

Glycomarkers in parasitic infections and allergy

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Abstract

Both helminth infections and contact with allergens result in development of a Th2 type of immune response in the affected individual. In this context, the hygiene hypothesis suggests that reduced prevalence of parasitic infections and successful vaccination strategies are causative for an increase of allergies in industrialized countries. It is therefore of interest to study glycans and their role as immunogenic structures in both parasitic infections and allergies. In the present paper we review information on the different types of glycan structure present in proteins from plant and animal food, insect venom and helminth parasites, and their role as diagnostic markers. In addition, the application of these glycan structures as immunomodulators in novel immunotherapeutic strategies is discussed.

Introduction

In recent years, there is at least a popular belief that we are experiencing an 'epidemic' of allergic and autoimmune disease in developed countries, even in the young. On the other hand, we have a reduction in serious bacterial infections and decreased levels of helminth infestation, owing to increased hygiene, use of antibiotics and vaccination campaigns. Furthermore there seems to be a difference in occurrence of these 'modern' diseases in relation to Western lifestyles as opposed to those in rural farm-based or poorer post-Communist societies [1–3]. Such observations have led to the formulation of the so-called 'hygiene' or 'old friends' hypothesis. Accordingly the various improvements in combating human pathogens are seen as having their down-side: the human immune system, which evolved in the presence of countless invaders, has not come to terms with the lack of the previous adversaries and so targets itself against inappropriate targets such as (glyco)proteins in food, pollens, venoms or indeed 'self' antigens present in the human host (autoantigens) [4].

Among the 'old friends' of humankind, particularly helminths as parasitic invaders are, upon infection, manipulating the host immune system in order to facilitate reproduction, dispersal and survival over a longer period. As compared with some protozoal or bacterial infections, helminth infestation is generally associated with high morbidity and low mortality, although the weakening of the host is nevertheless sometimes apparent, e.g. with filarial nematodes. There is a good amount of scientific evidence to indicate that helminths, either as whole organisms or their ES (excretory–secretory)

products, have effects on mammalian immune systems. These multicellular parasites have evolved to occupy a diverse range of niches within their hosts using a wide-range of infection strategies, yet the hosts respond in a rather stereotypical manner. In the immune response against helminth parasites, mainly the Th2 cytokines, as well as high levels of polyclonal IgE and eosinophils, are involved [5]. Since mammals and parasites have co-existed and co-evolved, it seems not to be speculative to claim that the misdirected Th2 response in allergies was originally meant to combat worm-based infections.

Antigens and allergens

Before discussing the glycobiological aspects of parasites and allergy, we should consider a few definitions. An antigen is a foreign agent which induces an immune response against it, as evidenced by the presence of antibodies in the serum of an animal exposed or immunized with this agent. An allergen is also an antigen, but to which a specific IgE antibody-based response has occurred in sensitized individuals. Specific IgE antibodies present on the surface of mast cells recognize the specific allergen. After cross-linking of at least two different epitopes on the allergen by IgE antibodies, a signal transduction cascade is induced which results in the release of bioactive amines responsible for the allergic symptoms in the sensitized individual (see Figure 1). If an allergen-specific immune response has been established, homologous proteins from other sources can be recognized by the cross-reactive IgE antibodies. In some cases, the binding of cross-reactive IgE to allergens has been found to be affected by pre-treatment of the allergens with chemical agents, such as periodate or trifluoromethanesulfonic acid, which are known to alter or destroy carbohydrate structures; the relevant epitopes have, therefore, been named CCDs (cross-reactive carbohydrate determinants).

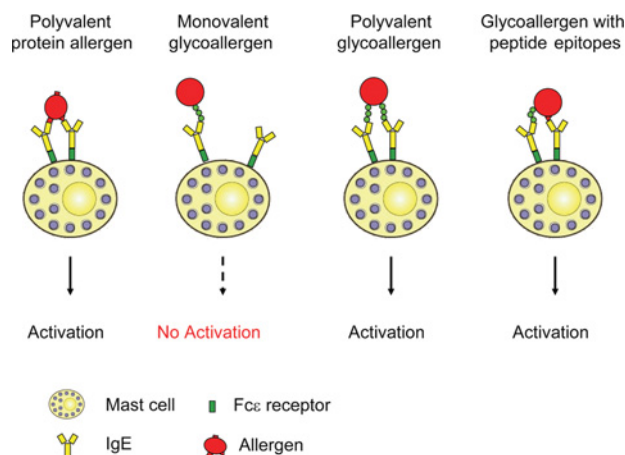
Key words: allergy, glycan, IgE, immune response, parasitic infection.

Abbreviations used: CCD, cross-reactive carbohydrate determinant; DC-SIGN, dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin; GalNAc, *N*-acetylgalactosamine; GlcNAc, *N*-acetylglucosamine; HRP, horseradish peroxidase; PC, phosphorylcholine.

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Figure 1 | Mast cell activation via cross-linking of the (glyco)allergen

Histamine release from the activated mast cell can only take place when two different epitopes are bound by IgE antibodies.



The immune response to glycans

In an adaptive immune response to proteins, the antigen is subject to processing by immunoproteasomes before presentation on the surface of an antigen-presenting cell, such as a dendritic cell. However, information regarding the exact mechanisms of the immune response to oligosaccharide structures is relatively scarce, although certainly O-glycopeptides can be presented in an MHC-dependent manner [6], and the polysaccharide portion of a glycoconjugate vaccine co-localizes with MHC class II molecules [7]. Studies on model N-glycosylated proteins would indicate that the oligosaccharide is removed before MHC presentation [8]; on the other hand, MHC-independent presentation is suggested to occur in the case of some glycoconjugates [9,10].

Presentation of an antigen is followed by proliferation of B-cells producing IgM. Another exposure to the antigen leads to the secondary response, which is typically accompanied by a class switch from IgM to IgG, IgA or IgE. Underlying this is a 'decision' for a Th1 or a Th2 response, the latter associated with IgE and IgG2 production. A Th2 response is also often induced by helminths and, indeed, this is related to higher levels of polyclonal IgE in the sera of mammals exposed to worms, as well as to production of a particular subset of cytokines [4,5]. In the case of *Brugia* and the model nematode *Caenorhabditis*, the Th2 response is apparently dependent on carbohydrate moieties [11]. Similarly, omega1, a glycoprotein from schistosome, is also a potent inducer of a Th2 response [12] and the involvement of the lectin DC-SIGN (dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin), a C-type lectin on the surface of dendritic cells, in the Th2 response to the peanut allergen Ara h 1 has also been shown [13].

When considering the immunogenicity of carbohydrates, it is unfortunate that much of our immunological knowledge stems from work on mice and that typical strains used, such as C57BL/6 or BALB/c, have an intrinsic bias towards Th1

or Th2 responses; indeed, BALB/c mice have a poor response to glycoprotein antigens [14,15]. Therefore it is noteworthy that many of the anti-glycan antibodies commonly used as reagents are polyclonals from rabbits or monoclonals from rats. In the context of human responses to glycans, allergic reactions in patients treated with monoclonal antibodies were found to be due to IgE recognizing the Gal α 1,3Gal non-reducing terminal modification of N-glycans on the antibodies produced from a hybridoma cell line [16]. Also α -galactosylation of cat IgM and IgA has been reported to induce IgE sensitization in humans [17]. In terms of the IgE response, non-mammalian glycans, core α 1,3-fucosylated N-glycans are recognized by the IgE in the sera of sheep infected with *Haemonchus contortus* [18], as well as by patients allergic to honeybee venom [19].

Chemical structures of glycans of allergens and parasites

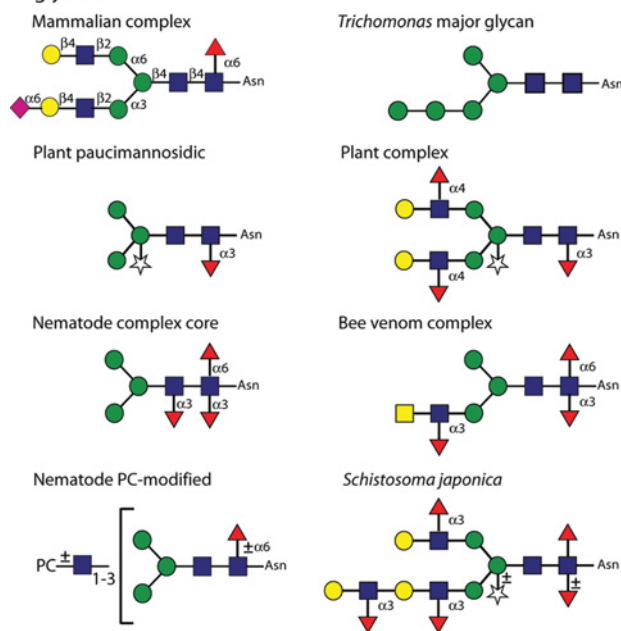
An aspect where molecular allergology and parasitology certainly meet is in the nature of the N-linked oligosaccharides of allergens and of parasites. Over the years, the N-glycans of a number of plant and venom allergens have been examined. A recurring structural theme is the presence of core α 1,3-fucose, i.e. the attachment of fucose in an α 1,3-linkage to the reducing-terminal (innermost) GlcNAc (N-acetylglucosamine) residue (see Figure 2). This type of fucose modification is absent from vertebrates, but also present in invertebrates (e.g. insects and nematodes) and slime moulds [20]. In animals, though, there is an alternative fucose modification of the core, the α 1,6-linkage. Therefore invertebrate glycoproteins can carry a double fucosylation of the reducing-terminal GlcNAc. As core α 1,3-fucosylation is absent from vertebrates, it is seen as being foreign and antibodies recognizing this element are known, in particular, rabbit antisera raised against HRP (horseradish peroxidase) recognize this structural feature of plant and invertebrate glycoproteins; in the case of insects, this epitope is found on venom glycoproteins, including known allergens such as honeybee phospholipase, as well as in insect neural systems [20].

Another element recognized by anti-HRP is the modification of the β 1,4-linked core mannose by xylose; the addition of xylose to N-glycans is also a widespread feature of plant allergen glycans often in combination with core α 1,3-fucose as, e.g. on the celery allergen Api g 5 or the orange allergen Cit s 1 [21,22]. Both the core α 1,3-fucose and β 1,2-xylose residues are recognized by IgE in the sera of allergic patients [22]. Xylose is also present on the N-glycans of trematode (but not nematode) parasites such as *Schistosoma mansoni* [23]. In addition, schistosomes express a range of glycans carrying Le^x structures, which are recognized by DC-SIGN [24] and may play a role in how schistosomes cause a bias towards the Th2 response [25]. A structural isomer of Le^x, known as Le^a, is also present on some plant glycoproteins such as the cypress pollen allergen Cup a 1 [26].

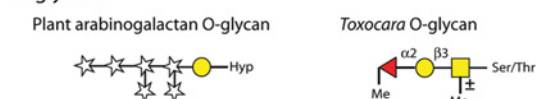
Figure 2 | Examples of glycans from mammalian hosts, from plant and insect allergens and from parasites

Glycans are depicted according to the nomenclature of the Consortium for Functional Glycomics: squares represent HexNAc residues (yellow for GalNAc and blue for GlcNAc), circles represent hexose (green for mannose and yellow for galactose), red triangles represent fucose, white stars represent pentoses (xylose and arabinose) and purple diamonds represent sialic acid. The plant complex glycan is depicted with antennal Le^a epitopes (α 1,4-fucose) and the schistosomal glycan is depicted with antennal Le^x epitopes (α 1,3-fucose).

N-glycans



O-glycans



Another structural element found on N-glycan antennae in some parasites is PC (phosphorylcholine) attached to non-reducing terminal GlcNAc residues [27]; this epitope is present in cestodes (tapeworms) and nematodes (roundworms), as well as on the lipopolysaccharide of some bacteria. PC is also present on a protein with known immunomodulatory properties, the ES-62 of *Acanthocheilonema viteae* which mediates its effects through TLR (Toll-like receptor) 4 [28]. On the other hand, in protozoal species, it is common that the N-glycan biosynthesis pathway has 'lost' certain components, such as mannosyltransferases, required to produce a normal Glc₃Man₉GlcNAc₂ precursor; the result is the presence of truncated N-glycans (or even none) ranging from one or two GlcNAc residues in *Plasmodium falciparum* through to Man₅GlcNAc₂ structures in *Trichomonas vaginalis* [29].

In contrast with the similarities of plant and invertebrate N-glycans, the O-glycans are completely different and are in

any case based on diverse core structures. In the case of plant allergens, the only O-glycans to be analysed originate from mugwort and ragweed; these contain galactose and arabinose residues linked to hydroxyproline [30,31]. Thus these structures are unlike the so-called 'mucin-type' O-glycans of animals which are based on the modification of serine or threonine by GalNAc (*N*-acetylgalactosamine). Descriptions of parasite O-glycans are rare, but the methylated and fucosylated O-glycans of *Toxocara* have been analysed and are also targets of the immune response in infected hosts [32].

In animals, another important set of glycoconjugates are the glycolipids. Owing to the presence of PC, the glycolipids of nematodes are of immunological relevance and have been analysed from a number of species, including *Ascaris suum* [33]. Different virulence-relevant glycolipid molecules are present on the surfaces of various protozoal species such as lipophosphoglycans in trypanosomatids and trichomonads or the lipopeptidophosphoglycans in *Entamoeba histolytica* [34].

Diagnostic approaches

The routine *in vitro* diagnosis of allergy is centred on the determination of IgE in serum, whereas in cellular assays such as the basophil degranulation test, the biological activity of the specific immune response is determined [35]. Whether glycan-based epitopes are truly inducing allergic symptoms in sensitized patients or are only able to bind cross-reactive IgE antibodies is one of the crucial questions/problems posed in refined allergy diagnosis. To identify truly relevant IgE binding components, the recent development of an allergen chip carrying both recombinant and native allergens is a valuable tool aiding definition of the original sensitizing agent. In particular, the highly identical or similar carbohydrate structures that are present across the plant kingdom give rise to clinically irrelevant cross-reactivity (the CCDs mentioned above). Examples are the IgE reactivity to glycoproteins from pollens, latex, plant food and hymenoptera venoms [36]. On the other hand, the aforementioned plant-type O-glycans identified from the major mugwort pollen allergen, Art v 1, seem to contribute significantly to the overall allergenic activity of the protein [30].

Regarding parasitic infections, there are some examples of serological diagnoses based on glycans. For instance, the sera from patients infected with *Echinococcus* recognize the Gal β 1,6Gal epitope found on glycolipids from a number of cestode (tapeworm) species [37], whereas a glycan-based ELISA for detecting antibodies against *Trypanosoma cruzi* has been proposed [38]. In terms of actual 'glycomarkers', glycans derived from schistosomes are excreted and can be detected in the urine of infected patients [39].

Immunoprophylaxis and glycan-mediated therapy

When considering the potential impact of our knowledge about parasites in connection to our knowledge about

allergies and autoimmune diseases, it is naturally interesting to relate various phenomenological data to the hygiene hypothesis. Following the promising results of crude therapies based on administering nematode eggs to patients with Crohn's disease and ulcerative colitis [40,41], similar approaches have been started for immunotherapy of allergies; in the latter case, the results are yet to be proven conclusive [42–44]. In these studies neither the active agents have been identified nor their glyco-relevance or glyco-irrelevance studied, although it is known that nematodes can secrete, e.g. lectins capable of interacting with the host [45]. Indeed, if we consider the preventive impact of the hygiene hypothesis, predominantly Gram-negative bacterial strains and their compounds have been the focus of various trials [46]. In particular, distinct carbohydrate components have been tested for their immune-modulating capacity [47]. Once the preventive effect of certain non-toxic bacteria or their compounds is proven, these could be provided as food additives to the daily diet in order to reduce the risk of the onset of an allergic disease.

In the case of parasitic diseases, especially those of live-stock, a common problem has been the inability to induce a response to recombinant parasite proteins, which indicates a role for the native glycosylation in the immune response during vaccination [48]. Therefore production of vaccine targets as well as of immunomodulatory proteins, such as the aforementioned ES62, displaying the correct glycosylation, presents an important future goal. Other potential avenues for 'glycan-based' therapy of nematode infections include the glycolipid-mediated sensitivity of nematodes to the Cry5A crystal toxin [49] or the nematotoxic action of a fungal galectin recognizing galactosylated core α 1,6-fucose on worm N-glycans [50].

Conclusion and perspectives

The wide phylogenetic distribution of many glycan structures foreign to mammals creates a problem if one wishes to use glycan-based markers for disease: thereby anti-glycan antibody cross-reactivity complicates *in vitro* diagnosis. On the other hand, common structures in a number of species present potential wide-spectrum therapeutic targets for parasitic infections. However, in order to make progress, a number of questions should be answered, including: (i) what is the biological significance between the common aspects, e.g. IgE and Th2 bias, of the response to allergens and to helminths; (ii) what is the 'gain' to the parasite by skewing the immune response; and (iii) what is the actual role of glycosylation in these processes? By understanding better the response to both helminths and allergens, we may be able not just to cure parasitic diseases and tackle the often low success of vaccination against other infectious agents in helminth-infected individuals, but to exploit the immunomodulatory strategies of these organisms in order to combat allergies and autoimmune diseases.

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