

## Research paper

## Immunoglobulin G glycosylation in aging and diseases

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## ABSTRACT

The Immunoglobulin G (IgG) glycome is well known for its heterogeneity and shows a significant degree of variation within populations. IgG glycome composition is influenced both by genes and by environment, making it an excellent biomarker of a person's general health state, i.e. biological age. IgG glycosylation appears to be highly regulated, both during homeostasis and in cases of its disturbance. Changes in IgG glycosylation patterns have been observed in aging and in various diseases. Differential IgG glycosylation is known to modulate IgG effector functions and is involved in disease development and progression, representing both a predisposition and a functional mechanism involved in disease pathology. This makes IgG glycosylation analysis a promising add-on to improve existing disease biomarkers.

## 1. Glycans are an integral part of the immunoglobulin G molecule

Immunoglobulin G (IgG) is the most abundant antibody in our body. It is secreted by plasma cells, and its serum concentration ranges from 7 to 18 mg/mL in healthy adults [1]. IgG is involved in multiple humoral immune processes: antigen neutralization, complement activation and complement dependent cytotoxicity (CDC), target opsonization for phagocytosis, antibody-dependent cell-mediated cytotoxicity (ADCC) and hypersensitivity reactions. Its fragment antigen binding (Fab) region binds a specific antigen, while its fragment crystallizable (Fc) region binds different receptors on the surface of various immune cells, thereby dictating the type of immune response elicited by antigen binding. Due to its broad spectrum of activity and its importance in the immune response IgG is one of the most studied glycoproteins – proteins that have glycans covalently attached to their polypeptide backbone.

Glycans are complex oligosaccharides composed of up to 15 monosaccharide residues. Most IgG glycans can be classified as N-glycans, because they are attached to the protein's peptide backbone through an amide linkage to the nitrogen atom of asparagine. Each IgG molecule carries two glycans covalently attached to conserved glycosylation sites at Asn-297 of the constant heavy 2 (CH2) domain on each

of its heavy chains (Fig. 1). They are positioned within the cavity formed by the polypeptide chains of the two CH2 domains and are generally partially processed [2,3]. The Fab region contains no conserved glycosylation sites, but it is estimated that about 15–20% of IgG molecules carry one or more N-glycosylation sites in the Fab variable regions [4–9]. These N-glycosylation sites result from somatic hypermutation during the antigen-specific immune response [4].

Glycans comprise up to 15% of IgG's weight [10] and represent an integral part of the molecule. Via variation in their composition (alternative glycosylation), they are known to influence IgG's structural stability, conformation and half-life, as well as its effector functions [2,11–21]. Indeed, their complete removal results in the loss of both the pro- and anti-inflammatory activity of IgG [10,15]. Due to the non-existence of conserved glycosylation sites, glycans attached to the IgG Fab region are much less studied, but are known to be mostly fully processed and exposed to solvent, and to affect the IgG's stability, half-life and antigen binding [8,10,22–29]. Fab glycans are also suggested to play a role in the modulation of immune response [27].

The IgG glycome of an individual denotes all glycans present on a person's IgG molecules. While the first glycan analyses were low-throughput and performed using lectin assays [30–33], today's techniques allow for high-throughput workflows with increased sensitivity

**Abbreviations:** ACPA, anti-citrullinated protein antibody; ADCC, antibody-dependent cell-mediated cytotoxicity; ANCA, anti-neutrophil cytoplasmic antibody; CDC, complement dependent cytotoxicity; CH2, constant heavy 2; Fab, fragment antigen binding; Fc, fragment crystallizable; FcγRs, Fcγ receptors; FNAIT, fetal and neonatal alloimmune thrombocytopenia; GlcNac, N-acetylglucosamine; HDFN, haemolytic disease of the fetus and newborn; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; IgG, immunoglobulin G; IVIg, intravenous immunoglobulin; MBL, mannose-binding lectin; NK, natural killer; RF, rheumatoid factor; SLE, systemic lupus erythematosus

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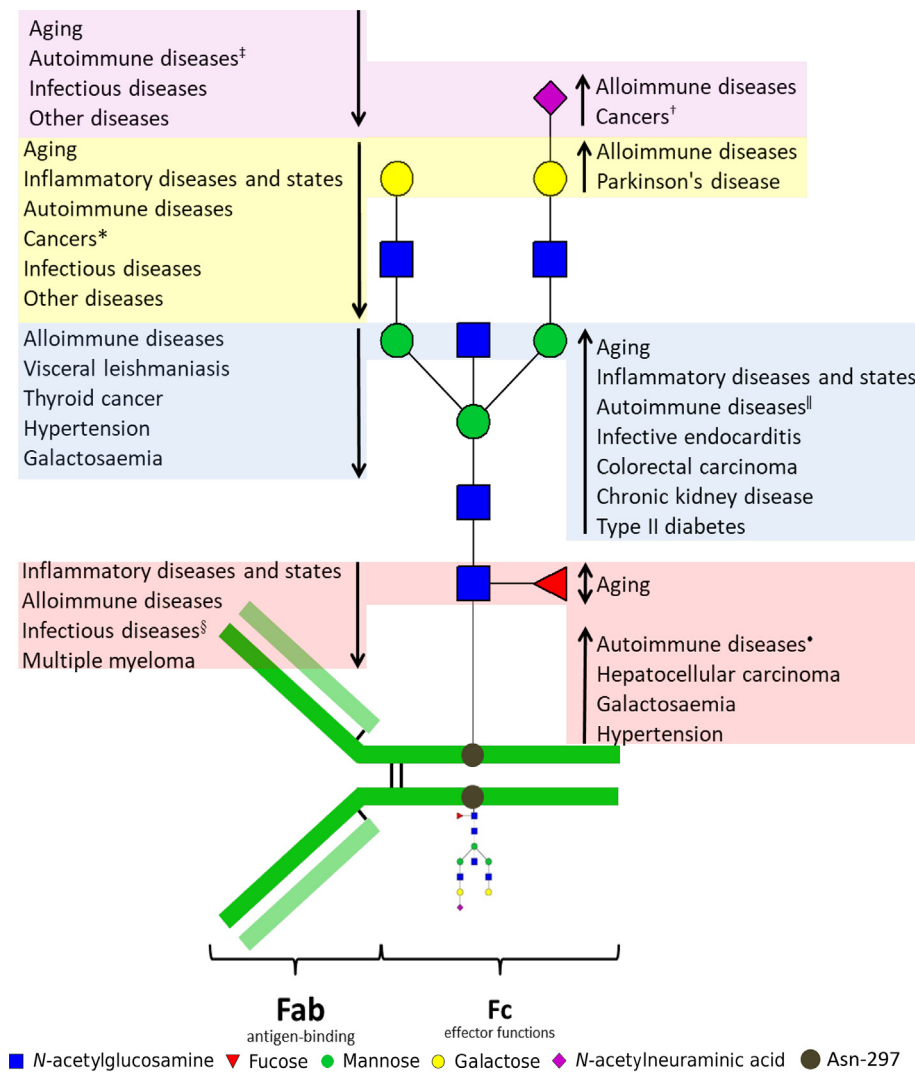
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**Fig. 1.** Alterations in IgG Fc glycosylation in aging and disease. Changes in aging are presented only for adulthood. Down arrow refers to a decreased and up arrow to an increased proportion of the corresponding IgG glycosylation trait during aging or in patients suffering from the disease compared to healthy controls and/or in active disease compared to remission state. The monosaccharide residues are color coded according to the recommendation by the Consortium for functional glycomics [313]. ‡except in autoimmune hemolytic anemia (anti-RBC); †except in ovarian and colorectal cancer; \*except in thyroid cancer and multiple myeloma; ‡except in osteoarthritis, ANCA-associated vasculitis (total and ANCA) and autoimmune hemolytic anemia (anti-RBC); †except in osteoarthritis, ANCA-associated vasculitis (total and ANCA) and autoimmune hemolytic anemia (anti-RBC); ‡except in visceral leishmaniasis and HIV infection; \*except in systemic lupus erythematosus, ulcerative colitis and ANCA-associated vasculitis (ANCA).

[34–42]. In our attempts to explain the functional role of differential IgG glycosylation in various physiological and pathological states, we should always keep in mind which (sub)set of IgG glycans is taken into account - with respect to origin (regarding IgG subclass, molecule parts and the tissue of origin), as well as possible antigen specificity and the method used to calculate different glycosylation traits from individual glycan measurements. All of these are known to influence the composition of glycans attached to IgG molecules [8,9,25,26,37,43–53].

Among all serum proteins, IgG is the most studied with regard to its glycosylation in different diseases. Due to its easy accessibility, it is mainly blood serum- or plasma-derived IgG that is analyzed, but several studies have been performed on other bodily fluids, such as cerebrospinal, synovial, gingival and salivary fluid, and spermal plasma [54–59].

Due to variable monosaccharide composition, asymmetric glycosylation (the presence of two different glycans at the two CH2 domains of the same IgG molecule), establishment of additional glycosylation sites in variable regions during somatic hypermutation, and a different glycoprofile among the four IgG subclasses, the IgG glycome is known for its heterogeneity. As a result, several hundred differentially glycosylated IgG variants can be present in an individual person at any given

time [3,10,46,60,61].

Under homeostatic conditions, IgG glycome composition shows little variation with time within an individual [62–64]. However, it alters gradually with age [65], and can be quickly changed in cases of homeostasis disturbance [63]. IgG glycome composition in healthy people is influenced by age and sex hormones (gender, pregnancy, menopause, endocrine manipulation in women and men) [34,37,66–71]. Significant alterations in the IgG glycome have also been reported in a number of diseases (Table 1). All of the above results in a very high level of variation in the IgG glycome composition found within human populations [21,61,72], which appears to be associated with both the genetic make-up of an individual and environmental influences experienced during lifetime [61,73–76].

## 2. IgG glycosylation modulates IgG inflammatory potential and immune cells effector functions

### 2.1. Galactosylation

In healthy adults, IgG-G0 (agalactosylated structures) and IgG-G1 (monogalactosylated structures) each represent about 35% of total IgG

**Table 1**

Diseases exhibiting an altered serum IgG glycosylation profile. Down arrow refers to a decreased and up arrow to an increased proportion of the corresponding IgG glycosylation trait (as calculated in the corresponding publication) in patients suffering from the disease compared to healthy controls and/or in active disease compared to remission state. In the case of antigen-specific IgG, the arrows refer to the comparison between antigen-specific and total IgG.

↓	↑
<p><b>G Inflammatory diseases and states</b>            Takayasu's arteritis [276]            Adult periodontal disease [54]  <b>Autoimmune diseases</b>            Rheumatoid arthritis – total [30,70,172–175,180,183,189,192,210,277,278], ACPA [51,186,211], RF [207]            Osteoarthritis [30,211]            Juvenile onset rheumatoid arthritis [31,173,279–281]            Systemic lupus erythematosus [172,193,199,211,277]            Inflammatory bowel disease: Crohn's disease and ulcerative colitis [81,172,194,195,197,200,202,211,282,283]            Sjögren's syndrome [211,278]            Neonatal lupus [284]            Spondyloarthropathy [211,285]            ANCA-associated vasculitis – total [25,196,201,212,286] and ANCA [201,212]            Coeliac disease [287]            Lambert-Eaton myasthenic syndrome [288]            Myasthenia gravis [288]            Myositis [289]            Guillain-Barré syndrome [198,290]            Poor glycemic control and impaired renal function in type I diabetes [291]            Autoimmune hemolytic anemia – total and anti-RBC [214]  <b>Cancers</b>            Multiple myeloma [235,236]            Ovarian cancer – total [244,248,253,262,292] and tumor-reactive [244]            Prostate cancer [246,261,293,294]            Non-small cell cancer [247]            Gastric cancer [245,249,251,252,261]            Lung cancer [245,261,295]            Colorectal carcinoma [256,257]            Breast cancer [263]  <b>Infectious diseases</b>            Leprosy - Erythema nodosum leprosum [296]            Tuberculosis [202,228,277,296–298]            Infective endocarditis [211]            HIV infection [232,299]            Hepatitis C: liver fibrosis, cirrhosis – anti-Gal [231]            Hepatitis B: chronic infection [227]; liver cirrhosis – total [227] and anti-Gal [231]            Visceral leishmaniasis [229]  <b>Other diseases</b>            Castleman's disease [300]            Galactosaemia [272–275,301,302]            Alzheimer's disease [303]            Asthma? [86,87]            Chronic kidney disease [84]            Hypertension [85,88]            Type II diabetes [162]</p>	<p><b>Alloimmune diseases</b>            Fetal or neonatal alloimmune thrombocytopenia – anti-HPA [222,226]            Haemolytic disease of the fetus and newborn – anti-c and anti-E [223]  <b>Cancers</b>            Thyroid cancer [304]            Multiple myeloma [243]  <b>Other diseases</b>            Parkinson's disease [305]</p>
<p><b>S Autoimmune diseases</b>            Rheumatoid arthritis – total [30,189,210], ACPA [56], RF [207]            Osteoarthritis [30]            ANCA-associated vasculitis – total [196,201,212] and ANCA [201,212]            Systemic lupus erythematosus – total [199,306], ANA [213]            Inflammatory bowel disease: Crohn's disease [200]            Juvenile onset rheumatoid arthritis [281]            Antiphospholipid syndrome [307]            Autoimmune hemolytic anemia – [214]  <b>Infectious diseases</b>            Visceral leishmaniasis [229]            HIV infection [308]  <b>Cancers</b>            Ovarian cancer [248]            Colorectal carcinoma [256,257]  <b>Other diseases</b>            Alzheimer's disease [303]            Chronic kidney disease [84]            Type II diabetes [162]            Hypertension [88]            Parkinson's disease [305]</p>	<p><b>Autoimmune diseases</b>            Autoimmune hemolytic anemia – anti-RBC [214]  <b>Alloimmune diseases</b>            Fetal or neonatal alloimmune thrombocytopenia – anti-HPA [222,226]  <b>Cancers</b>            Multiple myeloma [236,237]            Thyroid cancer [304]            Lung cancer [309]</p>
<p><b>F Inflammatory diseases and conditions</b>            Inflammation severity [63]            Low back pain [310]  <b>Autoimmune diseases</b>            Systemic lupus erythematosus? [199,208]</p>	<p><b>Autoimmune diseases</b>            Juvenile onset rheumatoid arthritis [31]            Rheumatoid arthritis – total [189,311] and ACPA [51]            Systemic lupus erythematosus [208]            ANCA-associated vasculitis [201]</p>

(continued on next page)

Table 1 (continued)

↓	↑
ANCA-associated vasculitis – ANCA [201] Inflammatory bowel disease: ulcerative colitis [283] <b>Alloimmune diseases</b> Fetal or neonatal alloimmune thrombocytopenia – anti-HPA [221,222,226] Haemolytic disease of the fetus and newborn – anti-D [220], anti-c, anti-E and anti-K [223] <b>Infectious diseases</b> Dengue fever progressing to dengue hemorrhagic fever or dengue shock syndrome – anti-ENV, anti-NS1, anti-HA [234] <b>Cancers</b> Multiple myeloma [243]	Inflammatory bowel disease: Crohn's disease [283] <b>Infectious diseases</b> Visceral leishmaniasis [229] HIV infection [308] <b>Cancers</b> Hepatocellular carcinoma [312] <b>Other diseases</b> Galactosaemia [274] Hypertension [88]
<b>B</b> <b>Autoimmune diseases</b> Osteoarthritis [211] ANCA-associated vasculitis – total [201,212] and ANCA [212] Autoimmune hemolytic anemia – anti-RBC [214] <b>Alloimmune diseases</b> Haemolytic disease of the fetus and newborn – anti-c [223] <b>Infectious diseases</b> Visceral leishmaniasis [229] <b>Cancers</b> Thyroid cancer [304] <b>Other diseases</b> Hypertension [85,88] Galactosaemia [274]	<b>Inflammatory diseases and conditions</b> Low back pain [310] <b>Autoimmune diseases</b> Rheumatoid arthritis [192,211,278] Juvenile onset rheumatoid arthritis [211,278] Inflammatory bowel disease: Crohn's disease and ulcerative colitis [211] Lambert-Eaton myasthenic syndrome [288] Systemic lupus erythematosus [199] <b>Infectious diseases</b> Infective endocarditis [211] <b>Cancers</b> Colorectal carcinoma [257] <b>Other diseases</b> Chronic kidney disease [84] Type II diabetes [162]

G = galactosylation, S = sialylation, F = core fucosylation, B = bisecting *N*-acetylglucosamine.

ACPA = anti-citrullinated protein antibody, ANA = anti-nuclear antibody, ANCA = anti-neutrophil cytoplasmic antibody, ENV = envelope protein, HA = hemagglutinin, HPA = human platelet antigen, NS1 = non-structural protein 1, RBC = red blood cell.

Fc glycan structures while IgG-G2 (digalactosylated structures) makes up around 15% [10,38]. Within an individual, the proportion of galactosylated structures is relatively stable [63], but it is the most variable IgG glycosylation trait on the population level [21,77]. In contrast to the slow and gradual change of IgG galactosylation level with aging (described in more detail in Section 3) [65], it can change quickly and in an “on and off mode” in acute inflammation [63]. IgG galactosylation also seems to be, at least in part, driven by the concentration of estrogen. This is evidenced by its raised level in pregnancy [70,78,79] and decreased level after menopause [65]. Additionally, an endocrine manipulation study confirmed estrogens as an *in vivo* modulator of IgG galactosylation in both women and men, thus suggesting a mechanism for gender-dependent modulation of immune response [80]. An increased abundance of agalactosylated IgG glycans has been found in patients suffering from various diseases and states with an underlying inflammatory component (Table 1), and is associated with a wide array of markers of inflammation and cardiometabolic health [41,65,81–90].

There are several lines of evidence that galactosylation of IgG acts as a modulator of its inflammatory activity. It is proposed that IgG lacking terminal galactoses acts in a pro-inflammatory manner through activation of complement via the alternative pathway [91], and via the lectin pathway after binding to mannose-binding lectin (MBL) [10,92–95], although this remains controversial [96,97]. In addition, Fc galactosylation of immune complexes was found to be necessary for the efficient initiation of the anti-inflammatory signaling cascade through binding to the inhibitory receptor FcγRIIB [98]. Likewise, highly galactosylated immune complexes have been reported to inhibit the pro-inflammatory activity of the complement component C5a [92,99]. At the same time, there are also reports of IgG galactosylation acting in a pro-inflammatory fashion. Terminal galactoses were found to enhance IgG's affinity for C1q complement component (necessary for the classical pathway of complement activation) thus boosting CDC [100–102]. Terminal galactoses were also found to enhance IgG's affinity for activating FcγRs thus boosting the downstream phenomena, most notably ADCC [19,103–105]. These data, at first sight contradictory, only prove that classifying IgG galactosylation, and indeed any

other IgG glycosylation trait, as either simply pro- or anti-inflammatory actually represents a gross over-simplification of complex biological pathways.

It should be noted here that complex IgG glycans are formed by sequential enzymatic addition of monosaccharide residues in the Golgi apparatus and that the products of many of these reactions represent substrates for subsequent monosaccharide additions by glycosyltransferases. For this reason, no IgG glycosylation trait should be considered on its own, without considering the rest of the glycoprofile, as exemplified by galactosylation. In this case, for instance, a decrease in the abundance of terminally galactosylated structures could be associated with a simultaneous decrease in sialylated structures and an increase in agalactosylated structures representing a scenario where most IgG molecules remained in the G0 glycosylation state, which would be interpreted as a highly inflammatory IgG glycoprofile. However, the same decrease in the abundance of the terminally galactosylated structures could also be associated with a simultaneous increase in sialylated and a decrease of agalactosylated structures. This may lead to a situation where most of the terminally galactosylated IgG was used as a substrate for subsequent sialylation, meaning that a large fraction of IgG was translated into the S glycosylation state. This in turn would be interpreted as a highly anti-inflammatory IgG glycoprofile. Another reason for the need to always reflect on all IgG glycosylation traits as a whole is the fact that the abundance of particular IgG glycans and glycan types (the so-called “derived traits”) is expressed using normalization to 100% - meaning that a change in absolute values of any given glycan type would automatically change the relative (%) values for the abundance of other glycan types even if their absolute abundancies remained unchanged.

## 2.2. Sialylation

In healthy adults, IgG-S (mono- and disialylated structures) represent about 10–15% of total IgG Fc glycan structures [10,38]. In contrast to galactosylation, which seems to represent an interface between physiological and pathological processes, terminal sialic acids

appear to mainly serve as a switch between IgG pro- and anti-inflammatory activity in cases of homeostasis disturbance. However, the mechanisms through which they act are still not fully elucidated. Sialylation is thought to be responsible for the anti-inflammatory activity of intravenous immunoglobulin (IVIg) administered at high doses (g/kg) [15,50,106–110], (although this remains controversial [111–113]), inhibition of IgG-mediated allergic reactions [114], and anti-rhesus D prophylaxis in pregnant women [115]. In Kawasaki disease, however, there seems to be no link between the level of sialylation of therapeutic IVIg and response to therapy [116]. Rather, higher sialylation of endogenous IgG predicted therapy response [116].

Fc sialic acids are thought to act through three types of mediators: activating type I FcγRs, type II (lectin) receptors and C1q complement component. Decreased affinity of sialylated IgG for activating FcγRs expressed on the surface of innate immune cells leads to dampening of their activation and pro-inflammatory cytokine release [3]. For instance, the decreased affinity of highly sialylated IgG for activating FcγRIIIA results in a greatly reduced ADCC by NK cells *in vivo* and *in vitro*, and enhanced anti-inflammatory effects [106,117–119], although there are conflicting reports [18,19,120]. Binding of sialylated IgG to lectin receptors, such as dendritic cell-specific intercellular adhesion molecule grabbing non-integrin, C-type lectin domain family 4 member A and B-cell receptor CD22, is thought to contribute to resolution of inflammation by the release of T helper 2 cytokines and the subsequent increase in the activation threshold of adaptive and innate immune cells [121,122]. However, pathways initiated by binding of sialylated IgG to lectin receptors are still not clear [3,98,106,107,123–134]. Finally, the effect of terminal sialic acids on C1q binding and proinflammatory IgG effector functions by the downstream CDC and the release of pro-inflammatory mediators is controversial [19,135].

Recently there were suggestions that IgG sialylation can also occur in the extracellular bloodstream environment independent of the B cell secretory pathway, which would enable a quick and dynamic anti-inflammatory response independent of the *de novo* IgG synthesis [136–138].

### 2.3. Core fucosylation

In contrast with other plasma proteins, the majority of which are not core fucosylated [139], over 90% of serum IgG contains a fucose attached to the first *N*-acetylglucosamine (GlcNAc) in the IgG glycan core structure [10,37,140,141]. Core fucose is known to clash with the glycan present on the activating FcγRIIIA and FcγRIIIB and consequently decrease the affinity of IgG to these receptors up to 100-fold, in parallel dampening the downstream processes, most notably ADCC [2,14,19,142–150]. The presence of a high proportion of IgG which is core fucosylated is thought to represent a “safety switch” against potentially harmful ADCC activity in homeostasis [151]. Reports on the association of core fucosylation with inflammation severity are inconclusive [52,63]. Core fucosylation of total and antigen-specific IgG is further reviewed in the sections describing different types of diseases.

### 2.4. Bisecting *N*-acetylglucosamine

A small proportion of IgG glycans (about 10–15%) contain a bisecting GlcNAc [10,27]. The addition of bisecting GlcNAc and the addition of core fucose are partially opposing processes at the level of glycan synthesis [152,153], and thus it is often difficult to disentangle the functional roles of these two modifications when changes in their abundance (in opposite directions) are linked to a particular disease state or condition. For example, higher levels of bisecting GlcNAc on IgG are often associated with a greater affinity for FcγRs and, consequently, with enhanced ADCC and other immune cells effector functions, although to a lower degree than the lack of core fucosylation [10,142,154,155]. However, whether this is just a consequence of the decreased level of core fucosylation that accompanies bisection remains

controversial [142].

## 3. Changes in the pattern of IgG glycosylation with chronological and biological aging

Changes in IgG N-glycome composition during aging have been known since 1988 when the abundance of agalactosylated IgG N-glycans was shown to decrease from > 30% to ~20% at 25 years of age and increase up to ~40% by 70 years of age, thus changing in a parabolic shape [66]. The abundance of digalactosylated structures changed inversely to this, while the abundance of monogalactosylated structures remained stable [66].

This pattern of changes in IgG galactosylation with age was confirmed by studies investigating changes in the IgG N-glycome during childhood and adolescence [87,156]. These studies additionally observed an increase of monogalactosylated structures during childhood [87,156]. Moreover, a high level of galactosylation, which disappeared in very young children, was reported in newborns, accompanied by an increase in fucosylation and decrease in bisection after birth [156]. In addition, gender-specific changes were reported for levels of bisecting GlcNAc, core fucosylation and sialylation [157]. The changes in the level of IgG core fucosylation and bisection move in opposite directions with aging during childhood, although in a subclass specific manner [87,156,157]. There are discrepancies regarding IgG sialylation: while in one study there was no change observed, in the others a decrease in the abundance of sialylated IgG glycoforms with age was noticed only in specific subclasses or only when calculated per galactose [87,156,157].

Most of the studies related to aging-associated IgG glycosylation alterations in adults reported that early adulthood IgG glycosylation is characterized by the highest abundance of digalactosylated and the lowest amount of agalactosylated structures, and that a decrease in galactosylation and an increase in agalactosylation can be seen with aging [37,52,61,65,66,68,158,159]. However, an isolated study reported that these changes are gender-dependent and can be noticed only in women [69]. The dynamics of the level of monogalactosylated structures was reported to depend on the distinct N-glycan structure [65,159]. All studies examining IgG bisection report a gender-independent increase in the level of IgG bearing bisecting GlcNAc with age [34,61,68,158]. Fucosylation and sialylation are also observed to change with aging [37,61,65,69,159]. However, there is no agreement on the direction of the changes for these traits, even though for sialylated IgG structures a decrease in abundance was more frequently reported [37,61,65,69,159]. Since the expression of glycosyltransferases in the B cell lineage in aging has not been investigated, no conclusion can be made on the mechanisms underlying the changes in IgG glycosylation that accompany aging. It remains to be elucidated whether the dynamic glycosylation of IgG associated with aging results from differential expression of various glycosyltransferases and/or other enzymes involved in glycan biosynthesis in the B cell line, a specific enrichment of B cell clones with a fixed IgG glycosylation pattern through clonal selection, or a combination of these processes. As already mentioned, recently post B-cell modifications of IgG glycans have been suggested as a means to modulate IgG glycosylation [137,138], however no association was found between the level of plasmatic glycosyltransferases and IgG glycosylation pattern [160].

Serum N-glycans have been shown to be the most reliable for age estimation when compared to other biomarkers of chronological age [161], with IgG glycans in particular explaining up to 64% of the variation in chronological age [65,159]. Age prediction models were significantly improved after inclusion of clinical traits [65,159], which indicates that these traits, in addition to other biological factors, are responsible for the rest of variability. Indeed, the pattern of IgG glycosylation was also reported to correlate with numerous clinical traits related to various unhealthy states and conditions: serum levels of glucose, insulin, hemoglobin A1c, triglycerides, total cholesterol, low-



density lipoprotein, high-density lipoprotein, fibrinogen, d-dimer, uric acid, creatinine, alanine aminotransferase, aspartate aminotransferase and C reactive protein, as well as body mass index and waist circumference, systolic and diastolic blood pressure, smoking, hypertension, kidney function and Framingham cardiovascular risk score [65,83–85,88–90,159,162,163]. Since the estimated average heritability of the IgG glycome is 55% (highly depending on glycan structure) [61,74], this means that the remaining variability is a result of environmental factors and different (patho)physiological variables related to age and lifestyle [61,74].

The inflammaging concept proposes that modulation of inflammation through IgG Fc glycosylation contributes to the process of biological aging [164,165]. It hypothesizes that the age-related gradual decrease in IgG galactosylation level due to chronic low-grade sterile inflammation in the elderly in turn exacerbates inflammation, creating a vicious loop in which the agalactosylated IgG species represent both a biomarker of aging and a contributor to its pathogenesis [166,167]. Interestingly, decreased inflammation, but not telomere length (the shortening of which is often associated with chronological/biological aging [168]), is shown to be a predictor of healthy aging [169], which further supports the hypothesis that the IgG N-glycosylation changes, which are associated with inflammation, are a more suitable biomarker of biological age.

In summary, due to their involvement in modulation of IgG effector mechanisms and their association with various diseases (Table 1) and disease risk factors, IgG glycans are a good predictor not only of chronological, but also of biological age [52,65,159,160,167,170,171]. Being at an interface between our genomic sequence and environmental conditions, IgG glycans represent an excellent metric of healthy aging – the difference between chronological and IgG glycan-predicted age represents the consequences of environmental and life-style influences on individuals with different genetic make-up. However, unless the glycosylation pattern of antigen-specific IgG is determined, the IgG glycosylation pattern cannot be used as a stand-alone disease-specific biomarker, and is of more value as a biomarker of general immune activation [86]. Since IgG glycosylation patterns in aging and many inflammatory and autoimmune diseases are very similar (decreased level of terminally galactosylated and sialylated structures, increased level of structures with bisecting GlcNAc), in order to assess a person's biological age their IgG glycosylation pattern should always be compared to the healthy population of same age, sex and ethnicity.

#### 4. Autoimmune diseases

The glycosylation pattern of total or antigen-specific IgG is altered in many autoantibody-dependent and autoantibody-independent autoimmune diseases [3]. The first disease-associated change in IgG glycome composition was reported in 1985: patients suffering from rheumatoid arthritis (RA) and primary osteoarthritis had a higher level of agalactosylated IgG glycan species than healthy controls [30]. This has in the meantime been confirmed in multiple studies, which also reported that it not only associated with clinical parameters (such as symptom severity), disease activity and progression, and extended to B cells *in vitro*, but also predicted response to therapy and preceded the development of RA by up to several years [172–191]. Moreover, patients suffering from RA entered a remission phase during pregnancy and this was associated with a pregnancy-related increase in IgG galactosylation [67,70,79,192]. Studies on antigen-specific IgG in RA found that glycoprofiles of anti-citrullinated protein antibodies (ACPA) of the IgG1 subclass differed from total IgG1 in both serum (more asialylated species) and synovial fluid (more agalactosylated and more asialylated species). Moreover, ACPA glycoprofiles differed in rheumatoid factor (RF) positive and negative patients [56]. Even more importantly, the ACPA IgG1 glycoprofile changed prior to the onset of the disease, exhibiting a lower level of galactosylation and a higher level of core fucosylation [51].

A decreased level of IgG galactosylation was reported to associate with many other autoimmune diseases (Table 1), and in some, such as systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD) and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, it also associated with disease progression, activity and/or symptom severity [193–201]. In ANCA-associated vasculitis, the decrease in the level of IgG galactosylation also precedes relapse [201].

As already discussed, it has been suggested that agalactosylated IgG species have an enhanced capacity to activate the complement system via the lectin pathway (by binding to MBL), thereby contributing to the development of inflammation as an underlying pathological mechanism of autoimmune diseases [82,92,94,167,173,184,202]. This has, however, been confuted by demonstrating that polymorphisms in MBL that lead to a change in MBL levels do not correlate with disease activity in RA [96,97], and that agalactosylated IgG is not associated with MBL level in IBD [197]. In RA patients, agalactosylated IgG molecules have also been proposed to be preferentially recognized by RF and thus involved in the process of formation of autoantibody aggregates [203–205].

Due to its anti-inflammatory and immunosuppressive properties, highly sialylated IgG is thought to play a major role in immune homeostasis and prevention of autoimmune and inflammatory diseases [99,206]. There is recent evidence that the protective high level of sialylation is (at least in part) driven by estrogen, thus offering a possible explanation for the difference in RA risk between women and men and between pre- and post-menopausal women [71]. Several autoimmune diseases were reported to associate with a decreased level of total IgG sialylation (Table 1). In some diseases a decreased total and/or autoantibody IgG sialylation level has been associated with autoantibody pathogenicity and activity [207], symptom severity [198], disease activity [51,135,196,201], and response to treatment [116,198]. Furthermore, this decrease also occurred before the onset of symptoms [201].

Most studies on IgG glycosylation in autoimmune diseases report no change in the level of core fucosylated glycans, while some report a change in both directions (Table 1), as well as an association with disease activity (PR3-ANCA associated vasculitis [201] and SLE [208]). Surprisingly, in relapsing patients suffering from PR3-ANCA associated vasculitis, an opposite trend was noted for total and antigen specific IgG: while total IgG showed an increase, PR3-ANCA IgG showed a decrease in the level of core fucosylation [201].

The exact role of differential IgG glycosylation in autoimmune diseases remains to be explained in detail. The common mechanism is probably the modulation of the general threshold of activation of immune effector cells, but the rest is most likely highly dependent on the pathogenesis of the particular disease. Current data suggest that there is no simple causal relationship between IgG glycosylation and disease development [209]. However, the fact that the IgG glycan profile changes prior to diagnosis but independent of the time to diagnosis [210] and that abnormal galactosylation of IgG frequently occurs in asymptomatic members of families with a high frequency of autoimmune diseases [193], combined with the significant heritability of IgG glycans [61,74] and the significant pleiotropic effects of a number of genes on both IgG glycome composition and autoimmune diseases [74], all suggest that particular IgG glycosylation patterns are associated with a predisposition towards disease development. In this sense, IgG glycome analysis could serve as an additional screening tool to identify or further stratify the population at risk of disease development. On the other hand, different glycosylation patterns of antigen-specific (auto)antibodies [51,56,186,201,207,211–214] and monoclonal antibodies [215] compared to bulk IgG combined with the changed activity of differentially glycosylated autoantibodies [207,216] together suggest that IgG glycosylation is carefully regulated at the clonal level and that different IgG glycoforms play a functional role in the pathology of autoimmune diseases. Differential IgG glycosylation might also explain why autoantibodies can be present in

patients with inactive or no disease, and might serve as an additional biomarker of disease development/activity/response to therapy. In addition, the fact that IgG glycans are involved in autoimmune disease pathology has the potential to be exploited therapeutically by administration of enzymes that deglycosylate the IgG Fc domain [3,217–219].

## 5. Alloimmune diseases

Two antibody-mediated alloimmune diseases of the newborn – fetal and neonatal alloimmune thrombocytopenia (FNAIT) and haemolytic disease of the fetus and newborn (HDFN) – display a markedly reduced level of antigen-specific IgG Fc core fucosylation, which also correlates with clinical parameters and disease severity [220–223]. This finding suggests that IgG fucosylation is an important pathological feature in these diseases. Due to enhanced binding to Fc $\gamma$ RIIIA, the low fucosylation of antigen-specific IgG was also correlated with Fc $\gamma$ RIIIA-mediated phagocytosis in FNAIT [221] and ADCC in HDFN [220]. Since these are mechanisms likely involved in the pathogenesis of diseases, in this case certain alloantibody glycotypes are considered active players in disease pathology. Most importantly, the antigen-specific IgG glycosylation pattern, especially core fucosylation, seems to predict the clinical outcome in FNAIT and HDFN [220–223], and therefore has the potential to be used in the clinical setting for improved patient stratification, i.e. identification of patients likely to develop a serious clinical phenotype requiring treatment. It seems that the generation of afucosylated IgG glycoforms is associated with the particulate, cell-bound and blood-borne nature of alloantigen causing the antibody response [49,224,225].

Studies on FNAIT also show increased galactosylation and sialylation of anti-human platelet antigen IgG [222,226], but a study examining IgGs specific to other (less common) antigens involved in HDFN pathogenesis showed the levels of galactosylation and sialylation of anti-RBC antibodies were dependent on the antigen [223]. The functional reasons, if any, behind these association remain enigmatic.

## 6. Infectious diseases

In contrast to autoimmune and alloimmune diseases, where antibodies are usually involved in disease pathology, in infectious diseases they are intended to play a protective role – whether they are naturally occurring or induced by vaccination. Most infectious diseases in which an altered pattern of total plasma/serum IgG glycosylation was measured are reported to be associated with a decreased level of galactosylation (Table 1). In chronic hepatitis B patients this trait also associates with decreased IgG opsonizing activity as well as with the severity of liver inflammation and fibrosis [227]. This aberrant glyco-pattern is reversed to normal upon administration of antiviral treatment [227]. An association of the level of agalactosylated IgG with response to therapy is also seen in tuberculosis patients [228]. In visceral leishmaniasis, a changed total IgG Fc glycosylation profile, including changes in other IgG glycosylation traits (Table 1), associates with clinical severity and response to therapy [229]. In filariasis, individuals asymptotically infected with *Wuchereria bancrofti* exhibit lower levels of disialylated IgG compared to endemic controls and patients with pathology, suggesting that total IgG sialylation may be involved in asymptomatic infection [230]. Aside from the known connection with general inflammatory status, no data are available that would pinpoint a direct link between infection and a changed total IgG glycosylation pattern.

When it comes to antigen-specific IgG, anti-Gal IgGs in hepatitis B and C show a specific glycosylation profile, which includes a decrease in galactosylation and also associates with disease severity and the degree of associated liver damage in hepatitis C [231]. Interestingly, spontaneous controllers of human immunodeficiency virus (HIV) infection display decreased galactosylation, sialylation and fucosylation of anti-envelope IgG as well as lowered total IgG galactosylation [232].

This is in contrast to tetanus, influenza, pneumococcal and meningococcal infection, where protective antigen-specific IgG induced by vaccination showed an increased level of galactosylation, sialylation and in some cases decreased bisection and increased core fucosylation compared to bulk IgG [49,233]. While no data are available on the functionality of the vaccine-induced IgG, in HIV controllers this IgG glycopattern also associates with increased viral clearing capacity of this antibody fraction due to activation of the innate immune system [232]. In dengue-infected patients that progress to dengue hemorrhagic fever or dengue shock syndrome, the increased level of afucosylated virus-specific IgG glycovariants correlates with disease severity [234]. This is thought to explain the antibody-dependent enhancement of dengue virus infection, since these IgG glycoforms trigger platelet reduction *in vivo* and are a significant risk factor for thrombocytopenia [234].

In conclusion, from the research performed on various autoimmune, alloimmune, and infectious diseases, it appears that shifts in total IgG glycopatterns are probably associated with total general inflammatory status. At the same time, B cells seem to have the capacity to tune antibody glycosylation actively and in an individually tailored way, regarding both antigen specificity and the immunological context or antigen introduction.

These findings have the potential to be used in optimizing the vaccine and immunotherapy formulations and protocols in the future, thus opening up a new area of research on clonal specificity of IgG glycosylation with the aim of inducing targeted glycoforms of protective antibodies. Some effort has already been invested into basic research on these topics. Different types of antigens (T-cell dependent vs. T-cell independent) and different immunization protocols (tolerance induction vs. inflammatory conditions) have been shown to result in distinct glycosylation patterns of induced antigen-specific IgG [121,122]. In the context of allergic diseases, the efficacy and safety of allergen-specific immunotherapy has been linked to sialylation of the induced allergen-specific IgG [114,121]. However, more basic and applied research is needed to translate these promising findings into useful prophylactic and therapeutic approaches.

## 7. Cancer

The first malignant disease in which IgG glycosylation was examined was conveniently a plasma cell disorder resulting in increased IgG production - multiple myeloma. In this disease, a decrease in IgG galactosylation in patients compared to healthy controls was observed, associating in particular with more advanced phases of the disease [235,236]. A stage-dependent increase in the level of terminally sialylated structures was also reported [236,237]. Interestingly, there are also studies pointing to the importance of Fab glycosylation in this disorder [238,239]. Furthermore, confirming the idea that IgG glycosylation machinery is B cell clone-specific, there are reports highlighting the considerable heterogeneity of different myeloma IgG glycosylation profiles [47,240–242], but instances of matching glycomic profiles of polyclonal (background) and monoclonal myeloma IgG have also been reported [242]. A very recent study observed that differences in all IgG glycosylation traits delineated particular phases of disease pathology (from benign to active myeloma) and also associated with response to therapy [243].

Studies examining changes of IgG glycosylation in various other types of cancer also report a decreased level of galactosylated glycoforms (Table 1). In some of them (gastric cancer, lung cancer, prostate cancer, non-small cell carcinoma, ovarian cancer) the abundance of agalactosylated IgG is also related to disease progression and increasing disease pathogenesis, including metastasis development [244–253], and in gastric cancer with survival [251,252].

It has been suggested that the decreased level of IgG galactosylation observed in patients suffering from cancer represents a part of the host's response to the presence of the tumor and reflects an inflammatory

response to the development of cancer [251]. Another explanation associates the agalactosylated IgG with acute-phase response pathways involved in the progression of cancer (such as cell growth and metastasis) that partly mimic the inflammatory processes [254]. Yet another hypothesis states that agalactosylation of the IgG Fc region leads to reduced CDC due to impaired binding to C1q complement component, resulting in cancer cells escaping from the immune system [255].

In contrast to galactosylation, which is almost uniformly decreased across different cancers, other glycosylation traits also show variable changes (Table 1). In gastric cancer, tumor progression is also associated with increased levels of core fucosylated and decreased levels of bisected IgG [252]. In contrast, a higher level of fully sialylated glycans and elevated expression of glycans with bisecting GlcNAc were associated with better survival rate [252]. In contrast to most studies that are usually performed on small to medium size subject groups, two large-scale studies (over 1.200 subjects each) were recently performed on colorectal cancer [256,257]. In addition to decreased galactosylation of total serum IgG as already established in other types of cancer, the development and poor prognosis of the disease were also associated with decreased IgG sialylation [256,257].

Studies on tumor-antigen-specific IgG mostly concentrate on the increased efficacy of afucosylated therapeutic monoclonal antibodies due to enhanced ADCC [258,259]. However, in a study examining the glycosylation pattern of endogenous tumorigenic anti-GRP78 IgG in malignant melanoma, increased mannose content of both Fab and Fc N-glycans was found in patients compared to healthy controls and it associated with disease progression [260]. This identifies aberrant glycosylation as a possible mechanism by which these autoantibodies promote malignant melanoma cell proliferation and survival [260].

Due to their easy accessibility when compared to tissue biopsy, IgG glycans remain in the spotlight of research as potential biomarkers of early disease development and tumor progression. Since the abundance of agalactosylated structures is shared not only among various cancer types but also among a vast range of other diseases, the most promising way forward probably involves using this IgG glycosylation trait as an additional layer of information to increase the performance of existing biomarkers. Indeed, agalactosylation of serum IgG is associated with prostate-specific antigen, currently considered the best disease biomarker in prostate cancer [246], and in lung, gastric and prostate cancer with the metastasis marker matrix metalloproteinase-2 [261]. Using the level of agalactosylated glycoforms resulted in improved specificity and sensitivity when compared to the routine clinical marker for ovarian cancer [262]. In a similar attempt, scores computed using 7 Fc IgG glycans could discriminate between breast cancer patients and healthy controls [263].

## 8. Other diseases

IgG glycosylation has been explored in many other chronic and non-chronic states (Table 1). A very recent large-scale study on type II diabetes, which involved more than 5000 subjects, reported a decrease in IgG galactosylation and sialylation, accompanied by an increase in bisection [162]. This is considered reflective of biological aging and an overall pro-inflammatory state [162]. IgG N-glycome changes have also been linked to clinical risk factors for type II diabetes, such as age, body mass index, smoking, and dyslipidemia [65,83,85,162,264]. Since there are also shared genes that have been associated with both IgG glycosylation and type II diabetes (FUT8, ST6GAL1) [73,265–267], and an established association between complement activation and type II diabetes incidence and complications [268,269], it is suggested that pro-inflammatory IgG is a contributor to the disease pathophysiology in this disease [162].

Not surprisingly, patients suffering from congenital disorders of glycosylation exhibit particular IgG glycosylation patterns [270,271]. In galactosaemia, an altered IgG glycoprofile that included a decreased level of galactosylation was observed (Table 1), which partly reverted

to normal in association with an improved clinical picture. This lead to a suggestion that IgG N-glycosylation can be used as an improved biomarker for monitoring the response to galactosemia therapy and interventions [272–275].

An altered total IgG glycosylation profile, above all a decrease in IgG galactosylation, observed in various diseases, likely reflects the underlying inflammatory processes accompanying disease development and progression.

## 9. Conclusions

- IgG glycans represent an interface between the genetic make-up of an individual and environmental factors.
- The composition of the IgG glycome is affected by various physiological and pathological states, thus being an excellent marker of a person's general health state, i.e. biological age.
- Glycosylation of IgG modulates its effector functions, thus being involved in the processes linking innate and adaptive immunity. The exact mechanisms are only starting to be elucidated.
- IgG glycosylation appears to be highly regulated during immune responses. Exactly how and when this is accomplished remains unclear.
- IgG glycosylation has the potential to serve as an add-on to improve existing biomarkers of disease predisposition, as well as the establishment, activity, prognosis and response to therapy.
- The induction of IgG with targeted glycosylation might be a way to improve vaccination and immunotherapy formulation and protocols.

## 10. Conflict of interest

GL is founder and CEO of Genos – a private research organization that specializes in high-throughput glycomic analysis and has several patents in this field. IG and MP are employees of Genos.

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