Review

Sweet and sour: the impact of sugars on disease

A. Alavi and J. S. Axford

The clinical relevance of glycobiology has become the focus of considerable research, as the role of glycosylation in the development, regulation and progression of disease is, slowly but surely, being unveiled. Recent strides in the design and refinement of analytical techniques—sugar profiling, glyco-arrays and functional studies—have helped us gain a better understanding of the complexity and richness of diversity that bestow sugars with an unsurpassed, biospecific coding capacity. Cracking this ‘sugar code’, and unravelling the structural frameworks and recognition strategies of sugar-based interactions in biological systems that relate to both health and disease, holds tremendous promise for deciphering disease mechanisms. It will also provide a cutting edge potential for the development of novel diagnostic and therapeutic interventions.

**Key words:** Glycosylation, RA, Autoimmunity, Sugar printing disease, Immunoglobulin G, RA biomarker.

**Introduction**

Glycomics, the study of oligosaccharides, is now emerging as the third informatics wave after genomics and proteomics [1–4]. The recent surge of interest in sugars and their impact on health and disease stems from the fact that glycosylation has, finally, gained recognition for the pivotal role that it plays in virtually all aspects of our system; from embryogenesis to pathogenesis [2, 3]. This comes as no surprise, since the surface of our entire cellular network, as well as those of bacterial and viral pathogens, and the backbone of most proteins and lipids, is decorated with a dense complement of complex sugar structures [2, 3, 5].

These sugar antennae, individually known as glycans and collectively as the glyocalyx, have numerous roles. These can be structural and/or functional, and reflect the inherent complexity of the sugar chains, as well as their topology, flexibility and the fact that they are the most diverse biopolymers found in nature [3, 6].

As biomolecules, glycans, by virtue of their multiple branched structures and diversity of linkages, can carry much more information per unit weight than proteins or nucleic acids [6]. This, as a co-/post-translational modification, not only has the potential to generate enormous physical and biochemical diversity (i.e. through the formation of large numbers of glycoforms), but more importantly, can also confer enormous coding capacity for transfer of biospecific information [6, 7]. And so, in addition to performing a structural and protective role, a large number of glycans have important functional roles as specific information tags or recognition epitopes.

These high-density information-bearing sugar epitopes (ranging from simple monosaccharide units to polysaccharides, and present in various forms; Table 1), provide a biological information transfer system beyond the genetic code [8], and are thus fundamental to the mediation and modulation of cellular function and physiology. Increasingly gaining recognition as key modulators in intra- and inter-cellular routing, molecular and cellular/matrix interactions, as well as initiation of signal transduction, these glycomodifications can affect many vital biological processes. They include almost all innate and adaptive immunological events such as cellular communication, proliferation, adhesion, apoptosis, infiltration, inflammation, oncogenic transformation and metastasis [2, 3, 5, 9–15].

The principal mode of action underlying the role of sugars in these biological processes is the selective molecular rendezvous between the sugar epitope and the extensive, not yet fully catalogued, spectrum of sugar receptors [8]. These receptors, which are primarily proteinaceous and ubiquitous, include lectins, collectins, adhesion molecules and anti-carbohydrate antibodies, collectively referred to as carbohydrate-binding proteins [3, 6, 16–20].

Enciphered by these receptors, the information encoded into these sugar epitopes can thus facilitate and control a vast, complex network of bimolecular interactions that coordinate molecular and cellular function in relation to both health and disease (Fig. 1).

The extent of the impact of glycosylation becomes even more evident when one considers the fact that despite the degree of complexity and reproducibility, the biosynthesis of glycan structures is not template driven, but is instead governed by a multiple sequential and competitive assembly line like system [3, 21]. The synthetic pathway encompasses a complex, cleverly orchestrated, deployment of hundreds of enzymes; namely glycosyltransferases and glycosidases (primarily located within the endoplasmic reticulum and the Golgi), which have very fine specificity and are encoded by distinct genes that comprise a large proportion (>1%) of the genome [2, 3].

The intricate interplay between this large array of glycoenzymes allows for the production of an exact, reproducible, glycan profile (also referred to as the glycome), which is as characteristic as a fingerprint/signature, distinguishing one type of cell, matrix, protein or lipid from another [2, 4, 22, 23]. Moreover, the inherent fluidity of the glycosylation process, together with the fact that many of the glycosyltransferases are expressed/regulated in a cell- or tissue-specific manner [21, 24, 25] empowers the cell with the versatility to rapidly modify a glycan code/profile in response to a given, dynamic, physiological/pathological state.

In this context, aberrant changes in cellular processes, such as those that accompany disease, are therefore likely to result in alterations of the glycan profiles of the cell surface and/or secreted glycoconjugates, in particular glycoproteins. And so, not surprisingly, most major diseases, when probed, are found to be directly/indirectly associated with a change in the glycosylation pattern of at least one central structure.

Sugar profiling of normal and diseased glycoproteins or tissues has provided new leads into various diseases such as tumour development, neuropathology (including Creutzfeldt–Jakob disease), asthma, RA, SLE, Crohn’s disease (CD), IgA nephropathy and muscular dystrophy [2, 4, 13, 19, 26–45].
This review will briefly highlight some specific examples of disease-associated glycosylation changes, notably that of immunoglobulin G (IgG) in RA, and address the exciting prospects that emerging glycomic techniques offer for the rapid discovery and exploitation of glyco-based diagnostic and therapeutic strategies.

Aberrant glycosylation: why and how?

Although naturally occurring gross genetic defects in the glycosylation machinery are relatively rare (Fig. 2), aberrant glycomodifications are extensive and invariably found to be associated with, or a prerequisite for, a wide-ranging myriad of disease phenotype. These range from the subtle to the palpable and can be acquired or inherited (Table 2).

Many of these aberrant glycomodifications are protein-, site- (different sites on a given protein undergo differential glycosylation) and cell- or tissue-specific, and reflect the influence of various intrinsic factors on the glycosylation process within a given cell type. These include the tertiary conformation of the peptide backbone and that of the nascent glycan chain, the availability of various substrates, sugar nucleotide and co-factors and most importantly the expression of the relevant glycosyltransferases.

The expression of these enzymes (one of the largest and most diverse enzyme groups in all living cells) is critical in
determining the final glycan profile, and is therefore tightly regulated in a cell- and tissue-specific, temporal manner. This changes significantly in response to a combination of many extrinsic, independent, regulatory factors, including stimulus by various hormones and cytokines associated with the immunoendocrine network (Table 3), and consequently may mirror the disease-associated changes in these parameters [2, 21, 46–49].

### TABLE 2. Aberrant N- and O-linked glycomodifications are associated with many, inherited as well as acquired diseases

<table>
<thead>
<tr>
<th>Aberrant glycosylation</th>
<th>Type of glycan abnormality</th>
<th>Example of diseases associated with this abnormality</th>
<th>Additional information</th>
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<tbody>
<tr>
<td>Inherited</td>
<td>Defective glyco-metabolism, e.g. mannose in carbohydrate-deficient glycoprotein syndrome (CDG) 1b syndrome</td>
<td>CDGs are multisystemic disorders; with defects in one of at least 20 genes</td>
<td>Congenital muscular dystrophy</td>
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<td>Devoid of sialyl Lewis-X (s Le[^a^]) structures, e.g. on neutrophils</td>
<td>Leucocyte adhesion deficiency type II</td>
<td>Congenital dyserythropoietic anaemia type II (also known as HEMPS)</td>
<td>Sialuria; overproduction of cytoplasmic sialic acid</td>
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<td>Abnormal O-glycans</td>
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<td>Abnormal Golgi processing of glycans</td>
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<td>Aberrant synthesis and overproduction of sugars</td>
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<td>Acquired</td>
<td>Changes in the level of expression of naturally occurring glycan motifs</td>
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<td>Neo-expression</td>
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<td>Changes in the level of expression of naturally occurring glycan motifs</td>
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In those instances where mutations do arise, the phenotypes are invariably unpredictable or pleiotropic, and span the spectrum of biological roles of glycans; from non-essential activities to those that are critical to development, function and survival.
As such, the glyco-enzyme profile of the cell can therefore act as a code for cellular physiology. An understanding of this code as it relates to disease states such as RA, at both molecular and functional levels, will help to unravel the ‘why and how’ of aberrant glycosylation.

Glycosylation and autoimmunity

Modification of self-antigens through glycosylation may represent one way in which immune tolerance can be bypassed. This can be caused by the glycoprotein/lipid being immunogenic in its own right, or by cross reaction with a pre-existing immune response.

Unlike classical peptide chain-based epitopes, glyco-epitopes (glycotopes) can share significant structural homologies [50]. These glycotopes, also referred to as cross-reactive carbohydrate determinants (CRCDs), are, thus prone to extensive cross-reactivity and can behave as ‘pan-epitopes’, which may, in some contexts, be mechanistically important in the pathogenesis of many autoimmune diseases [2, 26, 29, 51–55].

In this respect, it is interesting to note that naturally occurring (IgM, IgA and in some instances IgG) anti-carbohydrate antibodies, present at relatively high levels in our system, are the key components of our natural immunity [56]. Although the vast majority of these antibodies (Abs) are directed against immunoreactive non-human glycotopes, including those found in most expression systems used for recombinant technology [57], they are also cross-reactive against various blood group antigens, and therefore responsible for many of the haemolytic transfusion reactions and possibly some of the autoimmune ones too.

Glycan processing and presentation to T cells by MHC is key in many of the systems studied so far and includes the role of collagen and hyaluronan-derived remnant glycotopes in autoimmune arthritis and dermal injury, respectively [51, 52]. In the latter, the hyaluronan glycan has been shown to activate endothelial cells and induce IL-8 production, via a Toll receptor (TLR4)-dependent pathway [51].

Normal mammalian glycan structures can also function as self-antigens in facilitating the development of immune cell types e.g. the establishment of NKT cells [58]. These NKT cells are an unusual group of T lymphocytes, with potent immunomodulatory activities, which recognize glycolipid antigens, and are key players in regulating the immune response. Studies in mice have demonstrated that α-galactosyl ceramide and related glycolipids, through their interaction with NKT cells, can protect mice against a variety of diseases, including several autoimmune and inflammatory conditions.

In addition, there is also evidence to indicate that synovioocytes have a characteristic glycosylation phenotype that is altered in the presence of inflammatory cytokines such as TNF [49, 59], which may alter their signalling cascades, apoptosis, expression of adhesion molecules as well as their production of matrix-degrading enzymes, including glycosidases [60]. In this respect, it is interesting to note that the density of fucosylation differs significantly in particular glycoproteins of SF in joint diseases such as RA and juvenile idiopathic arthritis (JIA) [61], and that there is differential expression of genes encoding carbohydrate-binding proteins such as mannos-binding lectin (MBL) and galectins, such as galectin-1 and -3 [62–64], and various Toll-like receptors [65], all of which interact with various glycans structures and are known to be involved in autoimmune response and arthritis.

Other key links between glycosylation and autoimmune diseases such as RA and lupus include (i) the cascade of glycans-based ligands and the adhesion molecules involved in both cellular infiltration and neovascularization [64], (ii) the induction of an SLE-like autoimmune disease via the reduction or inactivation of α-mannosidase-II through genetic remodelling [54], (iii) the negative regulation of T-cell receptor signalling by N-acetylglycosaminyltransferase-V, which has been shown to down-regulate Th1 cytokine production by T cells, thereby altering the Th2/Th1 balance and autoimmune disease susceptibility [66] and (iv) the emerging role of sialylation on T- and B-cell homeostasis, e.g. through apoptosis/differentiation into memory cells, which is regulated, in part, by the expression of α2,3-sialyltransferase-1, and also via ligation and lectin (galectin) binding to heavily glycosylated cell surface glycoproteins [64, 67]. Sialylation is also critical for the regulation of Th1–Th2 [64, 68] polarization and thereby tolerance and autoimmunity.

These data not only prove the aetiopathogenic role or diagnostic significance of certain glycotopes but also show that targeting of these may be critical for the treatment of certain autoimmune diseases [58, 64, 69].

Is RA a glycosylation disease that is dysregulated?

During the past two decades particular emphasis has been placed on the glycosylation of human Igs, notably IgG and its role in autoimmune rheumatic diseases and RA in particular. The data generated suggest that RA may, in part, be a dysregulated glycosylation disease in which changes in the following parameters may have a contributory role: (i) changes in the glycosylation of glycoconjugates of cartilage [26, 52, 60, 70, 71] and synoviocytes [59]; (ii) changes in the glycosylation of cell surface receptors on chondrocytes [49]; (iii) changes in the glycosylation of synovial fluid glycoproteins [61]; (iv) changes in the differential expression of certain galectins and MBL [62–64]; (v) changes in the levels of, as yet unexplained, anti-MBL auto-Abs [72]; (vi) changes in the glycosylation of certain, as yet unidentified, plasma proteins [73]; (vii) changes in the glycosylation of the acute-phase proteins [74]; and finally, but not the least (viii) changes in the glycosylation of IgG [27, 47, 62, 75–80].

The research in relation to the latter has been extensive and has drawn together all aspects of aberrant IgG glycosylation, including: the structural anatomy of IgG; the impact of glyco-microheterogeneity on the effector functions of IgG; the clinical aspects of IgG glycosylation changes in both human disease and animal models; the associated glycosyltransferases and the genes that encode and regulate these enzymes and the possible...
pathogenicity of glyco-modified IgG in this disease [21, 27, 42, 47, 75, 77, 79, 81–85]. Together, these studies have provided a wealth of untapped diagnostic and prognostic information and have increased our understanding of the disease mechanisms involved in RA [19, 26, 47, 62, 75, 78, 79, 85–91].

Structural anatomy of IgG

IgG, with its 2.8% sugars, is one of the least glycosylated molecules in our system (Fig. 3). However, the glycans at the single, highly conserved, glycosylation site in the constant (C,2; and C,3 in IgG3) domain of its Fc region are critical features which have far-reaching structural and functional impact, affecting both the innate and adaptive arms of the immune response [2, 91–94].

These complex N-linked glycans have a constant core biantennary (heptapolysaccharide) region and variable terminal sugars i.e. the presence or absence of galactose (Gal), sialic acid (SA), bisecting N-acetylgalactosamine (bis-GlcNAc) and fucose (Fuc), resulting in ~30 distinct glycan moieties (Fig. 4) and consequently a large number of possible glycoforms (IgGs with identical polypeptide sequences, but different glycans that may consequently a large number of possible glycoforms (IgGs with identical polypeptide sequences, but different glycans that may consequently a large number of possible glycoforms (IgGs with identical polypeptide sequences, but different glycans that may consequently a large number of possible glycoforms (IgGs with identical polypeptide sequences, but different glycans that may consequently a large number of possible glycoforms (IgGs with identical polypeptide sequences, but different glycans that may consequently a large number of possible glycoforms (IgGs with identical polypeptide sequences, but different glycans that may consequently a large number of possible glycoforms (IgGs with identical polypeptide sequences, but different glycans that may consequently a large number of possible glycoforms (IgGs with identical polypeptide sequences, but different glycans that may consequently a large number of possible glycoforms (IgGs with identical polypeptide sequences, but different glycans that may consequently a large number of possible glycoforms (IgGs with identical polypeptide sequences, but different glycans that may consequently a large number of possible glycoforms (IgGs with identical polypeptide sequences, but different glycans that may consequently a large number of possible glycoforms (IgGs with identical polypeptide sequences, but different glycans that may consequently a large number of possible glycoforms (IgGs with identical polypeptide sequences, but different glycans that may consequently a large number of possible glycoforms (IgGs with identical polypeptide sequences, but different glycans that may consequently a large number of possible glycoforms (IgGs with identical polypeptide sequences, but different glycans that may consequently a large number of possible glycoforms (IgGs with identical polypeptide sequences, but different glycans that may consequently a large number of possible glycoforms (IgGs with identical polypeptide sequences, but different glycans that may consequently a large number of possible glycoforms (IgGs with identical polypeptide sequences, but different glycans that may consequently a large number of possible glycoforms (IgGs with identical polypeptide sequences, but different glycans that may consequently a large number of possible glycoforms (IgGs with identical polypeptide sequences, but different glycans that may consequently a large number of possible glycoforms (IgGs with identical polypeptide sequences, but different glycans that may consequently a large number of possible glycoforms (IgGs with identical polypeptide sequences, but different glycans that may consequently a large number of possible glycoforms (Fig. 4).

\[ \text{IgG} \rightarrow \text{N-linked} \]

\[ \text{IgA} \rightarrow \text{N-linked} \]

\[ \text{IgM} \rightarrow \text{N-linked} \]

\[ \text{IgD} \rightarrow \text{N-linked} \]

\[ \text{IgE} \rightarrow \text{N-linked} \]

The fine-tuning of the effector functions of IgG

As already discussed, sugars can make glycoprotein receptor interactions highly specific. This is important since all the effector functions of IgG are mediated through the interaction of the Fc moiety with various molecules including the FcRs (FcRI, II, III and neonatal receptor FcRn), C1q component of complement and RFs (antibodies against autologous IgG).

The interaction with the FcRs is of particular importance, in that it can result in either activation or curtailment of the immune response, as determined by the balance between activating and inhibitory signals of the Fc glycans [97, 99], as well as the FcRs on each cell [101]. In this respect, the glycans in the Fc, which form multiple non-covalent (at least 12 protein–carbohydrate and carbohydrate–carbohydrate) interactions with the protein backbone, play a pivotal role in directly/indirectly influencing the above IgG effector functions, as well other biological properties, including the rapid elimination of antigen–antibody complexes, induction of antibody-dependent cellular cytotoxicity (ADCC), IgG-mediated anaphylaxis and feedback immunosuppression [57, 78, 98, 99].

This fine-tuning of the Fc effector functions through glycosylation, in particular the degree of galactosylation, fucosylation and sialylation [57, 96, 97, 99, 100, 102], is a key factor in dictating whether IgG responses are deemed pathogenic or therapeutic, and may, for example, explain why intravenous immunoglobulin (IVIG) is sometimes found to be useful in the treatment of RA, lupus and asthma, among other autoimmune disorders [103].

Clinical implications of IgG glycosylation changes in RA

The first indication that glycosylation may affect IgG function came from studies that linked RA with a significant increase in IgG agalactosylation (IgG-G0). Following these initial observations, research in this field has followed an exponential path and has resulted in IgG-G0 becoming almost synonymous with RA [62, 78–80].

In vitro experiments and extensive analysis of B cells, from various animal models and RA patients, demonstrate a direct, but complex, link between IgG agalactosylation and reduced galactosyltransferase (GTase) enzyme activity, shedding more light on how these cellular glycosylation changes may induce/perpetuate the pathological processes in RA [80, 85, 104–106].

Although the majority of the earlier studies have addressed the amount of galactose alone, more recent studies have demonstrated that a high percentage of these IgG-G0 oligosaccharides may display an increased degree of fucosylation [27, 75, 76, 107], i.e. are predominantly G0–F structures. Fucosylation changes may in some instances be critical in differentiating between acute and remission phases of disease, as demonstrated in JIA [107].

IgG-G0 and IgG-GOF contribution to RA pathology appears to result from the fact that the absence of terminal sugar residues (Gal and SA) and the presence of the outer arm Fuc result in localized conformational changes in both the glycan moiety and in the polypeptide loop in the C,2 domain. This affects the interface between IgG-Fc and its interaction with other molecules [57, 78, 87, 88, 97, 98, 103, 108, 109], causing defective effector/regulatory mechanisms of the immune response as listed here:

Novel uptake and presentation of IgG peptides as autoantigens. Agalactosylation results in uptake of IgG-G0 through mannos receptor(s) on macrophages and dendritic cells. This novel mode of uptake by antigen-presenting cells can potentially generate epitopes recognized by T cells, which may have particular relevance for RA and other autoimmune disorders that are characterized by high levels of IgG-G0 and IgG-G0-containing immune complexes (ICs) [87].
High-affinity RF binding and IC formation. The unmasking of new epitopes in the Cy2 domain, which could be antigenic, triggers auto-sensitization and the subsequent production of anti-IgG-G0 Abs [86] and increased binding to pathogenic RFs [89, 91, 110, 111]. Importantly, the presence of raised levels of these antibodies in RA is considered a more sensitive indicator of disease activity than conventional RFs. This supports the findings of Soltys et al. [91], who found that the monoclonal RFs that bound better to agalactosyl IgG composed the high-affinity, pathogenic set of RFs in RA.

The presence of these anti IgG-G0 Abs and RFs results in the formation of pathogenic circulating ICs and aggregates (Fig. 5), consisting mainly of multimeric IgG-IgG or IgG-IgM/IgG/C3 (where IgM*/IgG* are RFs); in which IgG functions as both the antigen and the antibody. This is an important feature that may explain the increased levels of ICs and their atypical glycosylation status in RA [111]. It may also shed more light on how these ICs may induce/perpetuate the pathological processes in RA [2, 91, 111]; in particular, in the synovial joint which is the site for increased production of both IgG-G0 and RFs [2, 28, 86].

Inappropriate activation of complement (C’). The unmasked (agalactosylated) terminal GlcNAc residue, on the more mobile G0 glycan, which would not normally be accessible for recognition, can interact with lectin-like molecules such as MBL. This results in the activation of the C’ cascade through an alternative pathway [19, 88, 112], which subsequently triggers a series of reactions that culminate in the generation of inflammatory molecules and cellular destructive activities (Fig. 5).

Differential binding to FcRs and activation of inflammatory responses. The degree of sialylation and fucosylation influences the interaction of IgG-Fc with the differentially expressed activating or inhibitory FcRs on various leucocytes. The agalactosylation and subsequent absence of SA on RA IgG-G0 results in the mediation of pro-inflammatory responses through the engagement of specific FcRs on effector cells [97, 103].

The change in fucosylation is of particular interest since it is now known that the presence of fucose, even on just one heavy chain, may be sufficient to alter ADCC by affecting the binding of IgG to FcRIIIa [102]. Although Fc glycosylation changes are not the only characteristic of an RA autoantibody which determines its arthrogenicity, it is a significant factor determining the pathogenic potential of these autoantibodies, and in facilitating the co-engagement of various pathways that induce/perpetuate RA.

Clinical studies in this field strongly support the proposed relationship between IgG glycosylation changes, RF avidity, IC formation, MBBL binding and pathology in RA. They demonstrate that increased IgG-G0 (circulating in the serum and/or in ICs in the synovial fluid) correlates with increased RF avidity, with higher tender joint score and a higher frequency and number of subcutaneous nodules in RA patients [79, 84–86, 113]. Although the possibility that the increased expression of IgG-G0/IgG-G0F glycoforms may be a secondary marker of the disease process cannot be totally ruled out, the evidence in support of the hypothesis that glycosylation changes are intimately linked with the pathogenesis of RA is considerable [47, 62, 76, 77, 82, 86, 89–91].

Cause/effect?

Data that may address this come from a study of patients who present with early synovitis, as it is only those that have increased IgG-G0/IgG-G0F on presentation that go on to develop RA [75, 77, 93]. There is good evidence to suggest that presentation with both IgG-G0 and RF is a predictor of severe RA. Furthermore, IgG-G0 has been shown to antedate the initial
symptoms heralding the onset of RA by up to 10 yrs, and to be a useful diagnostic biomarker of RA [27, 75, 114].

Its usefulness and relevance to disease activity has prompted the use of sugar printing for the differentiation of rheumatic diseases [27, 75, 113, 115]. Sugar printing of serum IgG can differentiate early RA and RA from each other and from other rheumatic diseases (Fig. 6; prediction of RA in 71.2% of individuals, with a specificity of 84.2% and sensitivity of 50.0%), and hence may constitute a relatively rapid diagnostic test for patients presenting with arthritis [75].

IgG-G0 has also proved to be a good prognostic indicator; it correlates with severity and duration of disease, increases with disease progression [47, 75, 79, 84], and returns to normal levels following treatment, e.g. with anti-TNF [90], or when patients go into remission. This is of particular relevance in pregnancy where the decrease in IgG-G0 levels is associated with a remission in the disease, and where a rapid rebound increase in IgG-G0, post-partum, is associated with disease flares in RA patients [47]. The latter is of particular importance as it further supports the notion that IgG-G0 may be a susceptibility factor in the development of RA.

Are IgG glycosylation changes exclusive to RA?

When investigating a variety of diseases, Fc glycan changes link a number of them. Mycobacterium tuberculosis infection causes a decrease in IgG galactosylation and in cases of Borrelia burgdorferi and M. leprī, low levels of IgG galactose result, but at certain disease stages only, in chronic arthritis and erythema nodosum leprosum, respectively [93]. Such changes can also occur in a select group of other autoimmune rheumatic diseases [27, 75, 113, 115], where sugar printing of IgG (Fig. 7) has demonstrated
that each disease may be associated with a particular pattern of glycomodification, as in CD, JIA, SLE, primary SS and patients with PsA.

**The future: from fundamental principles to the frontiers of research**

The far-reaching impact of the significance of the sugar code in biological systems has fuelled vigorous investigations to probe the subtleties of glycosylation, and those of protein–carbohydrate interactions. These investigations span many medical specialties, from diabetes to dementia (Table 4) and are expected to not only provide a more in-depth insight into the intricate biochemical pathways that result in disease but to also pave the way to the discovery of novel diagnostic tools and more viable therapeutic intervention strategies [57, 64, 95, 102, 116–118].

**Conclusion**

Cracking the ‘sugar code’ offers a new post-genomic perspective with far-reaching implications. Although glycosylation is seldom featured in a general medical education, the tide is changing as an increasing number of clinicians and researchers are becoming acquainted with the field because it directly impacts patient diagnosis and care. Given this, and the novel perspective of using glycans/glycosylation inhibitors as possible therapeutics in pathological states, we can rest assured that the story of sugars and their impact on immunity is just starting.

### Rheumatology key messages

- Glycans are important to the development, regulation and progression of the disease.
- Analysis of glycans can provide insights into disease processes and cutting edge potential for the development of novel diagnostic and therapeutic interventions.
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