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# Fc Glycan-Modulated Immunoglobulin G Effector Functions

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**Abstract** Immunoglobulin G (IgG) molecules are glycoproteins and residues in the sugar moiety attached to the IgG constant fragment (Fc) are essential for IgG functionality such as binding to cellular Fc receptors and complement activation. The core of this sugar moiety consists of a bi-antennary heptameric structure of mannose and N-acetylglucosamine (GlcNAc), further decorated with terminal and branching residues including galactose, sialic acid, fucose, and GlcNAc. Presence or absence of distinct residues such as fucose and sialic acid can dramatically alter pro- and anti-inflammatory IgG activities which could be harnessed for immunotherapeutic purposes. Here we review recent advances in understanding the role of the IgG-Fc glycan during immune responses and for immunotherapy with a focus on sialic acid and intravenous immunoglobulin (IVIG) treatment.

**Keywords** IgG · Fc · sialic acid · IVIG · CIDP

## Immunoglobulin G Effector Functions

Immunoglobulins belong to the most abundant proteins found in serum [3]. Producing these vast amounts of proteins is a huge investment of the body with good cause: Antibodies are an essential component of the immune system bridging humoral and cellular immunity to fulfill inflammatory (assisting the killing of infected cells or tumor cells), non-inflammatory (obsonization, neutralization) and, as most recently recognized, also anti-inflammatory functions. Immunoglobulin G (IgG) represents 75 % of the immunoglobulins in serum reflecting its role in defending us against bacteria and viruses which have penetrated epithelial and mucosal barriers [1]. During a primary infection and if innate immunity and pre-existing low-affinity antibodies (natural antibodies) fail to neutralize the pathogen, immunoglobulins increase the visibility of the pathogen or the infected cell through opsonization and initiate immune responses through binding to cellular receptors specific for the antibodies' Fc region (Fcγ receptors; FcγRs) and the activation of the complement system. This activates phagocytes such as macrophages and dendritic cells which engulf, destroy, process and transport the pathogen to secondary lymphoid organs for the initiation of a protective adaptive immune response. Furthermore, infected cells can be lysed by a mechanism called "antibody-dependent cell mediated cytotoxicity" (ADCC) by which FcγR-receptor bearing innate immune cells such as natural killer cells lyse antibody-opsonized cells [53]. Similar to Fc-receptor expressing cells, the complement system uses antibodies as specific detectors to fulfill its dual role in both eradicating pathogens and infected cells by complement-dependent cytotoxicity (CDC) and simultaneously assisting their uptake by phagocytes for antigen presentation [1]. The four different subclasses of IgG molecules differ in their efficacy to initiate immune cell activation through FcγR binding and complement activation.

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## The IgG-Fc N-Glycan

Immunoglobulin G (IgG) molecules are glycoproteins with a sugar moiety attached to each of the asparagin 297 (N297) residues in the CH2-domains of the two Fc-fragments (Fig. 1). Removal of this sugar moiety impairs Fc-dependent effector functions [14, 38]. All human immunoglobulins are Fc-glycosylated and can, depending on the isotype and the sequence of the antigen-binding regions (complementary determining regions, CDR), carry additional glycans in the Fab

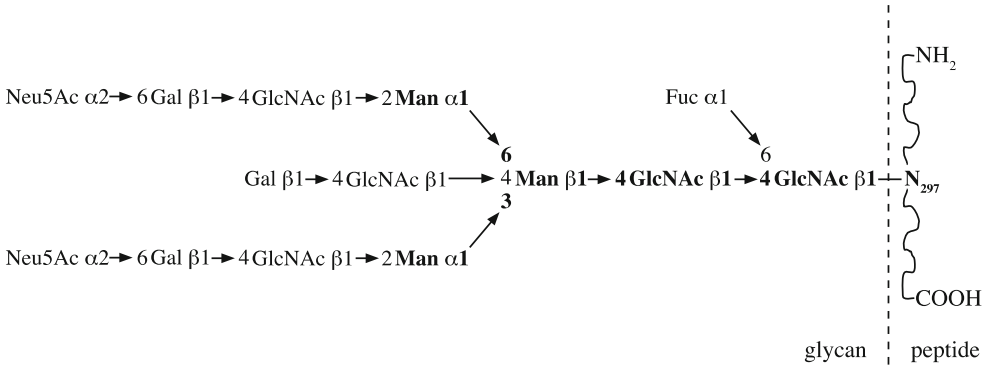


**Fig. 1** IgG-Fc glycan structure. The Asparagine 297 linked complex-type glycan found on the Fc domain of immunoglobulin G antibodies consists of a set of constant (depicted bold) and variable (depicted regular) sugars. Although theoretically possible, this fully processed glycan will be found only in trace amounts as the majority of antibodies will carry either no, one or two galactose residues and a fraction of those carrying galactose will additionally possess sialic acid. Further complexity is added by the addition of the bisecting N-acetylglucosamine. *Man* Mannose, *Neu5Ac* Neuraminic acid (Sialic acid), *Gal* Galactose, *GlcNAc* N-acetylglucosamine, *Fuc* Fucose, *N* Asparagine

domains. IgG is unique with respect to a single, highly conserved Asparagine(N)-Glycosylation site (N-X-S/T) in the CH2 domains while the isotypes carry multiple glycosylation sites [7]. Moreover, in contrast to other Ig isotypes, the IgG-associated sugar domain is not exposed on the IgG surface but rather buried within the hydrophobic core between the two Fc-fragments and, therefore, impacts Fc-structure [30, 36]. During protein translation a pre-formed lipid-linked glycan is transfered and covalently attached to asparagine at position 297 in the lumen of the endoplasmatic reticulum (ER). This initial glycan is composed of two N-acetylglucosamines (GlcNAc) followed by branched mannose (Man) residues. Its structure is highly conserved in eukaryotes and serves as an important mechanism for protein folding and quality control of proteins carrying N-glycans [48]. If successfully produced and folded, the IgG polypeptide is transfered from the ER to the Golgi where glycosyl-hydrolases and -transferases can modify the core glycan leading to such diverse and highly complex glycans as seen in the IgG-Fc. The monosaccharide composition of the glycan is impacted by the amino-acid sequence [29] as well as glycan modifying enzyme- and substrate availability. The presence of glycosylhydrolases and glycosyltransferases in the golgi can be regulated at the level of transcription and location within the secretory pathway [43]. Peptide-glycan interactions and the three-dimensional structure of the Fc are thought to limit the glycan variability and the extent of galactosylation and sialylation by limiting the accessability of the glycan to glycosyltransferases [29, 57]. A total of around 30 different glycan structures is found in the IgG-Fc pool [41]. Compared to the Fab glycans, reduced bisecting GlcNAc, less galactose and less sialylation is found on the Fc glycans [57]. The restricted diversity may be essential for the use of specific IgG-Fc glycan modification for the regulation of antibody effector functions. How and which immunological factors such as cytokines influence antibody glycosylation is yet to be defined but much progress has been made in understanding the structural and functional consequences of the presence or absence of different sugar moieties on the IgG-Fc carbohydrate. In addition to the oligosaccharide core, more than 95 % of the biantennary complex type structure of the final IgG glycan carries a N-acetylglucosamine on both arms [40, 41] and 85 % are fucosylated [34] (Fig. 1). In contrast, the presence of galactose is less homogenous with 40 % of glycans carrying one galactose (G1 glycan) and the frequency of non-galactosylated (G0) or bi-galactosylated glycans (G2) ranging between 20 and 40 % depending on age and gender [40, 51]. Additional heterogeneity is conferred by the addition of a bisecting N-acetylglucosamine present on approximately 10 to 15 % of total IgG-Fc glycans [58].

Based on the structure of the glycan, the conformation of the IgG-Fc homodimer in the binding interface to Fc-receptors and the complement protein C1q (CH2 domain) changes from an open (maximal C2-C2 domain distance) to a closed conformation (minimal C2-C2 domain distance) [16, 33]. Analysis of crystal structures revealed that removal of terminal galactose and N-acetylglucosamine residues favours a closed conformation which in turn disfavours Fc-receptor and C1q binding and impacts on the thermal stability [28, 32, 33]. The most distal sugar on the glycan is sialic acid (neuraminic acid, Neu5Ac). Around 10 % of glycans carry sialic acid on one arm and bi-sialylated glycans are found only in trace amounts. The linkage of sialic acid to the penultimate galactose is found in either α2-3 or α2-6 confirmation with a strong preference for the latter [7]. Addition of galactose has a strong preference for the 1–6 arm, whereas sialic acid is almost exclusively found on the 1–3 arm [57]. While the 1–6 arm bias of galactose may be largely explained by accessability [57] the 1–3 arm specific addition of sialic acid by human sialyltransferase is retained even in vitro using the released Fc glycan, substrate and recombinant human sialyltransferase arguing for an enzyme-intrinsic bias [8]. The opposing glycan arm-bias of galactose and sialic acid provides

a rationale for the inefficient addition of sialic acid. The functional consequence of sialylation may be reduced FcγR binding [45] and enhancing the anti-inflammatory properties of IgG molecules [6] as discussed below.

### Function of Fc N-glycan Fucose-Residues

The majority of circulating IgG is fucosylated [34], which has been shown to reduce the binding to the activating FcγRIII (CD16) and consequently antibody-dependent cell mediated cytotoxicity [50]. Direct carbohydrate-carbohydrate interactions between the FcγRIII Asn162 linked glycan and the Fc glycan are responsible for this effect [15]. The in vivo relevance of increased antibody binding to CD16 was first indicated in patients carrying a high affinity receptor polymorphism which increased the efficacy of the B cell depleting antibody Rituximab [10]. Similarly, clinical trials using non-fucosylated antibodies for cell depletion therapy in cancer have shown promising results [24, 37]. Largely reduced levels of fucosylated IgG have been reported on alloantigen-specific (anti-HPA1a) antibodies in neonatal alloimmune thrombocytopenia (FNAIT) in contrast to normal levels in the total antibody pool suggesting specific regulation of fucosylation and a potential role in autoimmunity [26].

### Function of Fc N-glycan Galactose-Residues

The absence of galactose in the core glycan (IgG-G0) has long been known to be associated with rheumatoid arthritis (RA) and primary osteoarthritis [41]. Similar observations were made in other autoimmune diseases, infectious diseases and cancer [20, 49]. The first suggested mechanism for a functional consequence of galactosylation was based on the in vitro finding that galactosylation prevents binding of the initiator of the lectin pathway of the complement system, mannose binding lectin (MBL) [31]. However, in vivo studies in mouse models could not confirm a role of MBL for the function of agalactosylated antibodies [35] and analysis of patients carrying MBL promotor polymorphisms leading to differential MBL expression level could not find a role for MBL in RA [55, 56]. A dual role for MBL was found in juvenile RA where MBL deficiency led to younger age of juvenile polyarthritis onset but more frequent remission of juvenile oligoarthritis [13]. A recent study in mice shows that antibody galactosylation can contribute to limiting anaphylatoxin C5a mediated complement-activation by a mechanism involving Dectin-1 and FcγRIIb dependent inhibition of C5a receptor signaling [27]. The observation that antiviral activity and spontaneous control of HIV infection is associated with increased prevalence of total and in particular antigen-specific IgG-G0 antibodies additionally argues for a functional significance of antibody galactosylation in humans [2]. An important aspect to consider when looking at the functional impact of galactose is that it provides the basis for the addition of sialic acid, the most distal sugar moiety on the IgG-Fc glycan.

### Function of Fc N-glycan Sialic Acid-Residues

In mice, T cell independent B cell activation or tolerogenic immunization (in the absence of pro-inflammatory stimuli) with protein antigens induces antigen-specific IgG with high levels of terminal galactose and sialic acid capable of blocking antigen-specific B and T cell responses [19, 39]. Similarly, successful treatment of birch pollen allergy was found to induce antigen-specific IgG partially carrying sialic acid [39]. The mechanisms that mediate such anti-inflammatory properties are not yet clear but may involve reduced binding to Fc receptors [25] or sialic acid binding lectins such as DC-SIGN [4].

### The Role of IgG Fc-glycosylation for IVIG Treatment of Autoimmunity

The anti-inflammatory effect of pooled high-dose gammaglobulins from healthy donors infused in patients (so-called intravenous immunoglobulin, IVIG) suffering from autoimmune diseases was first recognized during immunoglobulin replacement therapy of a patient suffering hypogammaglobulinemia and immune thrombocytopenia (ITP) [21–23]. Subsequently, IVIG has been approved for the treatment of the autoimmune diseases ITP, Kawasaki's disease, chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy but is used for many other neuromuscular, hematologic or dermatologic disorders [17]. Numerous mechanisms for the anti-inflammatory action of IVIG have been suggested. Examples therefore are ranging from increased clearance of pathologic antibodies due to the saturation of the neonatal Fc-receptor [18], anti-idiotypic antibodies [52] and suppression of dendritic cell maturation [9] to the activation of regulatory T cells via Fc-derived peptides [11]. Studies in mouse models [5, 44] and humans [12] clearly point towards a major role for the IgG-Fc for the anti-inflammatory properties of IVIG. Because an extremely high dose of IVIG is required for its efficacy (1–2 g per kg), it was speculated that the beneficial effect may be mediated by a small sub-fraction of IVIG. Ravetch and colleagues identified sialylated Fc fragments as the anti-inflammatory mediator of IVIG in the K/N experimental arthritis mouse model [5, 25]. Subsequent studies implicated a protective mechanism involving the inhibitory Fc receptor (FcγRIIb) and the C-type lectin SIGNR1 or its human ortholog DC-SIGN [4, 46].

Signaling downstream of DC-SIGN was found to induce IL-33 which in turn induces IL-4 in basophils leading to the upregulation of FcγRIIb on macrophages [4]. The requirement of sialic acid and FcγRIIb has been recently confirmed in four mouse models of antibody-mediated autoimmune diseases whereas SIGNR1 was not always required [47]. Although the relevance of DC-SIGN (or SIGNR1) for the initiation of a sialic-acid specific response is supported by several studies [4, 5, 46], it remains unclear whether direct binding of Fc-linked sialic acid to these receptors [6] is mandatory as no binding of IgG-Fc (independent of its glycosylation) to DC-SIGN was detected by others [59].

Studies in humans support a role for FcγRIIb expression as being associated with the clinical efficacy of IVIG therapy. Chronic inflammatory demyelinating polyneuropathy (CIDP) is the most common treatable acquired chronic polyneuropathy, and IVIG is widely used as a first-line initial and maintenance treatment. Untreated patients with CIDP, compared with demographically matched healthy controls, showed consistently lower FcγRIIb expression levels. FcγRIIb expression was, however, up-regulated on circulating monocytes and B cells after clinically effective IVIG therapy [54]. Preliminary data from our laboratory suggest that the frequency of sialic acid-containing IgG Fc-glycoforms is associated with disease remission (unpublished observation).

Thus, there is accumulating evidence that both FcγRIIb and sialic acid play a major role for the anti-inflammatory effect of IVIG but depending on the experimental conditions, other yet to be defined mechanisms might have additional Fc-glycan and FcγRIIb-independent effects. It is important to consider that all available data on the requirement of sialic acid for IVIG efficacy have been generated in mouse models infused with human IVIG (or modified derivatives thereof). Furthermore, all animal models that show a dependency on sialic acid involve the transfer of serum or pathogenic autoantibodies [4, 25, 46, 47], whereas expansion of protective regulatory T cells as well as augmentation of their effector function during HSV-induced encephalitis was found to be independent of sialylation [42]. Studies in humans and complementary humanized animal models are, therefore, mandatory to better define the role of Fc-glycosylation and the requirements for anti-inflammatory IgG activity.

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