1. Introduction

The immune system discriminates self from non-self and eliminates particles carrying such non-self determinants. Pathogens can evade immune recognition either by masking non-self antigens and/or by disguising with host self-antigens through molecular mimicry. However, some pathological conditions present altered-self determinants that cause breach of tolerance and lead to rejection through an autoimmune response. Cell surface glycosylation is universal to all living cells and strategically positioned to mediate such immune recognition processes.

Carbohydrate chains (glycans) that decorate glycoproteins and glycolipids (glycoconjugates) on the cell surface hold tremendous structural diversity. In vertebrates, glycans usually terminate with sialic acids (Sia) that function as markers of normal self and can be recognized by a variety of receptors (e.g., Siglecs) mediating inter- and intra-cellular communication. Cancer cells commonly present altered cell surface glycosylation, especially manifested in the expression of sialic acid at the termini of glycolipids and glycoproteins. Although tumor-associated carbohydrate antigens (TACAs) result in expression of altered-self, most such carbohydrates do not elicit strong humoral responses. Various strategies have been devised to elicit increased immunogenicity of such TACA aiming for potent immunotherapeutic antibodies or cancer vaccines. However some carbohydrates are immunogenic in humans and hold potential for novel glycotherapies. N-Glycolyneuraminic acid (Neu5Gc) is a foreign immunogenic sugar in humans originating from the diet (e.g., red meat) and subsequently expressed on the cell surface, especially accumulating on carcinoma. Consequently, the human immune system detects this non-self carbohydrate generating a broad anti-Neu5Gc antibody response. The co-existence of Neu5Gc/anti-Neu5Gc within humans spurs chronic inflammation mediated disease, including cancer. Concurrently, anti-Neu5Gc antibodies hold potential for novel targeted therapy. αGal is another foreign immunogenic carbohydrate antigen in humans and all humans have circulating anti-Gal antibodies. This review aims to describe the immunogenicity of Neu5Gc and its implications for human diseases, highlighting differences and similarities with αGal and its potential for novel targeted theranostics.

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immunogenicity, at least in animals. However, although several promising TACA-based cancer vaccines have entered clinical trials (including in Phase III), none have been approved for clinical use yet. Most tested vaccines failed in clinical trials mainly due to the lack of a robust T cell-mediated immunity and/or lack of survival benefit for patients. Importantly, many of the new strategies that trigger much stronger immune responses have not yet been tested in humans.

αGal is a foreign immunogenic carbohydrate antigen in humans due to a specific gene inactivation, and all humans have circulating anti-Gal antibodies that could potentially be used for immunotherapy if the antigen had been present on the target cells. αGal was used to generate autologous tumor-vaccines by incorporation of this xenogenic carbohydrate antigen through intra-tumoral injection of αGal glycolipids. This proved to then tag the cells for destruction by complement-mediated cytotoxicity (CDC) and by antibody-dependent cellular cytotoxicity (ADCC) following anti-Gal binding to the αGal epitopes de novo expressed on the tumor cells in mice. Another potent approach to increase tumor immunogenicity was to metabolically engineer cells to express unnatural TACA analogues followed by treatment with antibodies specifically generated against these unnatural carbohydrates that could promote CDC in vitro, though evidence for therapeutic efficacy in vivo is still pending.

However, recent research suggests that such metabolic engineering with a foreign carbohydrate actually occurs in humans through dietary consumption of N-Glycoly neuraminic acid (Neu5Gc) that accumulates on carcinoma and also provokes an immune response in humans. (Neu5Gc) that accumulates on carcinoma and also provokes an immune response in humans. This breakthrough allowed to generate a wide collection of sialosides that was further affinity-purified and extensively characterized as a Neu5Gc-containing ganglioside (Neu5Gc-GM3, Neu5Gc-GM1). Subsequently HD-antigens were defined in the late 1970s as a Neu5Gc-containing glycosidase (Neu5Gc–GM3, Neu5Gcα2,3Galβ1-4Glcβ1-1Ceramide) that was further characterized and implications for cancer and other human diseases, emphasizing its potential for novel targeted therapeutics (therapy and diagnostics). In addition, the differences and similarities between the immunogenic sugars αGal and Neu5Gc will be highlighted.

2. Sialic acid diversity

Sialic acids (Sias) are a diverse family of ~50 alpha-keto aldiconic acid carbohydrates with a nine-carbon carboxylated backbone, found predominantly as the terminal units on glycans and glycoconjugates in vertebrates. Sia diversity arises from various modifications at either the C5-amino group (with acetyl or glycolyl) or the hydroxyl groups at C4, C7, C8, and C9 by acetate, lactate, sulfate, or phosphate esters by methyl ethers. The two most common Sias in mammals are N-Acetylgalactosaminic acid (Neu5Ac) and its hydroxylated form N-Glycoly neuraminic acid (Neu5Gc), as described in Figure 1. Overall sialglyconjugate diversity results from Sia-modification, linkage to underlying sugars and their composition, the conjugated scaffold (protein/polymer), the glycan mode of attachment (e.g., O/N-linked to proteins), and finally their spatial organization (density).

3. Recent advances in the synthesis of sialic acid derivatives

Chemical sialylation was one of the most challenging glycosylation reactions in the past largely due to low yields, poor stereo-selectivity, and difficulties in product purification. Recent advancements in chemical and especially chemoenzymatic synthesis provided chemically well-defined and structurally homogeneous sialic acid-containing glycan s (sialosides). The newly developed chemical ‘one-pot glycosylation’ reaction allowed direct sequential assembly of monosaccharides into glycans in the same reaction flask without intermediates isolation. However, this approach remains impractical in generating sialosides, especially for certain Sia-derivatives that are labile to the final deprotection steps. Importantly, subsequent development of a highly efficient one-pot multiple-enzyme (OPME) system allowed the chemoenzymatic synthesis of naturally occurring and non-natural sialosides. This approach exploits the high regio-selectivity, chemo-selectivity, and stereo-selectivity of enzymes with the flexibility and diversity of chemical synthesis to achieve an efficient synthesis of such complex carbohydrates.

4. Hanganutziu–Deicher (HD) antigens and antibodies

Almost a century ago human ‘heterophile’ antibodies had been noticed and later on suggested to recognize Neu5Gc-antigens. In the 1920s Hanganutziu and Deicher independently noticed that injection of horse antiserum (e.g., to tetanus toxin or diphtheria) into humans caused ‘Serum-sickness’ with allergy-like symptoms due to hemagglutinins. These human ‘heterophile’ antibodies later named Hanganutziu–Deicher (HD)-antibodies could agglutinate animal erythrocytes from many species, except human and chicken. Such antibodies were then detected in patients who had never been exposed to animal sera, including patients with various inflammatory or infectious conditions and cancer (reviewed in ). Subsequently HD-antigens were defined in late 1970s as a Neu5Gc-containing ganglioside (Neu5Gc-GM3, Neu5Gcα2,3Galβ1-4Glcβ1-1Ceramide) or Neu5Gc-containing glycoprotein. However, these early studies used crude methods for detection of the HD-antigens or HD-antibodies, apparently assuming that normal human antibodies are negative. With the advent of modern glycochemistry tools detection of Neu5Gc-antigens and anti-Neu5Gc antibodies had been extensively revisited providing compelling evidence for their presence not only in patients but also in healthy individuals, followed by investigation of their implications for various human diseases, as described below.

5. Neu5Gc in human tissues

5.1. Neu5Gc in healthy humans

Healthy human tissues had been inspected in the past by various chromatographic and immunochemical techniques for detection of Neu5Gc, however those failed to provide unequivocal chemical evidence for its presence or failed to detect it at all. The expression of this sialic acid had been recently re-examined mainly by highly characterized antibodies to Neu5Gc-containing antigens, HPLC, and finally mass-spectrometry (Table 1). Vari and colleagues had generated a highly sensitive polyclonal chicken anti-Neu5Gc antibody (chickens immunized with GM3( Neu5Gc)) that was further affinity-purified and extensively characterized by various protocols (e.g. ELISA, Western blot, flow cytometry, immunohistochemistry, and glycans microarray) demonstrating broad monospecificity to various Neu5Gc-containing glycoconjugates. Immunohistochemistry staining with this
chicken anti-Neu5Gc IgY established for the first time the presence of low levels of Neu5Gc mostly in epithelium and endothelium in normal human tissues. 

31,146 Neu5Gc was detected on blood vessels endothelium and epithelium or secretory epithelia cells of lung, skin, colon, prostate, uterus, kidney, spleen, pancreas, liver, and fetal stomach. 

31,146 In addition, normal human placenta and most normal human tissues (either frozen or paraffin sections) consistently showed staining of blood vessels endothelium, and sometimes also of the glandular epithelial cells of breast, luminal edge of colonic mucosal epithelial cells, crypt epithelium of small intestine, some glandular epithelium of prostate, kidney glomeruli and interstitial capillaries, and lung bronchial epithelium. 

Another well-characterized antibody is the 14F7 murine monoclonal IgG1 antibody generated by immunizing mice with GM3(Neu5Gc) hydrophobically conjugated with very low-density lipoproteins (VLDL). 

16 This antibody was shown to be highly specific for the ganglioside GM3(Neu5Gc) without cross-reactivity with GM2(Neu5Gc) or their Neu5Ac-counterparts or a sulfated glycolipid. 

16,135 This antibody stained kidney and ovary normal tissue samples, but did not stain testis, prostate, and bladder. 

6 However, in addition to membrane staining, this antibody could also strongly stain the cytoplasmic region of breast malignant tumor cells suggesting it may also recognize other antigens, likely Neu5Gc-containing glycoproteins. 

16 It is worth noting that 14F7 had largely been tested in the presence of animal products (i.e. BSA) that are likely contaminated with Neu5Gc-antigens and therefore may reduce its efficacy. 

126 Nevertheless, specificity of anti-carbohydrate antibodies may be ambiguous, 

101 therefore conclusive evidence for the presence of Neu5Gc finally came from other detection methods. A highly sensitive HPLC was able to detect Neu5Gc at 1–3% of the total Neu5Ac in human liver, spleen, heart, and testis, 

110 and this was later also confirmed by mass spectrometry analysis of glycopeptides and some glycolipid fractions from human kidney, heart, liver, and spleen. 

5.2. Neu5Gc in cancer patients

In contrast to the limited evidence for the presence of Neu5Gc in normal human tissues, its presence on various cancers had been widely described (reviewed in Ref. 99; Table 1). Neu5Gc was detected by immunofluorescence on breast, colorectal, nasopharyngeal, uterine, leukemia, and malignant lymphoma, 

66 as well as in ovary, pancreas, embryonal, adenoidocystic, and teratoma. 

66 By thin-layer chromatography (TLC) immunostaining, Neu5Gc was detected in colon, 

62,69,106 melanoma, 

68,81 retinoblastoma, 

67 yolk sac tumor, 

105 and breast carcinoma. 

66 When using immunohistochemical methods, Neu5Gc was detected in colon, 

160 embryonal carcinoma, teratocarcinoma, choriocarcinoma, yolk sac tumor, 

105 melanoma, 

16,138 and breast. 

16,146 In addition, chemical analysis of cancer samples showed Neu5Gc in chondrosarcoma, 

21,146 gastric, 

16,146 liver, 

16,146 malignant lymphoma, 

16,146 breast, 

55,102, and uterine. 

102 More recently, the highly specific polyclonal chicken anti-Neu5Gc IgY 

11,124,146 was shown to detect Neu5Gc in most breast tumor cells and related blood vessels, 

46 as well as in melanoma and neuroblastoma. 

11 Moreover, malignant ovarian carcinoma showed staining of the tumor itself together with their angiogenic blood vessels. 

11 Neu5Gc was also detected by histochemical staining of non-small cell lung cancer with 14F7 monoclonal antibody. 

149 Using HPLC, Neu5Gc was detected in ovarian, breast, and pancreatic cancers at 1–4% of the total sialic acids, which is a higher

Table 1

<table>
<thead>
<tr>
<th>Human Tissue</th>
<th>Normal</th>
<th>Cancer</th>
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<tbody>
<tr>
<td>Brain</td>
<td>A,16,31</td>
<td>A,16,65,102,144,146, H,56, MS102</td>
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<tr>
<td>Breast</td>
<td>A,11,146</td>
<td>A,32,66</td>
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<td>Colon/colorectal</td>
<td>A,146</td>
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<tr>
<td>Fetal stomach</td>
<td>A,146</td>
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<tr>
<td>Gastric</td>
<td></td>
<td>MS62</td>
</tr>
<tr>
<td>Heart</td>
<td>H110,146, MS545</td>
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</tr>
<tr>
<td>Kidney</td>
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</tr>
<tr>
<td>Intestine</td>
<td>A,11,146</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>A,146, H110,146, MS146</td>
<td>MS62</td>
</tr>
<tr>
<td>Lung</td>
<td>A,146</td>
<td>A,16,149</td>
</tr>
<tr>
<td>Ovary</td>
<td>A,146</td>
<td>A,71, H54</td>
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<tr>
<td>Pancreas</td>
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<td>H10</td>
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<tr>
<td>Placenta</td>
<td>A,11,146</td>
<td></td>
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<tr>
<td>Prostate</td>
<td>A,146</td>
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<tr>
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</tr>
<tr>
<td>Spleen</td>
<td>A11,146, H110,146, MS146</td>
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</tr>
<tr>
<td>Testis</td>
<td>A,146</td>
<td>H10, MS146</td>
</tr>
<tr>
<td>Uterus</td>
<td>A,146</td>
<td>A96, MS10</td>
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<tr>
<td>Chondrosarcoma</td>
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<tr>
<td>Leukemia</td>
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<tr>
<td>Malignant lymphoma</td>
<td>A96, MS52</td>
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<tr>
<td>Nasopharyngeal</td>
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<tr>
<td>Neuroblastoma</td>
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<td></td>
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<tr>
<td>Retinoblastoma</td>
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<td></td>
</tr>
<tr>
<td>Teratoma</td>
<td>MS51</td>
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</tbody>
</table>

Most reports used chicken antibodies (A) recognizing Neu5Gc-containing antigens for immunohistochemistry or immune-staining of TLC, while only few used HPLC (H) or mass spectrometry (MS).
6. Circulating anti-Neu5Gc antibodies in humans

6.1. Anti-Neu5Gc antibodies in healthy individuals

The advent of modern chemoenzymatic synthesis of various sialoglycoconjugates allowed revisiting claims of lack of anti-HD antibodies in healthy humans.127 Using chemically defined sialoglycans it was shown that all normal humans have circulating anti-Neu5Gc antibodies.115,127,146,174 Furthermore, the extent of response seemed to reflect the diversity and complexity of sialoglycans revealing a broad and variable spectrum of anti-Neu5Gc antibodies (Fig. 3).127 These anti-Neu5Gc antibodies constituted IgM, IgA, and most commonly IgG15,127 that ranged at ~0.1–0.2% of total Igs (ranging at 0.1–23 μg/mL) against several potential targets.127 These antibodies could be affinity-purified from individual human sera or from pooled human IgG and showed that they could specifically bind to human carcinomas that had accumulated Neu5Gc in vivo.27,127 Furthermore, it was demonstrated that anti-Neu5Gc IgM and IgG arise in infants at 6 months, soon after the introduction of Neu5Gc in the diet (e.g., cow’s milk formula and baby foods containing red meat), and are likely induced via dietary-Neu5Gc uptake by commensal bacteria.148 This response can further be enhanced in certain pathological conditions125,141 and can sometimes remain high for over 30 years.141 Hence, like a ‘Trojan horse’, Neu5Gc metabolically incorporates into human cells as ‘self’ but then becomes presented on the cell surface in the context of novel ‘non-self’ antigens thus termed ‘xeno-auto-antigens’ and ‘xeno-autoantibodies’.127

6.2. Implications of anti-Neu5Gc antibodies in cancer

6.2.1. Low dose anti-Neu5Gc antibodies in tumor progression

Several epidemiological studies suggested a connection between certain dietary foods (e.g. red meat) with an increased risk of chronic diseases including cancer.128,136,147,163,173 Thus the co-existence of Neu5Gc with circulating anti-Neu5Gc in vivo prompted investigation of their contribution to pathological outcomes, especially in light of the numerous reports on their detection in cancer.99,114 The effect of anti-Neu5Gc antibodies on tumor growth was tested in the Neu5Gc-deficient (Cmah−/−) mouse model. When these mice were injected with Neu5Gc-positive tumors and then treated with low dose anti-Neu5Gc antibodies (either anti-Neu5Gc mouse serum or affinity-purified human anti-Neu5Gc IgG) the resulting tumors grew larger compared to the control treated mice.128 The enhanced tumor growth was suppressed by an anti-inflammatory treatment suggesting the effects were mediated by chronic inflammation and this notion was further supported by the detection of infiltration of inflammatory cells.58 This had suggested that the co-existence of Neu5Gc with circulating anti-Neu5Gc antibodies might serve as the missing molecular link between diet and cancer risk.128 Likewise, dietary Neu5Gc was shown to incorporate into human endothelium whereby anti-Neu5Gc antibodies could induce complement deposition and endothelial activation, suggesting they can initiate, propagate, and/or exacerbate an inflammatory response at the endothelium, potentially playing a role in vascular inflammation disease states such as atherosclerosis.130 Together, these findings implied a novel disease concept in which chronic inflammation-mediated disease is induced by a metabolized dietary-sugar that also stimulates an immune response.58 It was also later supported by follow up studies in humans facilitated by the development of a specialized sialylglycan-microarray with multiple Neu5Gc/- Neu5Ac-glycans.123 This array allowed high-throughput screening of anti-Neu5Gc IgG responses in sera samples of cancer versus non-cancer patients and led to discovery of the novel antibody carcinoma biomarker, anti-Neu5Gc-Sialyl-Tn IgG.127 Neu5Gc-Sialyl-Tn resembles the well-known cancer-associated carbohydrate antigen Sialyl-Tn (STn), only that Neu5Gc replaces Neu5Ac at the terminal position.112 Further longitudinal population studies are required to establish anti-Neu5Gc antibodies as potential biomarkers for increased risk of cancer and other chronic inflammation mediated diseases. Recently, a novel method for detection of the total polyclonal anti-Neu5Gc antibodies response was developed and may facilitate high-throughput screening of human sera samples for such high-throughput studies.125

6.2.2. High dose anti-Neu5Gc in tumor regression

Incorporation of Neu5Gc into cancer cells results in modification of the cell surface glycans resulting in a representation of an altered-self pattern. Anti-Neu5Gc antibodies could potentially recognize these unique neo-markers on cancer cells and therefore
7. Clinical potential of anti-Neu5Gc antibodies

Neu5Gc-glycoconjugates have been investigated as potential cancer vaccines, especially targeting gangliosides (sialylated glycolipids). Certain gangliosides (e.g. GM2 and GM3) are over expressed in cancer. These gangliosides can metabolically replace Neu5Ac with Neu5Gc and it was reported that GM2(Neu5Gc) ganglioside is found at high levels in several cancers and can be further increased by hypoxia-induced transcription of a sialic acid transporter. Similarly, GM3(Neu5Gc) was described as a cancer-associated antigen and potential therapeutic target and cancer vaccine.

Currently there are two clinical trials targeting GM3(Neu5Gc): (i) The antibody 1E10, commercially known as Racotumomab, is a monoclonal antibody that is used as a cancer vaccine. This is a murine monoclonal antibody (IgG1, k), which was obtained from BALB/c mice immunized with the purified P3 antibody (murine monoclonal IgM, k, that reacts specifically with a wide range of Neu5Gc-gangliosides, sulfated glycolipids, and with antigens expressed in human breast tumors) coupled to KLH (Keyhole Limpet Haemocyanin) in Freund's adjuvant. Thus, Racotumomab is an anti-idiotypic antibody reflecting a mirror image of the P3 antibody and is currently being tested in a randomized, controlled Phase II/III clinical trial.

There is compelling evidence that Racotumomab can elicit a strong humoral and cellular immune response that has a positive impact on patient's survival. However, since the P3 antibody is of broad specificity it is possible that Racotumomab may not be strictly reflecting GM3(Neu5Gc). (ii) The alternative vaccine is liposome-based, in which GM3(Neu5Gc) was incorporated into very small-sized proteoliposomes (VSSP) derived from Neisseria meningitides (also known as NeuGcGM3/VSSP). Patients treated with this vaccine showed benefit in progression free survival and overall survival. This vaccine seems to be safe with presumable specific humoral and cellular immune responses in patients and is currently being further investigated in Phase III clinical trials.

Another clinical aspect of anti-Neu5Gc antibodies involves glycosylation of biotherapeutics. Neu5Gc can be presented on clinically-used biotherapeutic glycoproteins (e.g., antibodies, inhibitors, cytokines etc.), likely due to usage of non-human mammalian cell lines and/or the addition of animal-derived tissue culture supplements during their production. In a Neu5Gc-deficient mouse model (Cmah−/−), it was shown that when Neu5Gc-biotepeutics is given to mice who have circulating anti-Neu5Gc antibodies, immune complexes are generated mediating clearance of the drug and resulting in reduction of its effective concentration and efficacy. This is likely also relevant in humans and may possibly explain common variability in efficacy of glycosylated-biotherapeutics. Consequently, if a patient that has circulating anti-Neu5Gc antibodies is treated with Neu5Gc-biotherapeutic the drug's efficacy might decrease. Similarly, anti-Neu5Gc antibodies may be involved in rejection of human cells prepared for allo-transplantation and auto-transplantation if those were grown in animal-derived tissue culture supplements. Finally, these effects are likely to vary between individuals reflecting the extent of the anti-Neu5Gc response as demonstrated by the antibodies level, recognition pattern, specificity, and isotype. Therefore, screening of patients for anti-Neu5Gc response should be considered as a variable for personalized-therapy. Recently, a simple method to screen for the overall anti-Neu5Gc response had been developed and may facilitate patient evaluation prior to selection of therapy.

8. Immunogenic alpha-Gal (αGal) xenoantigen in humans

In addition to Neu5Gc, another immunogenic sugar antigen in humans is the αGal that had been thoroughly investigated by Galili and colleagues. αGal shares some common features with Neu5Gc however there are some major differences in other critical aspects as highlighted in Table 2. While Neu5Gc can be found conjugated to multiple glycan to generate a collection of antigens on human cells, the αGal epitope is a unique tri-saccharide...
Galα1-3Galβ1-4GlcNAC-R that is never presented on human cells. This oligosaccharide can be found at the terminal end of glycoproteins and glycolipids on most mammalian cells except in old world monkeys, apes, and humans. This loss results from a single base deletion leading to frameshift and a premature stop codon in the α1-3GT encoding gene (GGTA1) (Table 2). Therefore αGal is immunogenic in all mammals that consequently have circulating anti-Gal IgM, IgA, and IgG with the latter reaching up to 1% of the total serum IgG. Unlike Neu5Gc, αGal cannot be acquired through the diet and it is not expressed on human tissues, yet the high titers of anti-Gal antibodies are due to a continuous stimulation of the gastrointestinal tract by αGal-presenting bacteria such as Klebsiella pneumoniae and Escherichia coli. The co-existence of Neu5Gc/anti-Neu5Gc within humans has clear implications for diseases as described. While αGal/anti-Gal do not normally co-exist in humans, there are certain situations when this does occur and lead to disease conditions. For example, the high anti-Gal titers are an obstacle to xenotransplantation due to expression of αGal in the donor tissues (e.g. pig-to-human) because the anti-Gal antibodies react with the αGal epitope which leads to hyperacute rejection of the graft. This has been described as the anti-Gal/αGal barrier and it prompted the generation of pigs that lack the αGal. Recently, Neu5Gc had also been suggested to negatively affect xenotransplantation. In addition, high titers of anti-Gal antibodies might mediate autoimmune-like responses when an invading pathogen expresses αGal, for example in Chagas disease caused by Trypanosoma cruzi that present multiple αGal epitopes on glycosylphosphatidylinositol and lipophosphoglycans on its cell membrane. On the other hand, the abundant anti-Gal antibodies in humans could be harnessed for therapy that is in cancer therapy or wound healing. To conclude, αGal and Neu5Gc are two immunogenic carbohydrate moieties in mammals that can be used to study potent immune recognition and responses to carbohydrates that are essential for development of novel theranostics.

9. Summary and outlook

This review aimed to provide an overview of immune recognition and response to carbohydrate antigens focusing on the non-human sialic acid Neu5Gc and its unique features compared to the immunogenic αGal. Sialic acids are highly diverse and recent progress in sialolectins chemoenzymatic synthesis was key for in depth investigation of their various biological roles. This was especially critical to address a century old hypothesis on the role of Neu5Gc in cancer and other diseases in humans. The new glyco-biological tools revealed a complicated immune response to diverse Neu5Gc-glycoconjugates that may contribute to chronic inflammation mediated diseases in humans but at the same time holds great promise for designing novel theranostics. Further investigation of the mechanisms allowing immune response to such carbohydrate antigens is critical for rational design of various carbohydrate-based vaccines including cancer vaccines and other novel therapeutic strategies.

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