Review Article

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Presence of Neu5Gc in Animal-Derived Products. Friend Or Foe?

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ABSTRACT

N-glycolneuraminic acid (Neu5Gc) is a sialic acid majorly found in mammalian species except for human. The irreversible mutation of CMP-Neu5Ac hydroxylase (CMAH) enzyme caused the human inability to synthesize Neu5Gc. However, anti-Neu5Gc antibodies are still produced by the human body in response to the metabolic incorporation of diet-derived Neu5Gc, especially red meat and dairy products. Neu5Gc have been found in varying quantities on some approved biotherapeutics for treatment of numerous medical ailments, leading to the debate of the potential risk or benefit of Neu5Gc in human. The effects of the interaction between anti-Neu5Gc antibodies and antigenic Neu5Gc-containing biotherapeutics in human are largely unknown and there are still many discrepancies in terms of scientific evidence. This review article discusses the current knowledge of the proposed deleterious and therapeutic role of Neu5Gc.

Keywords

N-glycolneuraminic acid, Neu5Gc, Immunity, Enzyme, Antibodies.

Introduction

Sialic acids are a family of nine-carbon sugar acid, monosaccharides displayed on the non-reducing termini of cell surfaces glycans in all vertebrates [1]. They have hydrophilic character with a negative charge and are involved in many biological, molecular and cellular interactions [2]. The two major mammalian sialic acids found in mammalian species are N-acetylneuraminic acid (Neu5Ac) and N-glycolneuraminic acid (Neu5Gc) [3]. Neu5Gc synthesis begins with the catalysis of Neu5Ac precursor by the CMP-Neu5Ac hydroxylase (CMAH) enzyme with the addition of hydroxyl group [4]. However, humans are genetically unable to produce Neu5Gc because the human gene CMAH is irreversibly mutated [5]. The loss of Neu5Gc in humans could affect the recognition process of endogenous and exogenous sialic-acid binding lectins [6].

Besides humans, several species of birds, reptiles, New World monkeys, and sperm whales have been reported to be absent of the CMAH homologs and therefore 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 anti-toxoid [8,9]. These are since referred to as Hanganutziu–Deicher (H–D) antibody or serum sickness antibodies. When Higashi et al. and Merrick et al. studied the characterisation of the antigenic determinants of the H-D antibody, it was found that some of the major epitopes recognized were gangliosides containing Neu5Gc [10,11].

Despite human's inability to produce Neu5Gc, accumulation of xenoglycan Neu5Gc has been reported in humans, although the amount of Neu5Gc is highly variable between individuals and between tissues within individuals. Neu5Gc has been detected in smaller quantities on certain human cell types, in particular epithelia and endothelia cells [5]. Tangvoranuntakul et al. reported small quantities of Neu5Gc were metabolically incorporated into newly synthesized glycoproteins in humans after the ingestion of porcine submaxillary mucin Sias (95% of Neu5Gc, 5% Neu5Ac) [13].

Most normal healthy humans would have circulating antibodies against Neu5Gc, but the amount of IgM, IgG and IgG may be variable [12,113]. Unfortunately, since anti-Neu5Gc antibodies recognise multiple Neu5Gc epitopes, it is currently difficult to determine the overall level of anti-Neu5Gc antibodies in individual human samples [14]. It is believed that anti-Neu5Gc antibodies begin to be generated in humans during infancy, particularly in relation to weaning and dietary exposure [15].

Many of the red meat we consume contain high amounts of Neu5Gc [4]. Among the red meats, the highest level of Neu5Gc is found in beef, followed by pork and lamb [17]. Minute traces of Neu5Gc, below than 0.7%, are also found in chicken [18]. Long term consumption and high intake of red meat have been associated with various types of cancer [16], and anti-Neu5Gc antibodies are alleged to be involved in many types of diseases. However, none of these mechanisms are conclusively proven. This review article further describes the deleterious or therapeutic role of Neu5Gc.

Cancer progression or anti-tumour activity of Neu5Gc

Humans are unable to produce Neu5Gc. However, during the exposure of Neu5Gc molecules, humoral immunity is activated and thus initiates the production of anti-Neu5Gc antibodies [15,19]. Studies have shown the metabolic incorporation of dietary Neu5Gc into human tissues as xeno-autoantigens will induce xenosialitis due to the reaction with circulating anti-Neu5Gc antibodies produced by human tissues [12,20]. Xenosialitis is an inflammation caused by the reaction against a xeno-sialic acid which has been associated with cancer progression, cardiovascular diseases and autoimmune diseases [5,12].

Although there are concerns that incorporation of Neu5Gc from human diet elicit an immune response that may result in chronic inflammation, rheumatism and cancer [21], a large cohort study of over 200,000 kidney transplant patients including 522 patients with colon cancer do not support the hypothesis that long term over-exposure to anti-Neu5Gc antibodies following induction ATG treatment, triggers malignancy in colon [22]. However, there was no estimation regarding red meat intake in this study, and patients with renal failure are typically advised to reduce meat intake. Furthermore, some such patients are also under immunosuppression, which would alter outcomes. Previous reports by Pearce et al. (2014) show that anti-Neu5Gc antibodies promote liver tumour progression by enhancing inflammation in Neu5Gc-deficient Cmah-/- mice [17]. In the later part, the same group of researchers 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 [23]. Additionally, 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 anti-Neu5Gc antibodies was found in healthy volunteers, suggesting that anti-Neu5Gc antibodies might possess antitumor immune surveillance function [24]. These findings provide potential implications for researchers to investigate further on the exact mechanism of Neu5Gc to promote or inhibit the progression of tumour.

Protection against allergies and asthma in the presence of elevated anti-Neu5Gc antibodies

Frei et al. (2018) investigated the role of exposure to Neu5Gc in farmers' children and found that higher levels of anti-Neu5Gc antibodies were detected in farmers' children when compared to nonfarmers' children, in which their higher anti-Neu5Gc IgG levels were correlated with less asthma and wheezing [25]. It was postulated that mice sensitized with ovalbumin and house dust mites resulted in reduced airway hyperresponsiveness and reduced inflammatory cell recruitment to the lungs, suggesting Neu5Gc might contribute protective effects in the farm environment [25]. Furthermore, the exposure to Neu5Gc by children in living in the rural areas showed protection against allergies, in which there was elevated anti-Neu5Gc antibodies [19].

Anti-inflammatory properties of Neu5Gc and its association to red meat

Anti-inflammatory properties of Neu5Gc were reported to protect against airway inflammation and colitis [25]. Other studies suggested that there was not enough evidence to support the association that red meat leads promote inflammations, although these studies did not specifically focus on Neu5Gc. For example, Hodgson et al. reveal that the intake of red meat does not increase oxidative stress and inflammation in human [26]. In contrast, an increase in lean meat consumption at the expense of partial carbohydrate- rich food replacement leads to the reduction of some inflammatory markers [26].

Unconfirm causal link between serum sickness and anti-Neu5Gc antibodies

Couvrat-Desvergnes et al. suggest a causal link between anti-Neu5Gc antibody levels and long-term graft survival, although this causal link was not confirmed in their study (2015) [27]. The author only addressed that serum sickness disease is a major contributing factor of late graft loss and that the anti-Neu5Gc antibodies levels are increased in patients with serum sickness disease. In addition, the author also did not indicate the food habit of those patients. However, the possible link between anti-Neu5Gc antibody levels and long-term graft survival cannot be confirmed from this clinical study.

Neu5Gc and animal-derived biotherapeutics products

In recent decades, pharmaceutical production from animal products has significantly diversified. Many different animal sources were investigated as purification techniques progressed, ranging from puffer fish in the 1960s to, most recently, genetically engineered animals [28]. These biotherapeutics production usually involves non-human mammalian cells (such as cow, horse, hamsters and pig), thus are likely to contain some levels of Neu5Gc [13]. Furthermore, Neu5Gc levels in biotherapeutics vary according to the production systems [29]. Examples of some of the pharmaceutical products derived from non-human mammalian cells are shown in Table 1 [28,30,31].

Neu5Gc has been found in many clinically used 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 contained 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) [32]. Cetuximab has been approved

by the US FDA on February 2004 and is used to treat patients with advanced colorectal cancer. Although an in vivo study using mouse model suggested that Cetuximab's efficiency was reduced by Neu5Gc/anti-Neu5Gc [32], clear evidence of their effects on Cetuximab's efficiency in humans is yet to be provided.

Further to that, the medical community has begun to turn towards animal-derived cell therapy products in recent years. For example, porcine pancreatic islet transplantation has been used to treat type 1 diabetes patients with great success, some even without the use of any immunosuppressant [33]. Another interesting approach is the transplantation of animal fetal stem cells, which is believed to not evoke immune response due to their low expression of MHC class I and no expression of MHC class II, resulting in reduced immunogenicity during transplantation when compared to their adult counterpart [34]. Research reveals that the absence or decreased number of dendritic cells may contribute towards the reduced immunogenicity of fetal cell, making them less susceptible to rejection and tolerated better in cross-species transplantations [35-37].

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	Vaccine
		Boostrix	
	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	Vaccine
		Havrix	
	Hepatitis B vaccine	Engerix-B	Vaccine
	Hydrocortisone	Hydrocortison Orion	Corticosteroid
	Influenza virus vaccine	Fluarix	Vaccine
	Isotretinoin	Acnotin	Antiacne, antineoplastic agent

Bovine-indirect	Itraconazole	Itrazol	Antifungal, azole derivative
		Inox	
	Loperamide	Colodium	Antidiarrheal
		Modim	
	Measles, mumps & rubella vaccine	Priorix	Vaccine
	Mebeverine HCl	Mebetin	Antispasmodics
	Mycophenolate Mofetil	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	Vaccine
		Rabipur	
	Recombinant antihaemophilic factor	Recombinate	Haemostatic agents
	Rivastigmine	Rivadem	Acethylcholinesterase inhibitor
	Tacrolimus	Prograf	Immunosuppressant agent
	Yellow fever vaccine	17D vaccine	Vaccine
Equine (horse)	Antithymocyte Immuglobulin (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	
		Taipan antivenom	
		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
	Choriogonadotropin alfa	Ovidrel	Pituitary hormone
	Corifollitropin alfa	Elonva	Pituitary hormones
	Darbepoietin	Aranesp	Haemopoietic agent
	Denosumab	Prolia	Monoclonal antibody
		Xgeva	
	Dornase alfa	Pulmozyme	Respiratory agent
	Epoetin lambda	Novicrit	Haemopoietic agent
	Epoietin beta	NeoRecormon	Haemopoietic agent

Chinese hamster ovary (CHO) cells	Epoietin alfa	Eprex	Haemopoietic agent
	Eptacog alfa	NovoSeven RT	Haemostatic agent
	Erythropoeitin alfa	Binocrit	Hematopoietic agent
	Etanercept	Enbrel	Tumour necrosis factor inhibitor
	Follitropin alfa	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
	Lutropin alfa	Luveris 75 IU	Pituitary hormone
	Methoxy polyethylene glycol-epoetin beta	Micera	Hematopoietic agent
	Moroctocog alfa	Xyntha	Haemostatic agent
	Nonacog alfa	BeneFIX	Haemostatic agent
	Octocog alfa	Advate	Haemostatic agent
		Kogenate FS	
	Omalizumab	Xolair	Other respiratory agent
	Panitumumab	Vectibix	Antineoplastic agents
	Recombinate antihaemophilic factor	Recombinate	Haemostatic agent
	Rituximab	Mabthera	Antineoplastic agent
	Tenecteplase	Metalyse	Fibrinolytic agent
	Trastuzumab	Herceptin	Antineoplastic agent
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
	Pancrelipase pancreatin	Creon	Digestive supplements and cholelitholytics
	Poractant alfa	Curosurf	Respiratory agent
	Rotavirus vaccine live oral pentavalent	RotaTeq	Vaccine
	Vancomycin Hydrochloride	Vancomycin HCl	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

Table 1: Pharmaceutical products derived from non-human mammalian cells [28,30,31].

Conclusion

There are still many discrepancies in terms of scientific evidence to support or refute the potential benefits or harm of Neu5Gc in humans. In fact, current data suggest that Neu5Gc have shown both promising therapeutic and deleterious role. Hence, further studies are required in order to gain a better understanding of the mechanism of this unique sialic acid.

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