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Review

Impact of autoantibody glycosylation in autoimmune diseases

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ABSTRACT

Recent outcomes enhanced the critical role of glycosylation pattern of autoantibodies (AAbs), especially *N*-glycans branched on immunoglobulin (Ig) asparagine-297, in the pathophysiology of Ab-mediated autoimmune diseases. In this review, we describe the critical role of Ig glycosylation on skewing immune response towards a pro- or anti-inflammatory pathway. Indeed, we first described the impact of glycosylation on Ig immune effector functions: antibody-dependent cell-mediated cytotoxicity (ADCC), complement activation, dendritic cell, macrophage or B-cell activation and maturation, neoantigens formation, or Ig-receptor binding. We then reviewed autoimmune diseases with abnormal Ig glycosylation trying to understand its role in the pathogenic process and discuss the usefulness of monitoring Ig glycosylation as a biomarker of disease activity as demonstrated in proteinase-3 anti-neutrophil cytoplasmic AAbs associated vasculitis.
After reporting environmental and immune factors known to affect Ig glycosylation process, we finally evoked therapeutic strategies currently being developed in order to modulate Ig glycosylation pattern and autoimmune disease evolution. This overview on Ig glycosylation mechanisms and impact on immune system modulation is necessary to face these new therapeutic approaches.

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1. Introduction

Protein synthesis is a well-known process whose last steps include post-translational modifications such as glycosylation, acetylation, phosphorylation, carboxylation, lipidation, creation of disulfide bonds, or amino-acid removal leading to changes in the protein behavior and affecting its biological functions. Protein glycosylation plays important roles in major biological events such as cell–cell and cell–matrix interactions, protein folding, and receptor binding or protein clearance.

Some glycomic analyses have already noticed altered protein glycosylation during HIV infection [1], allergy [2], or cancer [3–5], especially concerning metastatic and tumoral tolerance phenomenons [6].

Abnormal glycosylation of the target antigen has also been involved in the pathophysiology of autoimmune diseases. Hence, high levels of AAbs directed to glycated antigen (anti-*N*-acetylgalactosamine-β AAbs) were found in antiphospholipid syndrome (APLS) patients' sera and were associated with recurrent pregnancy loss [7]. In systemic sclerosis patients' sera, AAbs directed to 4-sulfated *N*-acetyl-lactosamine with specific sulfation at position C4 of galactose were associated with a higher prevalence of pulmonary hypertension [8]. In MRL-lpr mice, mutation of the gene encoding alpha-mannosidase II, which regulates the branching of asparagine (N)-linked oligosaccharide chains, results in a systemic autoimmune disease similar to human systemic lupus erythematosus with AAbs toward histone, Sm antigen, and DNA, circulating immune complexes and glomerulonephritis [9,10]. Altered glycosylation of antigenic targets was also suggested in several immune-mediated neurologic diseases. In multiple sclerosis, polymorphisms in the gene coding for the glycosylation enzyme MGAT5 have been found and were correlated to disease severity [11]. New strategies using glucopeptides mimetics such as the *N*-glycosylated peptide CSF114(Glc) are currently developed in order to identify novel autoantigens in multiple sclerosis and neuromyelitis optica [12,13]. In Sydenham chorea, the major neurological manifestation of acute rheumatic fever, a post-streptococcus infection neurological disorder, Abs targeting streptococcal A surface carbohydrates crosslink with glycosylated epitopes expressed at the surface of human neuronal cells, and lead to disease clinical manifestations through specific kinase activation [14].

Apart from antigen glycosylation status, many evidences have been obtained in the last years demonstrating that the modulation of AAb glycosylation could also modulate their effects. After describing the main features of protein glycosylation, we will focus on Ig glycosylation process and its impact on Ig effector functions and immune system modulation effects in the first part. Interestingly, insights on intravenous immunoglobulin therapeutic strategies are a good model to explore this modulation. In the second part, we will focus on the abnormalities of AAb glycosylation patterns observed in autoimmune diseases. The important outcomes on pathophysiological and critical role of glycans lead to new monitoring strategies of autoimmune diseases, such as granulomatosis with polyangiitis, evoked in the third part. Finally, after discussing the potential environmental and immune factors known actually to interfere with Ig glycosylation, we will describe in the fourth part the innovative therapeutic approaches currently developed in autoimmune disease field which concern Ig glycosylation modulation.

2. Protein and immunoglobulin glycosylation: impact on immunomodulation

2.1. Protein glycosylation: a fundamental biochemical reaction

Protein glycosylation is a common process in eukaryotic and prokaryotic cells. Cell membranes and secreted proteins are highly glycosylated, and nearly 50% of the plasma proteins are glycosylated. Glycoproteins have inherent structural complexity: monosaccharides can be branched one to each other, in a linear way or in ring forms, and all these moieties can be branched directly to the protein or on another glycans. Unlike transcription or translation, glycosylation process relies on several enzymes adding or removing sugars. A glycoprotein (also called "proteoglycan") is made from saccharides covalently attached to a peptide via the two main kind of linkage: *N*-glycosylation (*N*-glycans) and *O*-glycosylation (*O*-glycans).

Biosynthesis of *N*-glycans is a two-stage procedure. First, saccharide synthesis begins on the cytosolic face of the endoplasmic reticulum (ER) and is completed once the structure is flipped into the ER lumen. The polypeptide chain is synthetized in the ER in parallel. The 14-sugar precursor glycan, commonly ended by a *N*-acetylglucosamine (GlcNAc) residue, is then transferred to the asparagine (Asn) residue of the polypeptide chain in receptive Asn-X-Ser/Thr consensus sequence. In the second stage, the glycan maturation occurs in the Golgi apparatus, where complex branches of GlcNAc, galactose, fucose, or sialic acid are added. Conversely, *O*-glycosylation entirely occurs in the Golgi apparatus and results in the addition of sugars ended by *N*-acetylgalactosamine (GalNAc) to polypeptide chain through hydroxyl (β-OH) groups located on serine or threonine.

Protein glycosylation appears to play a critical role in biochemical phenomenons such as stabilization of the three-dimensional structure of proteins, thermal and physico-chemical stability of the protein (protecting them from acidic, alkaline, or osmotic aggressions), protein folding, protein trafficking upon the cellular membrane (contributing in membrane electric charge) and antigen recognition.

2.2. Immunoglobulin glycosylation patterns impact their effector functions

Interestingly, immunoglobulins (Igs) are glycoproteins, whose biological functions are modulated by their glycosylation patterns. For immunoglobulin G (IgG), effector functions are mostly modulated by two *N*-glycans linked to Asn 297 on each Fc constant fragment (Fc) (Fig. 1A). These *N*-glycans comprise sialic acid, galactose, fucose or GlcNAc branched on a core structure of four GlcNAc and three mannose residues. They are highly heterogeneous, containing up to thirty different glycans branched in complex patterns.

Heyman et al. proposed three different pathways of IgG-related immunoregulation: one remaining effective whatever the presence or absence of IgG constant domain receptor (FcγR), likely via epitope masking or cytokine neutralization; one depending on binding to activating or inhibitory FcγR, modulating FcγR expression and increasing antigen presentation by dendritic cells; and one depending on their ability to activate complement and to increase B-cell activation through immune complex co-crosslinking of the B-cell receptor with the complement-receptor 2/CD19 receptor complex [15,16]. All these steps could be partially mediated or modulated by Ig glycosylation pattern. Indeed, crystallographic analysis of IgG [17–20] revealed that minor changes in glycans could lead to important

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