributing for the migration and adhesion of immune cells [128]. E-cadherin, a key transmembrane glycoprotein involved in epithelial cells adhesion, is influenced by branched N-glycans, which can disrupt cell-cell adhesion and downstream signaling pathways, thereby promoting invasion and metastasis (Fig. 7) [129]. The terminal sialylation of integrins on tumor cell regulates intracellular signalling and cell adhesion, whilst, core fucosylation is crucial in integrin-mediated cell proliferation and migration [130, 131, 132]. The combination of selectins with their glycan ligands creates a system for cell-cell adhesion primarily between leukocyte and endothelial cell, which can mediate the rolling and migration of leukocyte at the inflammatory site [45]. Research has indicated that E-selectin within bone marrow vascular niche encourages breast cancer metastasis by triggering mesenchymal to epithelial transition through signaling activation (Fig. 7) [133]. ICAM-1, a member of the immunoglobulin superfamily, has typical chain of polysialic acid glycan that plays a role in leukocyte adhesion. Understanding that different N-glycoforms of ICAM-1 can mediate recruitment of different monocyte subsets is also of therapeutic interest [134].

Glycoproteins serve a variety of functions, including roles as enzymes, hormones, antibodies and lectins. The diversity

in their functions arises from their structural features, especially the diversified glycogen pool [8]. The intricate glycosylation processes indispensably participate in immune responses, pathogen antigen recognition and ligand-receptor interactions resulting in cellular activities [45, 85]. The microbial molecule is usually identified in glycoconjugate patterns at the beginning of innate immune response. In adaptive immunity, glycans play a role in organizing immunological synapses, and are involved in producing and loading of MHC I antigenic peptides and processing of MHC II antigens [69, 70]. On cell surface, protein glycosylation is believed to function as molecular spacer that positions signaling and adhesion molecules for effective intercellular communication, meanwhile, the extended glycan chains as spaced apart of glycosylated immune molecules to restrict lateral association of glycoproteins [68]. Glycoproteins on immune cell surfaces can detect pathogens and function either as receptors or transporters to facilitate communication between cells while recruiting various immune cells to infection sites [67, 135].

Therapeutic strategies targeting glycosylation

Protein glycosylation has become a promising focus for immune-related diseases therapy as cancer. In the field of therapeutics and biomarkers, glycosylation has proven to be an crucial element that enhances the available tools and strategies for precision medicine [129]. Most best-selling biotherapeutics are glycoproteins and numerous clinically and therapeutically important proteins are glycosylated, including monoclonal antibodies (mAbs), hormones, growth factors and vaccines [5, 136]. Consequently, approaches that utilize abnormal glycosylation patterns in cancer cells may offer new therapeutic avenues and synergize with existing targeted therapies to improve their specificity and effectiveness [137].

Immunotherapy for intervention in protein glycosylation process of tumour and immune cell

Glycosylation is significantly related to tumour development and abnormal glycosylation of proteins usually signals tumorigenesis [129]. For one thing, the glycosylation of tumour cells contributes to evade host immune detection, a hallmark feature of cancer [35]. Enveloped viruses like HIV may exploit host glycosylation processes to shield potential protein antigenic epitopes from immune recognition, thereby employing glycosylation inhibitors could serve as a viable antiviral strategy by disrupting proper folding of viral envelope proteins such as those found in hepatitis B virus and HIV [6, 75]. Additional, one significant alteration that increased expression of sialylated glycans linked to cancer progression has been observed in tumour glycosylation. Abnormal sialylation contributes to tumour growth, metastasis and evasion from immune responses. Thereby, blocking sialic acid biosynthesis can enhance interactions between tumour cells and T cells while improving cytotoxic T cell-mediated destruction of these tumour cells, which is of high therapeutic value in cancer [138, 139].

For another thing, abnormal glycosylation on cancer cell can be detected by immune cell, leading to immunosuppressive outcomes [35]. For example, in T cell, tumour cells may downregulate surface MHCI levels to alter TCR-mediated activation signals [140]; simultaneously, they can also have the capacity to upregulate PD-L1 levels that modulate PD-1 inhibitory signaling pathways [141]. CTLA-4 serves as immune checkpoint receptor on T cell that competes against CD28, a glycoprotein located on T lymphocytes, for binding sites on CD80/CD86 on APCs, resulting in diminished immune responses. The quantity and branching structure of N-glycans associated with CTLA-4 affect its expression at cell surface and TCR signaling can be mediated through the hexosamine and N-glycan branching pathways, which upregulate the level of CTLA-4 on cell surface impacting overall T-cell functionality [29]. Thus, enhancing the stimulatory immune receptors or blocking the activation of inhibitory immune receptors by altering glycosylation could revive the antitumour function of immune cells.

Immunotherapy targeting glycosylation modification of immune checkpoint molecules

Given that the majority of immune checkpoints are glycoproteins located in membrane, their glycosylation is necessary for proper ligand-receptor interactions and antitumour immune function across various cancers [35]. PD-1 acts inhibitory receptor located on activated T cell, which suppresses TCR signaling through interacting with the ligand PD-L1 present on tumour cells [142]. N-glycans is essential for maintaining the levels and localization of PD-1 at cell surface. When PD-1 lacks glycosylation, it becomes more susceptible to ubiquitination leading to rapid degradation within the cytoplasm before reaching cell surface. Studies have shown that genetic deletion or pharmacologic inhibitioncan reduce PD-1 levels by disrupting its glycosylation, which subsequently impedes T-cell-mediated immunity [143]. Furthermore, the glycosylation status of PD-1 influences its binds to PD-L1, a highly glycosylated member of the B7 family found on malignant and nucleated cells within tumour microenvironment [144]. Most of the PD-L1 present in human tumour tissue and cancer cell line undergoes glycosylation modifications, which stabilize this protein and enhances its ability to suppress immune responses [145, 146]. Cancer cells exploit immune checkpoints to evade and inhibit antitumour immune response, thus immunotherapies that target these checkpoints, especially PD-1 and PD-L1, have marked a significant advancement in cancer treatment [142, 146]. Glycans can indirectly promote immune evasion by enhancing immune checkpoints,

thereby therapeutic interventions using mAbs to block PD-1/PD-L1 interaction can rejuvenate T cell functionality and have shown effectiveness in fostering long-lasting anti-tumour immune responses [147].

Intervention of glycosylation in therapeutic monoclonal antibodies

Therapeutic monoclonal antibodies (mAbs) are a type of glycoproteins generated by living cell systems [148]. Recombinant monoclonal antibodies based therapeutics, which can capable of recognizing and binding to specific epitopes on identical or different antigenic surfaces, have been developed for treating tumour, infections and inflammation [149]. Optimisation and management of N-glycan profiles is a crucial aspect of bioprocess development for these antibodies [150]. Detailed glycan structure and function analysis help to confirm the presence of particular glycans within antibody and their influence on drug safety, effectiveness, and clearance, thereby understanding their role as critical quality attributes. For the past few years, impressive advancements have been achieved in therapeutic monoclonal antibodies whose therapeutic effects are largely mediated by interactions between Fc domain of these antibodies and their receptors on immune cells, and which can initiate various immunomodulatory responses. The nature of these effector functions is heavily influenced by the glycosylation patterns present in the Fc fragments which affect both antibody binding affinity and complement system activation. For example, afucosylated or asialylated of Fc region has a high binding affinity with Fc receptors to promote ADCC [151], terminal galactosylated IgG1 has a high binding affinity with C1q and promotes CDC [152], and sialylated antibodies are strongly associated with enhanced ADCP activity by increasing the binding affinity with Fc receptors [153]. Consequently, research into Fc glycosylation profiles alongside associated effector functions has sparked interest in engineering therapeutic antibodies. With advancements in glycosylation engineering targeting specific proteins or glycans themselves becoming increasingly popular strategies within therapeutic antibody development [41, 154].

Conclusions and perspectives

Protein glycosylation that is mainly occurred in ER and Golgi apparatus is an intricate PPTM that involves dynamic and non-templating processes. Proteins serve as fundamental components of life, and diversified forms of glycosylation grossly expand the spatial structure and diverse function of newly produced glycoproteins [32]. Intriguingly, a diverse repertoire of glycogen will be modified in protein, which may direct the glycoprotein folding to maintain specific exposure epitopes for recognition by the immune system. Meanwhile, these diverse and abundant glycoproteins precisely manipulate the processes of including antigen presentation, immune effector functions, immune recognition, receptor binding and activation, as well as cell adhesion and migration. Therefore, protein glycosylation it has become a promising target for immunological therapy of cancers.

In fact, glycosylation on proteins, lipids and carbohydrates are as integral to the immune pathway and function. Research that connects immunology with glycobiology will persist in yielding fresh insights into immunity and uncover novel therapeutic strategies for various disease. Based on the diversity of glycan, their regulation of glycoprotein interactions may be involved in mechanisms that control multiple immune responses to a variety of extracellular stimuli in ways that are currently unknown [155]. Moreover, due to the complex and diverse structure of glycans, it is difficult to achieve accurate analysis and functional study through conventional techniques, resulting in the field of glycoimmunology still faces many challenges, but also brings exciting opportunities. With the increasing availability of new technologies, applying glycobiology to explore fundamental aspects of immune function offers significant potential for acknowledging novel etiologies and providing precise therapeutic strategies on immune-related diseases.

Abbreviation

PPTM	Protein post-translational modification
ER	Endoplasmic reticulum
MHC	Major histocompatibility complex
Ig	Immunoglobulin
GlcNAc	N-acetylglucosamine
GalNAc	N-acetylgalactosamine
gal	galactose
glc	glucose
xyl	xylose
man	mannose
fuc	fucose
COP I	Coat protein I
COP II	Coat protein II
CNX	Calnexin
CRT	Calreticulin
ERAD	ER-associated degradation
UPR	Unfolded protein responses
TCR	T cell receptor
BCR	B cell receptor
mAbs	monoclonal antibodies

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Author contributions

MT and YYL wrote and conceived the manuscript. LCYY, JXQ, XYB and JY collected literature. RJD and XYL designed the figures. MT, YYL, HYZ and CL supervised and revised the manuscript. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Clinical trial number
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