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Review article

Immunogenic and cross-reactive carbohydrate determinants in ticks and other arthropods

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Abstract

Ticks are parasites that feed on the blood of humans and animals, using it as their sole source of food. Due to their lifestyle, ticks at each life stage transmit various tick-borne pathogens while feeding on their hosts. Unlike mosquitoes – another important group of pathogen-transmitting arthropods – ticks can feed on the same host for prolonged periods, which underscores the importance of tick mechanisms that inhibit or reduce the host's defence mechanisms and, consequently, allow the transmission of pathogens. This unique tick-host-pathogen triangle requires the involvement of various tick molecules to mediate interactions with both host and pathogen molecules at multiple levels. This review highlights the glycan molecules identified in various tick species that can trigger an immune response and thus primarily affect the interaction with the host.

As the enzymes involved in Golgi-mediated glycan maturation differ between ticks, insects, and their vertebrate hosts, these differences contribute to the glycan profiles observed in ticks. These differences in glycan structures influence the interactions ticks have with their hosts and pathogens. On one hand, they may participate in molecular mimicry and mechanisms that lower the host's immune reaction, blood clotting, and other defence mechanisms due to their different structures, but on the other hand they may also trigger the host's defence mechanisms, such as participating in delayed red meat allergy and facilitating the transmission of pathogens.

Tick glycobiology remains largely unexplored and deserves more attention, especially considering the potential of glycans and glycoproteins as targets for anti-tick vaccines.

Keywords: α1,3-core fucose; αGal; β1,2-xylose; N-glycolylneuraminic acid; Tick

Highlights:
- Tick glycans shape key interactions within the tick-host-pathogen triangle.
- Tick-specific glycans can modulate or trigger host immune and defence responses.
- Some tick glycans contribute to red-meat allergy/α-Gal syndrome.
- Tick glycobiology offers promising targets for next-generation anti-tick vaccines.

Abbreviations:
α-Gal – Galactose-alpha-1,3-galactose epitope; AGS – α-Gal syndrome; CCD – cross-reactive carbohydrate determinant; CMP – cytidine monophosphate; Fuc – fucose; Gal – galactose; GalNAc – N-acetylgalactosamine; GlcNAc – N-acetylglucosamine; HRP – horseradish peroxidase; MALDI TOF-TOF – Matrix-Assisted Laser Desorption/Ionization Time-of-Flight/Time-of-Flight; Man – mannose; Neu5Ac – N-acetylneuraminic acid; Neu5Gc – N-glycolylneuraminic acid; SG – salivary gland; Xyl – xylose

Introduction

Ticks are blood-sucking ectoparasites that transmit pathogens harmful to humans and livestock. The complex interactions between the transmitted pathogens, ticks, and their hosts require these parasites to produce various immunologically active molecules that influence the dynamics between the tick and its host, as well as between the tick and its tick-borne pathogens. Most interactions are mediated by proteins; however, protein-bound glycans in ticks may influence allergic responses, pathogen transmission, and modulation of the host immune system. In addition, some glycan moieties can trigger host immune responses due to shared structural motifs with other allergens, referred to as cross-reactive carbohydrate determinants (CCDs) (Aalberse et al., 1981). Moreover, tick salivary glycans can trigger host immune responses (e.g., basophil-dependent pathways) that inhibit subsequent feeding (Allen, 1973). Certain glycans, beyond classical CCDs, contribute to acquired tick resistance in some non-natural

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hosts, resulting in reduced engorgement, impaired feeding, or tick death upon re-exposure (Allen, 1989; summarised in Wikel, 1996). Overall, immune responses against antigenic structures in tick tissues, including glycans, can damage these tissues or interfere with salivary molecules, thereby reducing tick feeding efficiency. The presence of such molecules and the resulting immune response targeted against tick structures during blood feeding could hinder blood feeding.

Despite technological advances, research on tick glycans has been limited. A Web of Science search with 'tick + glycan', 'tick + glycoprotein', and 'tick + saccharide' found 88 publications, excluding studies on tick-borne viruses without glycosylation or pathogen interactions. Even recently, only a few publications have addressed this topic each year. The discovery of α-Gal syndrome (AGS) has underscored the importance of glycans as cross-reactive carbohydrate determinants (CCDs) and their immunological importance for both ticks and humans, bringing tick glycan research to the forefront. This review summarises information on known CCDs present in ticks and their effects on human health.

Cross-reactive carbohydrate determinants and their immunological relevance

During feeding, ticks introduce a complex mixture of salivary molecules into their host, including glycoproteins rich in carbohydrate motifs. Several of these motifs can act as cross reactive carbohydrate determinants (CCDs). CCDs are structures which are not produced by humans; therefore, their structural foreignness can elicit immune responses mediated by various antibody classes and subclasses. The known CCD epitopes include N-glycan α1-3 linked core fucose (α1-3 core Fuc), galactose α1-3 linked to galactose (α-Gal epitope), sialic acid variant N-glycolylneuraminic acid (NeuGc), and core N-glycan β1-2 linked xylose (Xyl) (Fig. 1) – Platts-Mills et al. (2021).

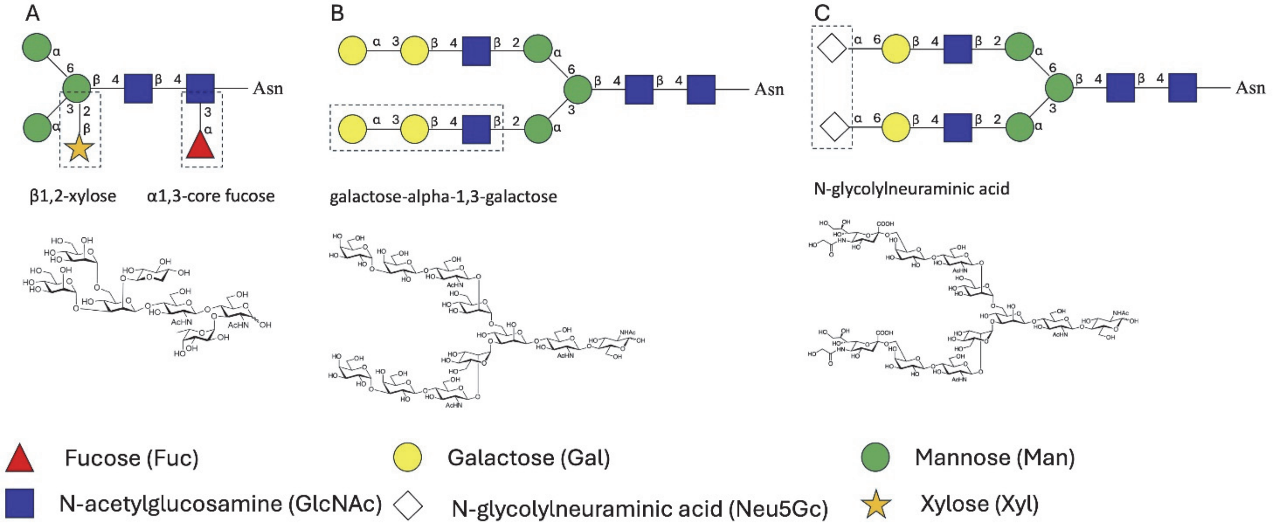

Fig. 1. Visualisation of the cross-reactive carbohydrate determinants structures; the specific epitopes are highlighted by frames in the structure of an N-glycan. Structures are shown both according to the Symbol Nomenclature for Glycans (Neelamegham et al., 2019) and as Reeves projections. **A** – paucimannosic N-glycan with linked immunogenic α1-3 linked core fucose (α1-3 core Fuc) and β1-2 linked xylose (Xyl), **B** – N-glycan containing α-Gal epitopes, and **C** – complex N-glycan with N-glycolylneuraminic acids (NeuGc). Symbol description of individual monosaccharides is shown.

Despite the rise of mass spectrometry analyses of various invertebrate glycomes, the knowledge of tick glycomes is, to date, limited to particular tick species and organs of tick nymphs and adults. Salivary glands and the gut have been heavily studied in *A. americanum*, *I. ricinus*, and *I. scapularis* ticks. High-mannose, paucimannose, complex glycans, and a small amount of hybrid N-glycans, all with two or three antennae, were detected in ticks (Park et al., 2020; Pedra et al., 2010; Vancova et al., 2012). In *I. scapularis* and *A. americanum* individuals, N-glycans containing α1,3-core Fuc were shown (Park et al., 2020; Pedra et al., 2010). In *I. ricinus* and *A. americanum*, N-glycans with terminal Neu5Gc and Neu5Ac were present (Park et al., 2020; Vancova et al., 2012). A unique combination of CCDs in one glycan was observed in *A. americanum* salivary glands: N-glycans containing, for example, both α-Gal and β-Xyl, α-Gal and α1,3-core Fuc, or two α-Gal epitopes (Park et al., 2020).

Although CCDs are commonly discussed in the context of IgE, humans also produce glycan-specific IgG (notably IgG1 and IgG3) and IgM against a broad range of carbohydrate epitopes (Schneider et al., 2015), with antibody isotypes and clinical relevance varying by structure.

For α1,3 core fucose, IgE levels are very high, but clinical relevance is generally low, despite frequent IgM and IgG1 production (Bardor et al., 2003) and elevated IgG1 in CCD positive individuals (Román-Carrasco et al., 2020); nonetheless, the biological activity of anti-α1,3 core Fuc IgE has been demonstrated (Plum et al., 2023). Polyclonal IgE that recognise α1,3 core fucose usually also recognise core N-glycan bound xylose due their presence in the same glycan molecules (Aalberse et al., 1981).

In contrast, α-Gal-specific IgE is directly responsible for allergic and anaphylactic reactions, as was shown for cetuximab (reviewed in Platts-Mills et al., 2021). While anti-α-Gal IgG and IgM are naturally present in humans due to gut microbiota, IgE triggered by α-Gal sensitisation is responsible for the allergic/anaphylactic reaction (Ailsworth et al., 2025; de la Fuente et al., 2019). Patients with red meat allergy have higher IgG1 and IgG3 anti-α-Gal antibody titres, while non-allergic patients have elevated IgG4 (Kollmann et al., 2017).

In patients with xenotransplants, α-Gal triggers IgG and IgM responses, but not IgA (Galili et al., 1993). Recently, tick feeding was shown to induce a strong IgG response to the α-Gal epitope in both mice and humans (Ailsworth et al., 2025; Hils et al., 2024).

NeuGc is another antigenic epitope, for which IgE antibodies are not detected, and differing titres of IgA, IgG, and IgM antibodies are naturally present in humans. The combination of these antibodies – together with the incorporation of NeuGc into human tissues – is responsible for (chronic) inflammation and resulting symptoms (Hutton et al., 2025; Padler-Karavani et al., 2008).

From a clinical perspective, IgE antibodies against CCDs may yield false-positive allergy test results because they bind structurally similar glycans attached to various molecules, particularly in the case of anti-α1,3 core Fuc found in plant allergens. Failure to recognise this phenomenon can result in an incorrect diagnosis and inadequate treatment (Ebo et al., 2004; Mari, 2002).

For a long time, anti-glycan antibodies were considered clinically insignificant, as proteins are considered the main allergenogenic epitopes. However, recent findings of type I allergies, which are caused by glycan structures, changed the view of this problem (Commins et al., 2009). Detailed insights into red meat allergy driven by IgE antibodies targeting the α-Gal have revealed that carbohydrate-mediated reactions may cause life-threatening systemic anaphylaxis.

Sensitisation to α-Gal after a repetitive tick bite can trigger anaphylaxis or other allergic symptoms upon the administration of α-Gal-containing drugs (as described for the chimeric human-mouse monoclonal antibody cetuximab) (Chung et al., 2008). These new understandings challenge previous beliefs and confirm the significant clinical importance of specific carbohydrate allergens.

α1,3-core fucose (α1,3-core Fuc)

Of the many possible types of glycan fucosylation, only one belongs to CCDs. Besides O-glycans, N-glycans can be fucosylated either at the core as α1,6-core Fuc, a characteristic feature of mammals, and α1,3-core Fuc found mainly in plants and insects – and additionally as a terminal modification of N-acetylgalactosamine (GalNAc) in the N-acetyllactosamine (LacdiNAc, GalNAcβ1-4GlcNAc) structure, incorporating an α1,3 fucose or the Lewis X epitope found also in mammals. α1,3-core Fuc in N-glycans is the sole fucose-containing CCD and is well-documented in invertebrates. It has been identified, in combination with the α1,6-core Fuc attached to N-glycans, for example, in mosquitoes and honeybees (Hykollari et al., 2019; Kubelka et al., 1993, 1995; Kurz et al., 2016). Based on previous research, the main honeybee venom allergens with α1,3-core Fuc were identified as phospholipase A2 (Api m 1), hyaluronidase (Api m 2), and icarapin (Api m 10) (summarised in Burzyńska and Piasecka-Kwiatkowska, 2021). Other identified molecules, for example, basic peptide melittin (Api m 4), dipeptidylpeptidase IV (Api m 5) (Blank et al., 2010), Api m 6 (Michel et al., 2012), and vitellogenin (Api m 12) (Blank et al., 2013), seem to be protein-based allergens (Köhler et al., 2014). Phospholipase A2 from *Apis mellifera* displays core-difucosylated N-glycans (thus containing the immunogenic α1,3-core Fuc) along with terminal fucosylation (Kubelka et al., 1993; Staudacher et al., 1992). Glycans with multiple antennae, which have unusually attached fucose, were also described (Hykollari et al., 2019). The study of Seismann et al. (2010) explored allergenic cross-reactivity of hyaluronidases (Api m 2 and Ves v 2a/b). Screening venom-sensitive sera revealed that Api m 2 has allergenic significance beyond carbohydrate epitopes. In contrast, Ves v 2b primarily exhibits carbohydrate-based reactivity, raising questions about its role in allergic reactions.

Tick glycans containing α1,3-core Fuc were shown to be involved in the tick-pathogen relationships. The significance of α1,3-core Fuc was highlighted by Pedra et al. (2010), who demonstrated that α1,3-core fucosylated glycans are crucial for the survival of *Anaplasma marginale*, the bacteria responsible for anaplasmosis, in ticks. They also found that this bacterium modifies the expression of three α1,3-fucosyltransferases. Furthermore, silencing fucosyltransferases significantly decreases the colonisation of tick cells by *Anaplasma* (Pedra et al., 2010). MALDI TOF-TOF analysis of SG (salivary gland) from fed nymphs revealed N-glycans with *m/z* values corresponding to α1,3-core Fuc. Protein extracts from SGs and midguts also showed a strong signal after western blot with anti-HRP (horseradish peroxidase) antibodies that recognise the α1,3-core Fuc (Pedra et al., 2010). Hebert et al. (2017) assume that AmOmpA, *A. marginale* outer membrane protein A, targets fucosylated residues on tick ISE6 cells. The hypothesis was supported by Vimonish et al. (2022) in the *D. andersoni* primary midgut cell culture system. The authors showed that expression of tick α-1,3-fucosyltransferases A1 and A2 is regulated by *A. marginale* infection of midgut cells. Moreover, the amount of α-1,3 core Fuc, along with the sensitivity of uninfected *D. andersoni* gut cells, was lowered after the silencing of α-1,3 fucosyltransferase A2.

Detailed analysis of α1,3-fucose and α1,6-fucose attached to the core of N-glycans was done in partially fed *Ixodes ricinus* females (Vancova and Nebesarova, 2015). A unique combination of fluorescence and scanning electron microscopy co-localised α1,3- and α1,6-core Fuc on the basement membranes of acini types II and III, as well as in the small secretory granules within the cytoplasm of "F" cells. Nevertheless, only α1,6-core Fuc was detected in secretory granules of acini type II, the place from which the active molecules are released to the host during the feeding.

The N-glycome of *Amblyomma americanum* salivary glands and carcasses was shown to display a high proportion of fucosylated glycans, with both core α1,3- and core α1,6-linked Fuc observed, occasionally appearing in difucosylated forms (Park et al., 2020).

Proteins bearing α1,3-core fucosylated N-glycans thus seem to be evolutionarily conserved. They present similarly to other arthropods and may potentially be excreted to the host. At the same time, it was shown that tick-borne pathogens coevolved utilising this epitope present in the vector but not in the hosts.

Galactose-alpha-1,3-galactose (α-Gal)

Generally, the Galactose-alpha-1,3-galactose is a saccharide that is attached terminally to N-glycans by the α1–3 galactosyltransferase that attaches Gal to the N-acetyllactosaminyl group (Galβ1-4GlcNAc-R) (Galili et al., 1988). α-Gal is an oligosaccharide widely present in glycoproteins/glycolipids of non-primate mammals, certain bacteria, and parasites, including ticks (summarised in Wilson et al., 2024), but it is absent in humans, apes, and Old-World monkeys because of the inactivated α1-3 galactosyltransferase. For that reason, α-Gal appears foreign to the immune systems of humans, apes, and Old-World monkeys.

In ticks, the α-Gal epitope was described in species all over the world from the genera *Amblyomma* (Araujo et al., 2016; Crispell et al., 2019; Murangi et al., 2022; Park et al., 2020), *Haemaphysalis* (Chinuki et al., 2016), *Hyalomma* (Mateos-Hernandez et al., 2017; Valcárcel et al., 2024), *Ixodes* (Hamsten et al., 2013), and *Rhipicephalus* (Mateos-Hernandez et al., 2017; Murangi et al., 2022). Its presence in ticks could cause α-Gal syndrome in humans upon tick feeding. AGS is triggered by tick bites, which introduce α-Gal into the body and sensitise the immune system. After this, eating red meat or exposure to products containing α-Gal can cause IgE-mediated allergic reactions (Van Nunen et al., 2009). A key study that fills a major gap in understanding how tick bites lead to delayed allergic reactions to mammalian meat demonstrates that *Ixodes scapularis* ticks endogenously synthesise α-Gal. The heterologous expression of identified galactosyltransferase genes *b4galt7*, *a4galt-1*, and *a4galt-2* induced α-Gal synthesis, and gene knockdown experiments in ticks demonstrated that these genes are essential for endogenous α-Gal production (Cabezas-Cruz et al., 2018).

Given the typical course of anaphylactic reactions, AGS is delayed by 1 to 6 months after tick exposure; moreover, research indicates that IgE levels specific to α-Gal rise with increasing numbers of tick bites (Hashizume et al., 2018). An allergic reaction to α-Gal can also be caused by ticks that do not specialise on humans as hosts, such as pigeon ticks (*Argas* spp.) (Rolla et al., 2018).

The range of clinical symptoms of AGS in humans is wide, spanning from the asymptomatic course, through mild symptoms, to severe anaphylactic shock. Many sensitised individuals remain asymptomatic or exhibit isolated gastrointestinal problems; others report urticaria, skin pruritus, and/or shortness of breath/coughing/wheezing (Binder et al., 2023; summarised in Commins, 2020). In certain individuals, the allergic reaction can lead to life-threatening anaphylaxis (Commins and Platts-Mills, 2009; Commins et al., 2009), and a fatal case only four hours after eating beef has already been described (Platts-Mills et al., 2025). This case also shows the importance of severe abdominal pain as a sole recognisable symptom of the severe anaphylactic reaction. AGS is also connected with the non-allergic symptoms. AGS, characterised by increased IgE levels against α-Gal, appears to be associated with cardiac diseases. Notably, it is associated with a higher risk of developing atherosclerotic plaques (Vernon et al., 2022; Wilson et al., 2018, 2019). Additionally, patients with AGS who receive bovine or porcine valves face a greater mortality risk compared to those who receive mechanical valves (Hawkins et al., 2016). AGS is regarded as the first allergic disease caused solely by a carbohydrate, triggering IgE-mediated allergic reactions.

α-Gal epitope was identified in vitellogenins and α-2-macroglobulin protein groups of *I. ricinus* larvae and adults, including in saliva (Apostolovic et al., 2020). Antibodies against α-Gal recognised this epitope in SG of *A. americanum* and *I. scapularis*. Moreover, α-Gal-containing protein extracts activated basophils from patients allergic to red meat (Crispell et al., 2019). An unusual combination of α-Gal and core-Fuc, α-Gal and Xyl, and di α-Gal structures were identified in SG of *A. americanum* (Park et al., 2020). Because SGs contain high levels of α-Gal, the authors also suggest that α-Gal may mimic proteins secreted into non-primate hosts, with α-Gal potentially acting as an allergy sensitiser in the atypical human host (Contreras et al., 2023; Park et al., 2020). Female and male *A. americanum* ticks fed on human blood showed significantly higher α-Gal levels in their salivary glands than those fed on bovine, rabbit, or dog blood (Maldonado-Ruiz et al., 2023). Moreover, α-Gal levels increase over the course of feeding, reaching a peak within 3 days. Large tick-to-tick variation and differences between various field-collected ticks of α-Gal levels were observed. It was reported that host-derived factors may modulate glycosylation patterns in ticks, which could help explain the differences in sensitisation observed in α-Gal syndrome (Maldonado-Ruiz et al., 2023). Cabezas-Cruz et al. (2018) also demonstrated that silencing of galactosyltransferases responsible for α-Gal attachment (*b4galt7*, *a4galt-1*, and *a4galt-2*) impaired tick feeding. Moreover, α-Gal levels increased during *Anaplasma phagocytophilum* infection. The authors conclude that ticks can produce endogenous α-Gal, and its expression is needed for tick feeding and controlling bacterial infection.

The presence of host protein (immunoglobulins), adsorbed in the tick midgut and subsequently secreted into the tick saliva, supports the idea that some of the α-Gal in tick saliva comes from a mammalian blood meal (Jasinskas and Barbour, 2005). Endogenous production of α-Gal and incorporation of α-Gal-containing constituents from a mammalian blood meal were also concluded in *I. ricinus* (Fischer et al., 2020). α-Gal production together with the responsible galactosyltransferases was shown in *I. scapularis*, together with the confirmation of their importance for tick physiology (Cabezas-Cruz et al., 2018).

N-glycolylneuraminic acid (Neu5Gc)

Sialic acids are an abundant terminal modification of glycans in mammals and higher Eukaryotes; among them, N-acetylneuraminic acid (Neu5Ac) and N-glycolylneuraminic acid are the major forms (Lewis et al., 2022). The hydroxyl group that distinguishes Neu5Gc from Neu5Ac is located on the glycolyl part of the substituent attached to the nitrogen at position C5. The conversion of Neu5Ac to Neu5Gc is catalysed by CMP-N-acetylneuraminic acid hydroxylase (Fig. 2), which is mutated in humans; therefore, they are unable to synthesise it (summarised in Angata and Varki, 2002). For that reason, Neu5Gc is highly immunogenic in several ways.

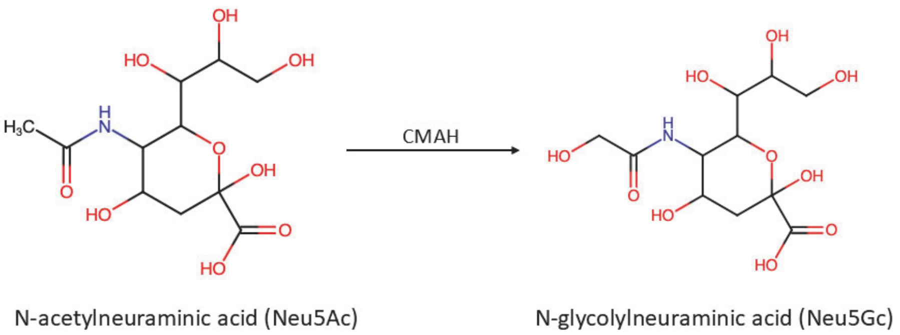

Fig. 2. The chemical structures of Neu5Ac and Neu5Gc. Schema for the enzymatic conversion of Neu5Gc from Neu5Ac via the action of CMP-N-acetylneuraminic acid hydroxylase, an enzyme which is inactive in humans.

Firstly, due to the dietary uptake, Neu5Gc is displayed on human cells. Neu5Gc is present in human tissues in minimal amounts due to the consumption of red meat, milk products, etc. Mammalian-derived glycoproteins are absorbed into the human body via micropinosis (Banda et al., 2012; Bardor et al., 2005; Malykh et al., 2001), digested, and amino acids, as well as saccharides, are subsequently metabolically incorporated into newly synthesised glycans (Banda et al., 2012; Bardor et al., 2005; Bergfeld et al., 2012; Samraj et al., 2015; Tangvoranuntakul et al., 2003). Therefore, human tissues present a "foreign" but cell-bound antigen. Secondly, humans naturally develop circulating anti-Neu5Gc antibodies that arise due to persistent exposure to dietary Neu5Gc and possibly through microbial presentation of Neu5Gc-containing glycans (summarised in Altman and Gagneux, 2019). Thirdly, when anti-Neu5Gc antibodies bind Neu5Gc, as a foreign antigen, this coexistence seems to worsen diseases mediated by chronic inflammation, like cancer, cardiovascular diseases, and autoimmunity (summarised in Alisson-Silva et al., 2016; Dhar et al., 2019; Okerblom and Varki, 2017; Samraj et al., 2014, 2015; Varki, 2017).

In cancer tissues, Neu5Gc was found at high levels (Malykh et al., 2001; Samraj et al., 2014, 2015) and seems to be a potential biomarker in oncology (Cao et al., 2022; Teng et al., 2022). The dietary source, antigen properties of the epitope itself, and ubiquity/abundance on the cell surface render Neu5Gc a distinctive antigen, deserving further attention and investigation.

In ticks, researchers identified traces of N-glycans containing Neu5Gc and Neu5Ac in the gut of partially fed *I. ricinus* females using MALDI TOF/TOF (Vancova et al., 2012). Further MS/MS analysis showed the presence of the complex glycans containing two antennae with one or two Sialic acids (Sias) and three antennae with one Sia. Localisation of NeuGc using immunolabelling with gold particles showed its presence in the basement membranes and cytosolic structures of SG acini, as well as in digestive cells and the gut lumen of partially fed ticks. Considering the structure of glycans, their placement within tick tissues, and the type of tick samples, the authors hypothesise about the host origin of the identified glycans. The host-origin theory of most of the sialic acid in ticks was supported by Sterba et al. (2014), who quantified Sia levels in tick tissues. Using a commercial Sia quantification kit, the total Sia concentration was determined in the gut, SG, and OV, expressed as mmol Sia per gram of protein. Conversely, the enzymatic assay indicated that the amount of tick-origin Sia was approximately 1,000 times lower. By comparing the total Sia amount with the metabolically produced one, the authors conclude that the majority of the Sia in tick tissues is of host origin (Sterba et al., 2014). Trace amounts of terminal NeuGc attached to the terminal galactose in male SGs were also shown in *A. americanum* (Park et al., 2020). The enzymes necessary for NeuAc production were identified in *I. ricinus* and *I. scapularis*, and the expression and activity of sialyltransferase needed for Neu5Ac attachment to glycans was confirmed. However, the presence of CMP-N-acetylneuraminic acid hydroxylase necessary for Neu5Gc production was not confirmed in ticks (Sterbova et al., 2026). Thus, the exact role of sialylated glycoproteins in ticks remains to be elucidated.

β1,2-xylose

Generally, xylose is a typical CCD found in plants that does not occur in human and mammalian glycans (van Ree et al., 2000). Therefore, it is immunologically foreign to those organisms and, in sensitised patients, can cause an increased IgE antibody titre. Structurally, xylose is attached in N-glycans in the position β1,2- to the core Man, and it could accompany core α1,3-fucose or α-Gal epitope.

In invertebrates, Xyl, together with core α1,3- and α1,6-fucose, has been reported in *Schistosoma* (Khoo et al., 2001; Smit et al., 2015) and in snails (Lommerse et al., 1997). Xylosyltransferases responsible for the attachment of Xyl residue were identified in *C. elegans* (Hwang et al., 2003) and in *D. melanogaster* (Lee et al., 2013; Wilson, 2002a, b).

The presence of β1,2-xylose in ticks was reported by Crispell et al. (2019), who did MS profiling of glycans in saliva and salivary glands of various North American tick species. The structures containing core-mannose pentasaccharide modified by Xyl were found in *I. scapularis*, *A. americanum* and *A. maculatum* in unfed and partially fed females and also in the saliva of these species. A deep MS analysis of *A. americanum* N-glycome revealed the presence of complex glycans, with Xyl attached to the core-mannose in 8% of the total N-glycan profile in unfed females, 5% in females fed for five days, and 16% in males. A unique combination of Xyl and α-Gal was also detected (Park et al., 2020).

Conclusion

Recent research has highlighted the significant immunological functions of glycan epitopes in ticks. These unique carbohydrates, absent in humans, can trigger immune responses, occasionally leading to allergic reactions or false-positive allergy-test results. Moreover, they play critical roles in the complex triad of tick-host-pathogen interactions, potentially affecting pathogen transmission, tick survival, and host sensitisation to allergens. Evidence of endogenous synthesis and host-derived glycan incorporation demonstrates the dynamic nature of tick glycomes. Although previously considered clinically insignificant, these glycan structures are now recognised as crucial elements in allergy and immunology, with promising potential as future vaccine or diagnostic targets.

An important aspect of CCD epitopes' presence in tick tissues and saliva is their immunogenicity, which is in contradiction to the need of the tick to lower the defence responses of the host during blood feeding. We hypothesise that the presence of various inhibitory signals, like the presence of sialylated glycoproteins of tick or host origin (summarised by Vechtova et al., 2018; Wickramasekara et al., 2008), may be one of the reasons why ticks transport undigested host proteins during blood feeding from the gut to the salivary glands and saliva as a form of molecular mimicry.

To better understand glycan-based relationships within the tick-host-pathogen triangle, further studies spanning multiple levels are needed. The molecular biology-based level could focus on the identification and characterisation of glycan-modifying enzymes, as well as the description of corresponding glycosylation pathways, as in the work of Cabezas-Cruz et al. (2018). Mass spectrometry analyses characterising glycomes from various tick species, their developmental stages, and organs, could extend knowledge at the glycomics-based level – as in the work of Park et al. (2020). Finally, exploring the ecological and physiological factors underlying host- and tick-dependent expression of CCDs could shed light on differences in CCD expression, as illustrated by the case of α-Gal reported by Maldonado-Ruiz et al. (2023). Furthermore, detailed characterisation of tick cell lines, including their glycomic profiles, would enhance their use as models for tick research (Bell-Sakyi et al., 2018).

Ongoing research is crucial for deepening our understanding of tick-derived glycan biology, developing effective strategies to prevent tick-borne diseases and manage allergies, and advancing novel, animal-free medications for patients with AGS (Altomari et al., 2025). The importance of such research is evidenced by the alarming increase in the number of cases of anaphylactic reactions. In the US, hundreds of thousands of cases are reported (Thompson et al., 2023), while substantial case numbers are also documented in Asia, Australia, or Europe, including the Czech Republic (Müller et al., 2023), Austria (Pisazka et al., 2019), Germany (Fischer et al., 2017), Poland (Brzozowska et al., 2021), or Italy (Villalta et al., 2017). The reason for this rapid increase is not yet known (van Nunen, 2025). Anti-αGal vaccines were proposed to lower anti-αGal IgE production and basophil activation (summarised in Propst and Thompson, 2025; Saunders et al., 2024), as well as to serve as a pan-vector and pan-pathogen vaccine (summarised in Hodžić et al., 2020). Until such a vaccine is developed, avoidance of tick bites, together with the elimination of red meat and beef-originating foods, is the only means to prevent AGS (Commins et al., 2011; summarised in Propst and Thompson, 2025; Young et al., 2021).

In recent years, awareness and clinical relevance of cross-reactive carbohydrate determinants (CCDs) have also increased within the Czech Republic, and anaphylactic reactions have been described in Czech patients (Müller et al., 2023). Several clinical laboratories now offer testing for a range of CCD epitopes, including facilities such as Thomayerova Hospital, St. Anne's University Hospital, the General University Hospital in Prague, and selected EUC Clinics.

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Ethical aspects and conflict of interest

The authors have no conflict of interest to declare.

References

Aalberse RC, Koshte V, Clemens JG (1981). Immunoglobulin E antibodies that crossreact with vegetable foods, pollen, and Hymenoptera venom. J Allergy Clin Immunol 68(5): 356–364. DOI: 10.1016/0091-6749(81)90133-0.

Ailsworth SM, MacCallum M, Richards NE, Workman LJ, Schoppee Bortz P, Makin T, et al. (2025). IgG to galactose-alpha-1,3-galactose: impact of alpha-gal IgE sensitization, blood type, and tick bites. Antibodies (Basel) 14(2): 43. DOI: 10.3390/antib14020043.

Alisson-Silva F, Kawanishi K, Varki A (2016). Human risk of diseases associated with red meat intake: Analysis of current theories and proposed role for metabolic incorporation of a non-human sialic acid. Mol Aspects Med 51: 16–30. DOI: 10.1016/j.mam.2016.07.002.

Allen JR (1973). Tick resistance: basophils in skin reactions of resistant guinea pigs. Int J Parasitol 3(2): 195–200. DOI: 10.1016/0020-7519(73)90024-6.

Allen JR (1989). Immunology of interactions between ticks and laboratory animals. Exp Appl Acarol 7(1): 5–13. DOI: 10.1007/BF01200448.

Altman MO, Gagneux P (2019). Absence of Neu5Gc and presence of anti-Neu5Gc antibodies in humans – an evolutionary perspective. Front Immunol 10: 789. DOI: 10.3389/fimmu.2019.00789.

Altomari C, Uchi J, Carpenter C, Shah S (2025). Emerging need for animal-free medications in alpha-Gal syndrome. J Allergy Clin Immunol 155(2): AB293. DOI: 10.1016/j.jaci.2024.12.904.

Angata T, Varki A (2002). Chemical diversity in the sialic acids and related alpha-keto acids: an evolutionary perspective. Chem Rev 102(2): 439–469. DOI: 10.1021/cr000407m.

Apostolovic D, Mihailovic J, Commins SP, Wijnveld M, Kazimirova M, Starkhammar M, et al. (2020). Allergenomics of the tick reveals important α-Gal-carrying IgE-binding proteins in red meat allergy. Allergy 75(1): 217–220. DOI: 10.1111/all.13978.

Araujo RN, Franco PF, Rodrigues H, Santos LCB, McKay CS, Sanhueza CA, et al. (2016). *Amblyomma sculptum* tick saliva: alpha-Gal identification, antibody response and possible association with red meat allergy in Brazil. Int J Parasitol 46(3): 213–220. DOI: 10.1016/j.ijpara.2015.12.005.

Banda K, Gregg CJ, Chow R, Varki NM, Varki A (2012). Metabolism of vertebrate amino sugars with N-glycolyl groups: mechanisms underlying gastrointestinal incorporation of the non-human sialic acid xeno-autoantigen N-glycolylneuraminic acid. J Biol Chem 287(34): 28852–28864. DOI: 10.1074/jbc.M112.364182.

Bardor M, Faveeuw C, Fitchette AC, Gilbert D, Galas L, Trottein F, et al. (2003). Immunoreactivity in mammals of two typical plant glyco-epitopes, core alpha(1,3)-fucose and core xylose. Glycobiology 13(6): 427–434. DOI: 10.1093/glycob/cwg024.

Bardor M, Nguyen DH, Diaz S, Varki A (2005). Mechanism of uptake and incorporation of the non-human sialic acid N-glycolylneuraminic acid into human cells. J Biol Chem 280(6): 4228–4237. DOI: 10.1074/jbc.M412040200.

Bell-Sakyi L, Darby A, Baylis M, Makepeace BL (2018). The Tick Cell Biobank: A global resource for *in vitro* research on ticks, other arthropods and the pathogens they transmit. Ticks Tick Borne Dis 9(5): 1364–1371. DOI: 10.1016/j.ttbdis.2018.05.015.

Bergfeld AK, Pearce OM, Diaz SL, Pham T, Varki A (2012). Metabolism of vertebrate amino sugars with N-glycolyl groups: elucidating the intracellular fate of the non-human sialic acid N-glycolylneuraminic acid. J Biol Chem 287(34): 28865–28881. DOI: 10.1074/jbc.M112.363549.

Binder AM, Cherry-Brown D, Biggerstaff BJ, Jones ES, Amelio CL, Beard CB, et al. (2023). Clinical and laboratory features of patients diagnosed with alpha-Gal syndrome-2010–2019. Allergy 78(2): 477–487. DOI: 10.1111/all.15539.

Blank S, Seismann H, Bockisch B, Braren I, Cifuentes L, McIntyre M, et al. (2010). Identification, recombinant expression, and characterization of the 100 kDa high molecular weight Hymenoptera venom allergens Api m 5 and Ves v 3. J Immunol 184(9): 5403–5413. DOI: 10.4049/jimmunol.0803709.

Blank S, Seismann H, McIntyre M, Ollert M, Wolf S, Bantleon FI, Spillner E (2013). Vitellogenins are new high molecular weight components and allergens (Api m 12 and Ves v 6) of *Apis mellifera* and *Vespula vulgaris* venom. PLoS One 8(4): e62009. DOI: 10.1371/journal.pone.0062009.

Brzozowska M, Mokrzycka N, Porebski G (2021). Alpha-gal syndrome: the first report in Poland. Cent Eur J Immunol 46(3): 398–400. DOI: 10.5114/ceji.2021.108766.

Burzyńska M, Piasecka-Kwiatkowska D (2021). A review of honeybee venom allergens and allergenicity. Int J Mol Sci 22(16): 8371. DOI: 10.3390/ijms22168371.

Cabezas-Cruz A, Espinosa PJ, Alberdi P, Simo L, Valdés JJ, Mateos-Hernández L, et al. (2018). Tick galactosyltransferases are involved in α-Gal synthesis and play a role during infection and tick vector development. Sci Rep 8(1): 14224. DOI: 10.1038/s41598-018-32664-z.

Cao X, Yu S, Wang W, Sun R, Wu Z, Gao Z, et al. (2022). Lamprey immunity protein enables detection for bladder cancer through recognizing N-hydroxyacetylneuraminic acid (Neu5Gc)-modified as a diagnostic marker and exploration of its production mechanism. Biochem Biophys Res Commun 614: 153–160. DOI: 10.1016/j.bbrc.2022.04.121.

Chinuki Y, Ishiwata K, Yamaji K, Takahashi H, Morita E (2016): *Haemaphysalis longicornis* tick bites are a possible cause of red meat allergy in Japan. Allergy 71(3): 421–425. DOI: 10.1111/all.12804.

Chung CH, Mirakhur B, Chan E, Le QT, Berlin J, Morse M, et al. (2008). Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1,3-galactose. N Engl J Med 358(11): 1109–1117. DOI: 10.1056/NEJMoa074943.

Commins SP (2020). Diagnosis & management of alpha-gal syndrome: lessons from 2,500 patients. Expert Rev Clin Immunol 16(7): 667–677. DOI: 10.1080/1744666x.2020.1782745.

Commins SP, Platts-Mills TA (2009). Anaphylaxis syndromes related to a new mammalian cross-reactive carbohydrate determinant. J Allergy Clin Immunol 124(4): 652–657. DOI: 10.1016/j.jaci.2009.08.026.

Commins SP, James HR, Kelly LA, Pochan SL, Workman LJ, Perzanowski MS, et al. (2011). The relevance of tick bites to the production of IgE antibodies to the mammalian oligosaccharide galactose-α-1,3-galactose. J Allergy Clin Immunol 127(5): 1286–1293.e6. DOI: 10.1016/j.jaci.2011.02.019.

Commins SP, Satinover SM, Hosen J, Mozena J, Borish L, Lewis BD, et al. (2009). Delayed anaphylaxis, angioedema, or urticaria after consumption of red meat in patients with IgE antibodies specific for galactose-alpha-1,3-galactose. J Allergy Clin Immunol 123(2): 426–433. DOI: 10.1016/j.jaci.2008.10.052.

Contreras M, Vaz-Rodrigues R, Mazuecos L, Villar M, Artigas-Jerónimo S, González-García A, et al. (2023). Allergic reactions to tick saliva components in zebrafish model. Parasit Vectors 16(1): 242. DOI: 10.1186/s13071-023-05874-2.

Crispell G, Commins SP, Archer-Hartman SA, Choudhary S, Dharmarajan G, Azadi P, Karim S (2019). Discovery of alpha-Gal-containing antigens in North American tick species believed to induce red meat allergy. Front Immunol 10: 1056. DOI: 10.3389/fimmu.2019.01056.

de la Fuente J, Pacheco I, Villar M, Cabezas-Cruz A (2019). The alpha-Gal syndrome: new insights into the tick-host conflict and cooperation. Parasit Vectors 12(1): 154. DOI: 10.1186/s13071-019-3413-z.

Dhar C, Sasmal A, Varki A (2019). From "Serum sickness" to "Xenosialitis": past, present, and future significance of the non-human sialic acid Neu5Gc. Front Immunol 10: 807. DOI: 10.3389/fimmu.2019.00807.

Ebo DG, Hagendorens MM, Bridts CH, De Clerck LS, Stevens WJ (2004). Sensitization to cross-reactive carbohydrate determinants and the ubiquitous protein profilin: mimickers of allergy. Clin Exp Allergy 34(1): 137–144. DOI: 10.1111/j.1365-2222.2004.01837.x.

Fischer J, Lupberger E, Hebsaker J, Blumenstock G, Aichinger E, Yazdi AS, et al. (2017). Prevalence of type I sensitization to alpha-gal in forest service employees and hunters. Allergy 72(10): 1540–1547. DOI: 10.1111/all.13156.

Fischer J, Riel S, Fehrenbacher B, Frank A, Schaller M, Biedermann T, et al. (2020). Spatial distribution of alpha-gal in *Ixodes ricinus* – A histological study. Ticks Tick Borne Dis 11(5): 101506. DOI: 10.1016/j.ttbdis.2020.101506.

Galili U, Anaraki F, Thall A, Hill-Black C, Radic M (1993). One percent of human circulating B lymphocytes are capable of producing the natural anti-Gal antibody. Blood 82(8): 2485–2493. DOI: 10.1182/blood.V82.8.2485.bloodjournal8282485.

Galili U, Shohet SB, Kobrin E, Stults CLM, Macher BA (1988). Man, apes, and old-world monkeys differ from other mammals in the expression of alpha-Galactosyl epitopes on nucleated cells. J Biol Chem 263(33): 17755–17762.

Hamsten C, Starkhammar M, Tran TA, Johansson M, Bengtsson U, Ahlen G, et al. (2013). Identification of galactose-alpha-1,3-galactose in the gastrointestinal tract of the tick *Ixodes ricinus*; possible relationship with red meat allergy. Allergy 68(4): 549–552. DOI: 10.1111/all.12128.

Hashizume H, Fujiyama T, Umayahara T, Kageyama R, Walls AF, Satoh T (2018). Repeated *Amblyomma testudinarium* tick bites are associated with increased galactose-α-1,3-galactose carbohydrate IgE antibody levels: A retrospective cohort study in a single institution. Am Acad Dermatol 78(6): 1135–1141.e3. DOI: 10.1016/j.jaad.2017.12.028.

Hawkins RB, Frischtak HL, Kron IL, Ghanta RK (2016). Premature bioprosthetic aortic valve degeneration associated with allergy to galactose-alpha-1,3-galactose. J Card Surg 31(7): 446–448. DOI: 10.1111/jocs.12764.

Hebert KS, Seidman D, Oki AT, Izac J, Emani S, Oliver LD, Jr., et al. (2017). Outer membrane protein a is an adhesin that recognizes sialylated and fucosylated glycans and functionally depends on an essential binding domain. Infect Immun 85(3): e00968–16. DOI: 10.1128/IAI.00968-16.

Hils M, Hoffard N, Iuliano C, Kreft L, Chakrapani N, Swiontek K, et al. (2024). IgE and anaphylaxis specific to the carbohydrate alpha-gal depend on IL-4. J Allergy Clin Immunol 153(4): 1050–1062.e6. DOI: 10.1016/j.jaci.2023.12.003.

Hodžić A, Mateos-Hernández L, de la Fuente J, Cabezas-Cruz A (2020). α-Gal-based vaccines: advances, opportunities, and perspectives. Trends Parasitol 36(12): 992–1001. DOI: 10.1016/j.pt.2020.08.001.

Hutton E, Uno Y, Scott E, Robson C, Fascione MA, Signoret N (2025). A general and accessible approach to enrichment and characterisation of natural anti-Neu5Gc antibodies from human samples. RSC Chem Biol 6(7): 1135–1147. DOI: 10.1039/d5cb00073d.

Hwang HY, Olson SK, Brown JR, Esko JD, Horvitz HR (2003). The *Caenorhabditis elegans* genes sqv-2 and sqv-6, which are required for vulval morphogenesis, encode glycosaminoglycan galactosyltransferase II and xylosyltransferase. J Biol Chem 278(14): 11735–11738. DOI: 10.1074/jbc.C200518200.

Hykollari A, Malzl D, Stanton R, Eckmair B, Paschinger K (2019). Tissue-specific glycosylation in the honeybee: analysis of the N-glycomes of *Apis mellifera* larvae and venom. Biochim Biophys Acta Gen Subj 1863(11): 129409. DOI: 10.1016/j.bbagen.2019.08.002.

Jasinskas A, Barbour AG (2005). The Fc fragment mediates the uptake of immunoglobulin G from the midgut to hemolymph in the ixodid tick *Amblyomma americanum* (Acari:Ixodidae). J Med Entomol 42(3): 359–366. DOI: 10.1093/jmedent/42.3.359.

Khoo KH, Huang HH, Lee KM (2001). Characteristic structural features of schistosome cercarial N-glycans: expression of Lewis X and core xylosylation. Glycobiology 11(2): 149–163. DOI: 10.1093/glycob/11.2.149.

Köhler J, Blank S, Müller S, Bantleon F, Frick M, Huss-Marp J, et al. (2014). Component resolution reveals additional major allergens in patients with honeybee venom allergy. J Allergy Clin Immunol 133(5): 1383–1389, 1389.e1–6. DOI: 10.1016/j.jaci.2013.10.060.

Kollmann D, Nagl B, Ebner C, Emminger W, Wöhrl S, Kitzmüller C, et al. (2017). The quantity and quality of α-gal-specific antibodies differ in individuals with and without delayed red meat allergy. Allergy 72(2): 266–273. DOI: 10.1111/all.12948.

Kubelka V, Altmann F, März L (1995). The asparagine-linked carbohydrate of honeybee venom hyaluronidase. Glycoconj J 12(1): 77–83. DOI: 10.1007/bf00731872.

Kubelka V, Altmann F, Staudacher E, Tretter V, März L, Hård K, et al. (1993). Primary structures of the N-linked carbohydrate chains from honeybee venom phospholipase A2. Eur J Biochem 213(3): 1193–1204. DOI: 10.1111/j.1432-1033.1993.tb17870.x.

Kurz S, King JG, Dinglasan RR, Paschinger K, Wilson IB (2016). The fucomic potential of mosquitoes: Fucosylated N-glycan epitopes and their cognate fucosyltransferases. Insect Biochem Mol Biol 68: 52–63. DOI: 10.1016/j.ibmb.2015.11.001.

Lee TV, Sethi MK, Leonardi J, Rana NA, Buettner FF, Haltiwanger RS, et al. (2013). Negative regulation of Notch signaling by xylose. PLoS Genet 9(6): e1003547. DOI: 10.1371/journal.pgen.1003547.

Lewis AL, Chen X, Schnaar RL, Varki A (2022). Sialic acids and other nonulosonic acids. In: Varki A, Cummings RD, Esko JD, Stanley P, Hart GW, Aebi M, et al. (Eds). Essentials of Glycobiology 4th ed. Cold Spring Harbor (NY): Cold Spring Harbor Laboratory Press, pp. 185–204. DOI: 10.1101/glycobiology.4e.15.

Lommerse JP, Thomas-Oates JE, Gielens C, Preaux G, Kamerling JP, Vliegenthart JF (1997). Primary structure of 21 novel monoantennary and diantennary N-linked carbohydrate chains from alphaD-hemocyanin of *Helix pomatia*. Eur J of Biochem 249(1): 195–222. DOI: 10.1111/j.1432-1033.1997.00195.x.

Maldonado-Ruiz LP, Reif KE, Ghosh A, Foré S, Johnson RL, Park Y (2023) High levels of alpha-gal with large variation in the salivary glands of lone star ticks fed on human blood. Sci Rep 13(1): 21409. DOI: 10.1038/s41598-023-48437-2.

Malykh YN, Schauer R, Shaw L (2001). N-Glycolylneuraminic acid in human tumours. Biochimie 83(7): 623–634. DOI: 10.1016/s0300-9084(01)01303-7.

Mari A (2002). IgE to cross-reactive carbohydrate determinants: analysis of the distribution and appraisal of the *in vivo* and *in vitro* reactivity. Int Arch Allergy Immunol 129(4): 286–295. DOI: 10.1159/000067591.

Mateos-Hernandez L, Villar M, Moral A, Rodriguez CG, Arias TA, de la Osa V, et al. (2017). Tick-host conflict: immunoglobulin E antibodies to tick proteins in patients with anaphylaxis to tick bite. Oncotarget 8(13): 20630–20644. DOI: 10.18632/oncotarget.15243.

Michel Y, McIntyre M, Ginglinger H, Ollert M, Cifuentes L, Blank S, Spillner E (2012). The putative serine protease inhibitor Api m 6 from *Apis mellifera* venom: recombinant and structural evaluation. J Investig Allergol Clin Immunol 22(7): 476–484.

Müller J, Radej J, Kriz M, Hunkova E, Kasparek J, Matejovic M (2023). Alpha-gal Syndrome – A case report of tick-borne anaphylactic shock. Eur J Case Rep Intern Med 10(7): 003939. DOI: 10.12890/2023_003939.

Murangi T, Prakash P, Moreira BP, Basera W, Botha M, Cunningham S, et al. (2022). *Ascaris lumbricoides* and ticks associated with sensitization to galactose α1,3-galactose and elicitation of the alpha-gal syndrome. J Allergy Clin Immunol 149(2): 698–707.e3. DOI: 10.1016/j.jaci.2021.07.018.

Neelamegham S, Aoki-Kinoshita K, Bolton E, Frank M, Lisacek F, Lütteke T, et al. (2019). Updates to the symbol nomenclature for glycans guidelines. Glycobiology 29(9): 620–624. DOI: 10.1093/glycob/cwz045.

Okerblom J, Varki A (2017). Biochemical, cellular, physiological, and pathological consequences of human loss of N-glycolylneuraminic acid. Chembiochem 18(13): 1155–1171. DOI: 10.1002/cbic.201700077.

Padler-Karavani V, Yu H, Cao H, Chokhawala H, Karp F, Varki N, et al. (2008). Diversity in specificity, abundance, and composition of anti-Neu5Gc antibodies in normal humans: potential implications for disease. Glycobiology 18(10): 818–830. DOI: 10.1093/glycob/cwn072.

Park Y, Kim D, Boorgula GD, De Schutter K, Smagghe G, Simo L, et al. (2020). Alpha-Gal and cross-reactive carbohydrate determinants in the N-glycans of salivary glands in the Lone star tick, *Amblyomma americanum*. Vaccines (Basel) 8(1): 18. DOI: 10.3390/vaccines8010018.

Pedra JH, Narasimhan S, Rendić D, DePonte K, Bell-Sakyi L, Wilson IB, Fikrig E (2010). Fucosylation enhances colonization of ticks by *Anaplasma phagocytophilum*. Cell Microbiol 12(9): 1222–1234. DOI: 10.1111/j.1462-5822.2010.01464.x.

Pisazka V, Duscher G, Hodžić A, Reider N, Allerberger F (2019). Alpha-gal allergy after a tick bite in Austria. Wien Klin Wochenschr 131(15–16): 385–388. DOI: 10.1007/s00508-019-1506-5.

Platts-Mills TA, Hilger C, Jappe U, van Hage M, Gadermaier G, Spillner E, et al. (2021). Carbohydrate epitopes currently recognized as targets for IgE antibodies. Allergy 76(8): 2383–2394. DOI: 10.1111/all.14802.

Platts-Mills TAE, Workman LJ, Richards NE, Wilson JM, McFeely EM (2025). Implications of a fatal anaphylactic reaction occurring 4 hours after eating beef in a young man with IgE antibodies to galactose-α-1,3-galactose. J Allergy Clin Immunol Pract 13(12): 3422–3424. DOI: 10.1016/j.jaip.2025.09.039.

Plum M, Tjerrild L, Raiber T, Bantleon F, Bantleon S, Miehe M, et al. (2023). Structural and functional analyses of antibodies specific for modified core N-glycans suggest a role in TH 2 responses. Allergy 78(1): 121–130. DOI: 10.1111/all.15417.

Propst SBH, Thompson DK (2025). Alpha-gal syndrome and the gastrointestinal reaction: a narrative review. Front Allergy 6: 1535103. DOI: 10.3389/falgy.2025.1535103.

Rolla G, Heffler E, Boita M, Doyen V, Mairesse M, Cvackova M, et al. (2018). Pigeon tick bite: A neglected cause of idiopathic nocturnal anaphylaxis. Allergy 73(4): 958–961. DOI: 10.1111/all.13344.

Román-Carrasco P, Hemmer W, Klug C, Friedrich A, Stoll P, Focke-Tejkl M, et al. (2020). Individuals with IgE antibodies to α-Gal and CCD show specific IgG subclass responses different from subjects non-sensitized to oligosaccharides. Clin Exp Allergy 50(9): 1107–1110. DOI: 10.1111/cea.13695.

Samraj AN, Läubli H, Varki N, Varki A (2014). Involvement of a non-human sialic acid in human cancer. Front Oncol 4: 33. DOI: 10.3389/fonc.2014.00033.

Samraj AN, Pearce OMT, Läubli H, Crittenden AN, Bergfeld AK, Banda K, et al. (2015). A red meat-derived glycan promotes inflammation and cancer progression. Proc Natl Acad Sci US 112(2): 542-547. DOI: 10.1073/pnas.1417508112.

Saunders MN, Rival CM, Mandal M, Cramton K, Rad LM, Janczak KW, et al. (2024). Immunotherapy with biodegradable nanoparticles encapsulating the oligosaccharide galactose-alpha-1,3-galactose enhance immune tolerance against alpha-gal sensitization in a murine model of alpha-gal syndrome. Front Allergy 5: 1437523. DOI: 10.3389/falgy.2024.1437523.

Seismann H, Blank S, Braren I, Greunke K, Cifuentes L, Grunwald T, et al. (2010). Dissecting cross-reactivity in hymenoptera venom allergy by circumvention of alpha-1,3-core fucosylation. Mol Immunol 47(4): 799–808. DOI: 10.1016/j.molimm.2009.10.005.

Schneider C, Smith DF, Cummings RD, Boligan KF, Hamilton RG, Bochner BS, et al. (2015). The human IgG anti-carbohydrate repertoire exhibits a universal architecture and contains specificity for microbial attachment sites. Sci Transl Med 7(269): 269ra1. DOI: 10.1126/scitranslmed.3010524.

Smit CH, van Diepen A, Nguyen DL, Wuhrer M, Hoffmann KF, Deelder AM, Hokke CH (2015). Glycomic analysis of life stages of the human parasite *Schistosoma mansoni* reveals developmental expression profiles of functional and antigenic glycan motifs. Mol Cell Proteomics 14(7): 1750–1769. DOI: 10.1074/mcp.M115.048280.

Staudacher E, Altmann F, März L, Hård K, Kamerling JP, Vliegenthart JF (1992). Alpha 1-6(alpha 1-3)-difucosylation of the asparagine-bound N-acetylglucosamine in honeybee venom phospholipase A2. Glycoconj J 9(2): 82–85. DOI: 10.1007/bf00731703.

Sterba J, Vancova M, Sterbova J, Bell-Sakyi L, Grubhoffer L (2014). The majority of sialylated glycoproteins in adult *Ixodes ricinus* ticks originate in the host, not the tick. Carbohydr Res 389: 93–99. DOI: 10.1016/j.carres.2014.02.017.

Sterbova J, Ondrus J, Fussy Z, Vechtova P, Grubhoffer L, Sterba J (2026). Click chemistry reveals sialylated glycoprotein biosynthesis in *Ixodes ricinus* ticks and tick-derived cells. Int J Biol Macromol 365: 152305. DOI: 10.1016/j.ijbiomac.2026.152305.

Tangvoranuntakul P, Gagneux P, Diaz S, Bardor M, Varki N, Varki A, Muchmore E (2003). Human uptake and incorporation of an immunogenic nonhuman dietary sialic acid. Proc Natl Acad Sci U S A 100(21): 12045–12050. DOI: 10.1073/pnas.2131556100.

Teng H, Li Q, Gou M, Liu G, Cao X, Lu J, et al. (2022). Lamprey immunity protein enables early detection and recurrence monitoring for bladder cancer through recognizing Neu5Gc-modified uromodulin glycoprotein in urine. Biochim Biophys Acta Mol Basis Dis 1868(12): 166493. DOI: 10.1016/j.bbadis.2022.166493.

Thompson JM, Carpenter A, Kersh GJ, Wachs T, Commins SP, Salzer JS (2023). Geographic distribution of suspected alpha-Gal syndrome cases – United States, January 2017–December 2022. MMWR Morb Mortal Wkly Rep 72(30): 815–820. DOI: 10.15585/mmwr.mm7230a2.

Valcárcel A, Montero AB, Rodero M, Fernández JG, Olmeda AS, Valcárcel F, Cuéllar C (2024). Alpha-Gal, epitope responsible for allergy to red meat, in the Mediterranean tick. Med Vet Entomol 38(3): 366–371. DOI: 10.1111/mve.12724.

van Nunen S (2025). Quantifying the allergenic potency of mammalian meat sources, an important step in providing a framework for improved management of mammalian meat allergy after tick bite (alpha-gal syndrome/AGS). Allergy 80(1): 9–11. DOI: 10.1111/all.16381.

Van Nunen SA, O'Connor KS, Clarke LR, Boyle RX, Fernando SL (2009). An association between tick bite reactions and red meat allergy in humans. Med J Aust 190(9): 510–511. DOI: 10.5694/j.1326-5377.2009.tb02533.x.

van Ree R, Cabanes-Macheteau M, Akkerdaas J, Milazzo JP, Loutelier-Bourhis C, Rayon C, et al. (2000). Beta(1,2)-xylose and alpha(1,3)-fucose residues have a strong contribution in IgE binding to plant glycoallergens. J Biol Chem 275(15): 11451–11458. DOI: 10.1074/jbc.275.15.11451.

Vancova M, Nebesarova J (2015). Correlative fluorescence and scanning electron microscopy of labelled core fucosylated glycans using cryosections mounted on carbon-patterned glass slides. PLoS One 10(12): e0145034. DOI: 10.1371/journal.pone.0145034.

Vancova M, Sterba J, Dupejova J, Simonova Z, Nebesarova J, Novotny MV, Grubhoffer L (2012). Uptake and incorporation of sialic acid by the tick *Ixodes ricinus*. J Insect Physiol 58(9): 1277–1287. DOI: 10.1016/j.jinsphys.2012.06.016.

Varki A (2017). Are humans prone to autoimmunity? Implications from evolutionary changes in hominin sialic acid biology. J Autoimmun 83: 134–142. DOI: 10.1016/j.jaut.2017.07.011.

Vechtova P, Sterbova J, Sterba J, Vancova M, Rego ROM, Selinger M, et al. (2018). A bite so sweet: the glycobiology interface of tick-host-pathogen interactions. Parasit Vectors 11(1): 594. DOI: 10.1186/s13071-018-3062-7.

Vernon ST, Kott KA, Hansen T, Finemore M, Baumgart KW, Bhindi R, et al. (2022). Immunoglobulin E sensitization to mammalian oligosaccharide galactose-α-1,3 (α-gal) is associated with noncalcified plaque, obstructive coronary artery disease, and ST-segment-elevated myocardial infarction. Arterioscler Thromb Vasc Biol 42(3): 352–361. DOI: 10.1161/atvbaha.121.316878.

Villalta D, Cecchi L, Farsi A, Chiarini F, Minale P, Voltolini S, et al. (2017). Galactose-α-1,3-galactose syndrome: an Italian survey. Eur Ann Allergy Clin Immunol 49(6): 263–269. DOI: 10.23822/EurAnnACI.1764-1489.35.

Vimonish R, Capelli-Peixoto J, Johnson WC, Hussein HE, Taus NS, Brayton KA, et al. (2022). Infection of primary midgut cell culture is dependent on fucosylated glycans. Front Cell Infect Microbiol 12: 877525. DOI: 10.3389/fcimb.2022.877525.

Wickramasekara S, Bunikis J, Wysocki V, Barbour AG (2008). Identification of residual blood proteins in ticks by mass spectrometry proteomics. Emerg Infect Dis 14(8): 1273–1275. DOI: 10.3201/eid1408.080227.

Wikel SK (1996). Host immunity to ticks. Annu Rev Entomol 41: 1–22. DOI: 10.1146/annurev.en.41.010196.000245.

Wilson IBH (2002a). Functional characterization of *Drosophila melanogaster* peptide O-xylosyltransferase, the key enzyme for proteoglycan chain initiation and member of the core 2/I N-acetylglucosaminyltransferase family. J Biol Chem 277(24): 21207–21212. DOI: 10.1074/jbc.M201634200.

Wilson IBH (2002b). Glycosylation of proteins in plants and invertebrates. Curr Opin Struct Biol 12(5): 569–577. DOI: 10.1016/S0959-440x(02)00367-6.

Wilson JM, Erickson L, Levin M, Ailsworth SM, Commins SP, Platts-Mills TAE (2024). Tick bites, IgE to galactose-alpha-1,3-galactose and urticarial or anaphylactic reactions to mammalian meat: The alpha-gal syndrome. Allergy 79(6): 1440–1454. DOI: 10.1111/all.16003.

Wilson JM, McNamara CA, Platts-Mills TAE (2019). IgE, α-Gal and atherosclerosis. Aging 11(7): 1900–1902. DOI: 10.18632/aging.101894.

Wilson JM, Nguyen AT, Schuyler AJ, Commins SP, Taylor AM, Platts-Mills TAE, McNamara CA (2018). IgE to the mammalian oligosaccharide galactose-α-1,3-galactose is associated with increased atheroma volume and plaques with unstable characteristics-Brief report. Arterioscler Thromb Vasc Biol 38(7): 1665–1669. DOI: 10.1161/atvbaha.118.311222.

Young I, Prematunge C, Pussegoda K, Corrin T, Waddell L (2021). Tick exposures and alpha-gal syndrome: A systematic review of the evidence. Ticks Tick Borne Dis 12(3): 101674. DOI: 10.1016/j.ttbdis.2021.101674.