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Understanding the presence of xeno-derived Neu5Gc in the human body, and its significance: a review

Abstract

N-glycolneuraminic acid (Neu5Gc) is a sialic acid mainly found in mammalian species. It is absent in humans. This is due to an irreversible mutation of the CMP-Neu5Ac hydroxylase (CMAH) enzyme in humans, rendering them unable to synthesize Neu5Gc. The human body identifies Neu5Gc as "foreign"; and anti-Neu5Gc antibodies are produced by the human body in response to any metabolically incorporated, diet-derived Neu5Gc, as found in ingested red meats and dairy products.Varying quantities of Neu5Gc is found in some approved biotherapeutics used for the treatment of numerous medical conditions. This leads to the debate of potential risks and/or benefits of Neu5Gc in humans. The effects of the interaction between anti-Neu5Gc antibodies and antigenic Neu5Gc-containing biotherapeutics in humans are largely unknown and there are many discrepancies in terms of scientific evidence. This article reviews and discusses the current knowledge in the understanding of Neu5Gc in the human body and its potential significance.

Keywords: N-glycolneuraminic acid, Neu5Gc, anti-Neu5Gc antibodies, sialic acid, CMAH

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Introduction

Sialic acids are a family of nine-carbon sugar acids. They are monosaccharides displayed on the non-reducing termini of cell surface glycans in all vertebrates.[1] These acidic 9-carbon saccharides cover the ends of millions of glycan chains per cell. In mammalian species and other vertebrates, the sialic acids N-acetylneuraminic acid (Neu5Ac) and its derivative N-glycolylneuraminic acid (Neu5Gc) are the two most common forms, each a family of molecules with various modifications of the canonical, 9-carbon monosaccharide. They are hydrophilic, with a negative charge; and are involved in many biological, molecular and cellular interactions.[2,3] Catalysis of the Neu5Ac precursor by the enzyme CMP-Neu5Ac hydroxylase (CMAH) produces Neu5Gc by the addition of a hydroxyl group.[4] However, the human species is genetically unable to produce Neu5Gc, due to the irreversibly mutated CMAH gene.[5] This absence of Neu5Gc in humans possibly affects the recognition process of endogenous and exogenous sialic-acid binding lectins.[6]

Besides the human species, absence of the *CMAH* homologs has been reported in several species of birds, reptiles, New World monkeys, and sperm whales. These species are unable to produce Neu5Gc.[7] Nonhuman Neu5Gc was first discovered in humans when Hanganutziu and Deicher independently observed heterophilic antibody in sera of patients who had received therapeutic injections of horse serum-based anti-toxoid.[8,9] These nonhuman Neu5Gc have since been referred to as Hanganutziu–Deicher (H–D) antibodies or serum sickness antibodies. When Higashi et al. (1977) and Merrick et al. (1978) studied the characterisation of the antigenic determinants of the H-D antibodies, it was found that some of the major epitopes recognized were gangliosides containing Neu5Gc.[10,11]

In spite of the inability of the human species to produce Neu5Gc, accumulations of xenoglycan Neu5Gc have been reported in humans; the amounts of Neu5Gc are highly variable between individuals, and between tissues within individuals. Neu5Gc has been detected in smaller quantities on certain human cell types, in particular epithelial and endothelial cells.[5] Tangvoranuntakul et al. (2003) had reported that small quantities of Neu5Gc were being metabolically incorporated into newly synthesized glycoproteins in humans after the ingestion of porcine submaxillary mucin sialic acids (95% of Neu5Gc, 5% Neu5Ac).[12] How ingested Neu5Gc becomes incorporated into the human body is still unclear. It seems that Neu5Gc is first converted to GalNGc and then incorporated into the glycosaminoglycan chondroitin sulfate, an important component of extracellular matrices and skeletal bone.[13]

Normal healthy humans would have circulating antibodies against Neu5Gc, but the levels of IgMs and IgGs anti-Neu5Gc antibodies may be variable.[12,14] Unfortunately, since anti-Neu5Gc antibodies recognise multiple Neu5Gc epitopes, it is difficult to determine the overall level of anti-Neu5Gc antibodies in individual human samples.[15] It is believed that anti-Neu5Gc antibodies begin to be generated in humans during infancy, specifically in relation to weaning and dietary exposure.[16]

Many of the red meats we consume contain high amounts of Neu5Gc.[4] Among the red meats, the highest levels of Neu5Gc are found in beef, followed by pork and lamb.[17] Minute traces of Neu5Gc, less than 0.7% of total sialic acid fraction, are also found in chicken.[18] Long term consumption and high intake of red meats have been associated with various types of cancer,[19] and anti-Neu5Gc antibodies are alleged to be involved in these and many other diseases. However, none of these mechanisms is conclusively proven. This article attempts to assess the possible deleterious and/or therapeutic roles of this xeno-sialic acid Neu5Gc and its associated antibodies.

Cancer progression and anti-tumour activities of Neu5Gc

The human body is unable to produce Neu5Gc, and regard these as foreign. When exposed to Neu5Gc molecules, humoral immunity is activated, and this initiates the production of anti-Neu5Gc antibodies.[16,20] Studies have shown that the metabolic incorporation of dietary Neu5Gc into human tissues as xeno-autoantigens, induces xenosialitis, caused by the reaction with circulating anti-Neu5Gc antibodies in human tissues.[14,21] This inflammatory process, xenosialitis, has been associated with cancer progression, cardiovascular diseases and autoimmune diseases.[5,14]

There are concerns that the incorporation of dietary Neu5Gc could elicit an immune response which may result in chronic inflammation and cancer.[22] However, a large cohort study of over 200,000 kidney transplant patients including 522 patients with colon cancer did not support the hypothesis that long term over-exposure to anti-Neu5Gc antibodies triggers malignancies in the colon.[23] In the study, there was no estimation regarding red meat intake, as patients with renal failure are typically advised to reduce meat intake. In addition, some of these patients were also under immunosuppression, which would alter the outcomes. Pearce et al. (2014) have shown that anti-Neu5Gc antibodies promote liver tumour progression by enhancing inflammation in Neu5Gc-deficient *CMAH*null mice.[24] The same group of researchers also reported that tumour growth was stimulated at low anti-Neu5Gc antibody concentrations; however, tumour growth was inhibited at higher anti-Neu5Gc concentrations in Neu5Gc deficient mice.[24] Rodríguez-Zhurbenko et al. (2013) found that low levels of anti-Neu5Gc antibodies are found in non-small cell lung cancer patients, while a higher level of the antibodies was found in healthy volunteers, suggesting that anti-Neu5Gc antibodies might possess antitumor immune surveillance function.[25] The study led by De villliers and ZurHausen's group demonstrate another potential carcinogenic mechanism arising from red meat that revealed by the isolation of a number of small DNAs derived from specific plasmids of Acinetobacter bacteria from commercially available cow milk.[26–28]Possible host infections from replicating plasmids are potential risk factors for human colon and breast cancers,[29] that incorporated Neu5Gc from dietary sources could present receptors for the viruses, and antibodies against these viral proteins orchestrate together Neu5Gc-induced xenosialitis. Further research is warranted to further investigate the exact mechanism of how Neu5Gc promotes or inhibits the progression of tumour.

Significance of elevated anti-Neu5Gc antibodies in allergies and asthma

Frei et al. (2018) investigated the role of exposure to Neu5Gc in children of farmers and non-farmers. The findings were that higher levels of anti-Neu5Gc antibodies were detected in these farmers' children when compared to nonfarmers' children. Their results showed that the higher anti-Neu5Gc IgG levels were correlated with less asthma and wheezing.[30] It has been shown that mice sensitized with ovalbumin and house dust mites resulted in reduced airway hyperresponsiveness and reduced inflammatory cell recruitment to the lungs.[30] This suggests that the exposure to Neu5Gc in children living in rural areas induced an elevated anti-Neu5Gc antibodies, which reduces their response to allergens, thus providing a reduced incidence of allergies.[20]

Properties of anti-Neu5Gc antibodies, and its association to red meats

The presence of anti-Neu5Gc antibodies has been reported to protect against reactive airways, inflammation, and colitis.[30] However, there is inadequate evidence to support the association of red meats consumption with increased inflammations. Hodgson et al. (2007) revealed that the intake of red meats did not increase oxidative stress and inflammation in humans.[31] In contrast, increased lean meats consumption at the expense of partial carbohydrate-rich food, leads to a reduction of some inflammatory markers.[31]

Causal link between serum sickness and anti-Neu5Gc antibodies

Couvrat-Desvergnes et al. (2015) suggested a causal link between anti-Neu5Gc antibody levels and long-term graft survival, although this causal link was not confirmed.[32] The author noted that serum sickness disease is a major contributing factor to late graft loss, and that the anti-Neu5Gc antibodies levels are increased in patients with serum sickness disease. The author made no mention of the dietary habits of these patients. Any plausible link between anti-Neu5Gc antibody levels and long-term graft survival cannot be confirmed from this clinical study.

Neu5Gc and xeno-derived biotherapeutics

In recent decades, pharmaceutical products that have animal-based and animal-derived components, have significantly diversified. Many different animal sources were investigated as technology advances and purification techniques progress; this ranged from pufferfish in the 1960s to, most recently, genetically engineered animals.[33] These biotherapeutic products involve non-human mammalian cells (such as cow, horse, hamsters and pig); which contain Neu5Gc.[12] The levels of Neu5Gc in these biotherapeutics vary according to the production systems.[34] Examples of some of these pharmaceutical products that incorporate animal-derived components are as shown in Table 1.[33,35,36]

Neu5Gc is found in many biotherapeutic agents such as Alemtuzumab (Campath®, Mabcampath®), Bevacizumab (Avastin®), Cetuximab (Erbitux®), Daclizumab (Zenapax®), Erythropoietin (Procrit®), Rituximab (Rituxan®, Mabthera®) and Trastuzumab (Herceptin®). Among these therapeutic agents, Cetuximab has the highest Neu5Gc content (1.77 mol Neu5Gc/mol antibody), followed by Daclizumab (0.081 mol Neu5Gc/mol antibody) and Erythropoietin (0.014 mol Neu5Gc/mol antibody).[37] Cetuximab has been approved by the US FDA on February 2004 and is used to treat patients with advanced colorectal cancer. In in-vivo studies using mouse models, Cetuximab's efficiency was noted to be reduced by Neu5Gc/anti-Neu5Gc antibodies.[37] However, there is no clear evidence of their effects on Cetuximab's efficiency in humans.

Table 1 Pharmaceutical products derived from non-human mammalian cells[33,35,36]

Origin	Generic name	Product name	Therapeutic class
Bovine	Allantoin	Allantoin	Cosmetics, treatment of wounds & ulcers
	Sealer protein solution + thrombin solution	Tisseel VH S/D Solution	Haemostatic agent
	Bovine colostrum	Travelan	Anti-diarrhoeal
	Calfactant	Infasurf	Treatment of premature infant lungs
	Calporo	Calporo	Herbal daily supplements
	Cartilag	Cartilag	Herbal analgesics & anti inflammatories
	Collagen	Zyderm Collagen implants	Dermatological preparations
	Epinephrine	Adrenaline	Neurotransmitter
	Hepatitis A vaccine	Vivaxim	Vaccine
	Insulin	Hypurin injection	Insulin preparations
	Polygeline	Haemaccel	Plasma volume expander
	Survanta	Beractant	Treatment of premature infant lungs
	Varicella zoster vaccine, live	Varivax	Vaccine
Bovine-indirect	Acitretin	Novatretin	Antipsoriatic
	Amoxycillin	Synamox	Antibiotic, Penicillin
	Ampicillin Sod + Sulbactam Sod	Unasyn	Antibiotic, Penicillin
	Calcitriol	Osteocap	Vitamin D Analog
	Celecoxib	Celebrex	NSAID, Cyclooxygenase-2 inhibitor
	Clindamycin HCl	Tidact	Antibiotic, Lincosamide
	Clofazimine	Fazim	Antibiotics, Leprostatic
	Cyclosporin	Sandimmun	Immunosuppressant, Calcineurin inhibitor
	Danazol	Nazo	Androgen
	Didanosine	Aurobindo	Antiretrovirals
	Diphtheria toxoid	ADT Booster Boostrix	Vaccine
	Doxycycline	Xidox	Antibiotics, Tetracyclines derivatives
	Dutasteride	Avodart	5-alpha-reductase inhibitor
	Essential Phospholipids	Livovid	Cholelitholytics
	Fluconazole	Fluconazole	Antifungals
	Gemfibrozil	Gemfibrozil	Dyslipidaemic agents
	Haemophilus B influenzae vaccine	Hiberix	Vaccine
	Heparin sodium injection	Heparinol	Anticoagulant
	Hepatitis A vaccine	Avaxim Havrix	Vaccine
	Hepatitis B vaccine	Engerix-B	Vaccine
	Hydrocortisone	Hydrocortison Orion	Corticosteroid
	Influenza virus vaccine	Fluarix	Vaccine
	Isotretinoin	Acnotin	Antiacne, antineoplastic agent
	Itraconazole	Itrazol Inox	Antifungal, azole derivative
	Loperamide	Colodium Modim	Antidiarrheal
	Measles, mumps & rubella vaccine	Priorix	Vaccine
	MebeverineHCl	Mebetin	Antispasmodics
	MycophenolateMofetil	Cellcept	Immunosuppressant agent
	Nilotinib	Tasigna	Antineoplastic agent, thyroxine kinase inhibitor
	Omeprazole	Omeprazole	Gastric acid secretion inhibitor, proton pump inhibitor
	Oseltamivir phosphate	Fluhalt	Antiviral, influenza, neuraminidase inhibitor
	Oxycodone HCl	Oxynorm	Opioids analgesic
	Pancreatin	Creon	Pancreatic enzyme replacement
	diphtheria, tetanus &acellular pertussis vaccine	Adacel	Vaccine
	Phenytoin sodium	Dilantin	Anti-epilepsy
	Pneumococcal vaccine	Prevenar	Vaccine
	Pregabalin	Lyrica	Anticonvulsant
	Rabies human diploid cell vaccine	Verorab	Vaccine
	Rabies vaccine	Merieux Rabipur	Vaccine
	Recombinant antihaemophilic factor	Recombinate	Haemostatic agents
	Rivastigmine	Rivadem	Acethylcholinesterase inhibitor
	Tacrolimus	Prograf	Immunosuppressant agent
	Yellow fever vaccine	17D vaccine	Vaccine

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Table Continued...

Origin	Generic name	Product name	Therapeutic class
Equine (horse)	Antithymocytelmmuglobulin (ATG)	ATGAM	Immunosuppressant
	Conjugated oestrogen	Premarin	Gonadal hormone, Oestrogen
	Medroxyprogesterone acetate	Premia	Gonadal hormone
	Snake antivenom	Sea snake antivenin	Antivenom
		Polyvalent Snake Antivenin	
		Cobra Antivenin	
		King Cobra Antivenin	
		Green Pit Viper Antivenin	
		Red back spider antivenom	
		Taipanantivenom	
		Tiger snake antivenom	
	Stonefish antivenom	Stonefish antivenom	Antivenom
Chinese hamster ovary (CHO) cells	Abatacept	Orencia	Immunomodifier
	Aflibercept	Eylea	Ophthalmic medication
	Agalsidase beta	Fabrazyme	Enzyme replacement therapy
	Alemtuzumab	Mabcampath	Antineoplastic agent
	Bevacizumab	Avastin	Antineoplastic
	Choriogonadotropinalfa	Ovidrel	Pituitary hormone
	Corifollitropinalfa	Elonva	Pituitary hormones
	Darbepoietin	Aranesp	Haemopoietic agent
	Denosumab	Prolia	Monoclonal antibody
		Xgeva	
	Dornasealfa	Pulmozyme	Respiratory agent
	Epoetin lambda	Novicrit	Haemopoietic agent
	Epoietin beta	NeoRecormon	Haemopoietic agent
	Epoietinalfa	Eprex	Haemopoietic agent
	Eptacogalfa	NovoSeven RT	Haemostatic agent
	Erythropoeitinalfa	Binocrit	Hematopoietic agent
	Etanercept	Enbrel	Tumour necrosis factor inhibitor
	Follitropinalfa	Gonal-f	Pituitary hormone
	Follitropin beta	Puregon	Pituitary hormone
	Imiglucerase	Cerezyme	Enzyme replacement therapy
	Interferon beta-1a	Avonex	Immunomodifier
		Rebif	
	Laronidase	Aldurazyme	Enzyme replacement therapy
	Lenograstim	Granocyte	Supportive therapy
	Lutropinalfa	Luveris 75 IU	Pituitary hormone
	Methoxy polyethylene glycol-epoetin beta	Micera	Hematopoietic agent
	Moroctocogalfa	Xyntha	Haemostatic agent
	Nonacogalfa	BeneFIX	Haemostatic agent
	Octocogalfa	Advate	Haemostatic agent
		Kogenate FS	
	Omalizumab	Xolair	Other respiratory agent
	Panitumumab	Vectibix	Antineoplastic agents
	Recombinateantihaemophilic factor	Recombinate	Haemostatic agent
	Rituximab	Mabthera	Antineoplastic agent
	Tenecteplase	Metalyse	Fibrinolytic agent
	Trastuzumab	Herceptin	Antineoplastic agent

Table Continued...

Origin	Generic name	Product name	Therapeutic class
Porcine	Amylase, lipase, pancrelipase, protease	Panzytrat	Digestive supplement
	Coagulation factors II, IX, X, V & VII	Prothrombinex-VF	Haemostatic agent
	Dalteparin	Fragmin	Anticoagulant
	Danaparoid	Orgaran	Haemostatic agent
	Enoxaparin	Clexane	Anticoagulant, Antithrombotics
	Heparin sodium	Heparinised saline	Anticoagulant
	Human rotavirus live attenuated vaccine	Rotarix	Vaccine
	Pancrelipasepancreatin	Creon	Digestive supplements and cholelitholytics
	Poractantalfa	Curosurf	Respiratory agent
	Rotavirus vaccine live oral pentavalent	RotaTeq	Vaccine
	Vancomycin Hydrochloride	VancomycinHCl	Antibiotic, miscellaneous
	Zoster virus vaccine live	Zostavax	Vaccine
Murine	Abciximab	Reopro	Anticoagulant
	Antihemophilic Factor VIII (human)	Hemofil M	Antihemophlic Agent
	Basiliximab	Simulect	Immunomodifier
	Bevacizumab	Avastin	Antineoplastic agent
	Cetuximab	Erbitux	Antineoplastic agent
	Golimumab	Simponi	Antirheumatic agent
	Infliximab	Remicade	Monoclonal antibody
	Palivizumab	Synagis	Immunomodifier
	Rituximab	MabThera	Antineoplastic agent; Monoclonal antibody
	Somatropin	Saizen	Pituitary hormone
	Trastuzumab	Herceptin	Antineoplastic agent

Breakthrough advances in medical science have been in the fields of transplantations, stem cells therapy, and use of xeno-derived biotherapeutics. Porcine pancreatic islet transplantation has been used to successfully treat type 1 diabetes patients, even without the use of any immunosuppressant.[38] Xeno-derived fetal stem cells, that have low expression of MHC class I, and no expression of MHC class II, do not evoke an immune response during transplantation when compared to their adult counterpart.[39] This may be link to the absence, low levels, or lack of expression of Neu5Gc. Research has shown that the absence or decreased number of dendritic cells linked to a reduced immunogenicity of the progenitor stem cell makes these cross-species transplantations less susceptible to rejection and are better tolerated.[40–42] The significance of the roles and effects of Neu5Gc in these transplanted xeno-derived biotherapeutics are yet to be determined.

Conclusion

Neu5Gc is a 'foreign entity' to the human body. It is antigenic and provokes the production of anti-Neu5Gc antibodies. Its entry into the body is via ingestion of animal proteins, via xeno-derived pharmaceuticals, via xeno-transplantations of tissues and organs, and via injections of xeno-derived progenitor stem cells and peptides. There are many discrepancies in terms of scientific evidences to support or refute the potential benefits or harm of Neu5Gc and anti-Neu5Gc antibodies in humans. Current literature and research suggest that Neu5Gc and anti-Neu5Gc antibodies have shown both a therapeutic and deleterious role. Further studies in the field of Neu5Gc will allow us to gain a better understanding of the roles and mechanisms of actions of this unique sialic acid. Studies on the anti-Neu5Gc antibodies will allow an understanding of the possible modulating effects to the immune system of the human body. For instance, the details of particular Neu5Gc metabolism processes might provide a variety of potential targets for new drug development as clinicians use a huge range of products derived from non-human mammalian cells and organs and it is very important which of them produce significant amounts of antigen-antibodies reactions especially to those in critical condition with compromised immune system.

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None.

Conflicts of interest

None.

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