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Tick bite induced α -gal syndrome highlights anticancer effect of allergy

Péter Apari, Gábor Földvári 

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Abstract

Tick bite induced α -gal syndrome (AGS) following consumption of mammalian meat is a recently described intriguing disease occurring worldwide. Here we argue that AGS and delayed allergy in general is an adaptive defence method against cancer. Our hypothesis synthesizes two lines of supporting evidence. First, allergy has been shown to have direct anti-cancer effects with unknown mechanism. Second, eating processed meat was shown to be linked to developing cancer. Humans lost their genes encoding molecules α -gal 30 MYA and Neu5Gc 2 MYA, the latter co-occurring with the start of using fire. These molecules are acquired from external sources, as tick bite for α -gal and mammalian meat for Neu5Gc, the latter accumulating in tumors. The resulting specific delayed allergic response is a molecular adaptation to fight cancer. By further testing and applying our hypothesis, new avenues in cancer research and therapy will open that might save lives and decrease human suffering.

INTRODUCTION

Ticks (Acari: Ixodidae and Argasidae) are obligate hematophagous arthropods well known for transmitting a wide spectrum of viruses, bacteria, and protists.^[1] Besides their important role as vectors of pathogens of medical and veterinary importance, ticks can also cause different kinds of toxicoses that probably give selective advantage for their own survival.^[2] Recently, a new type of disease has been associated with tick bites: a delayed allergic reaction after consumption of mammalian meat (often referred to as red meat).^[3]

During the tick-bite induced α -gal syndrome (AGS) a type of allergy develops that leads to IgE antibody response against the carbohydrate Galactose- α -1,3-galactose (α -gal). The latter is present in glycoproteins from tick saliva and tissues of non-catarrhine mammals, with other words, this molecule is absent in old-world monkeys and apes including humans. Repeated tick bites of the same individual induce high levels of anti- α -gal IgE antibodies that results in a delayed hypersensitivity to consumed mammalian meat products in humans.^[3] For the first time, tick glycoproteins were shown to play an important role in allergy development. This newly described condition can potentially cause fatal delayed anaphylaxis to α -gal-containing foods and drugs and immediate anaphylaxis to tick bites. The disease has been reported in every continent where hard ticks occur and it has been associated with several tick species and genera. At the time of the first reports, the origin of tick-derived α -gal was thought either to be blood meal remnants from mammalian glycoproteins containing α -gal or bacteria present in tick midgut producing this glycan. Recent studies gave new insights and tick galactosyltransferases were reported to be responsible for α -gal synthesis that might play substantial roles in the life cycle of both ticks and tick-borne pathogens.^[3]

The α -gal epitopes are abundantly expressed on cells of nonprimate mammals and New World monkeys, whereas non-catarrhine mammals like humans lack this epitope but produce against it a large amounts of anti- α -gal antibodies. The α -gal molecule has been lost from these groups nearly 30 million years ago supposedly to protect them from pathogenic organisms like viruses, bacteria and protists that are abundantly decorated with this glycan.^[4] It is supposed that immunological reaction against α -gal molecules is an effective evolutionary solution to protect the hosts from life threatening pathogenic organisms. However, the recently discovered mysterious delayed allergic reaction to mammalian meat, the tick bite induced AGS, can also lead to deadly anaphylactic shock in some patients after 3–6 h.^[5]

We assume that anti- α -gal immune response not only effects important high-virulence acute infections but also low virulence chronic ones that can have hidden prolonged debilitating consequences. A recent report has suggested a relationship between anti- α -gal antibodies and Alzheimer's disease.^[6] The elevated level of anti- α -gal molecules in Alzheimer patients is well in line with our hypothesis because there are studies linking this disease to chronic pathogen activities.^[7-9] Moreover, according to some research amyloid plaques themselves have antimicrobial effects.^[10, 11] Consequently, anti- α -gal response might be effective against different kinds of cancers if we consider the frequent infectious background of this serious disease group.^[12] There is an inverse relationship between allergy and cancer affecting mouth, throat, brain glia, colon, rectum, pancreas, skin, and cervix.^[13, 14] One explanation to this enigmatic phenomenon comes from Margie Profet who proposed a very attractive hypothesis to solve this mystery. According to her the immediate symptoms of allergy namely sneezing, coughing, diarrhea, etc., are preventive reactions activating in seconds or minutes against potentially deadly toxins even carcinogens.^[15] At first sight the

inverse relationship between cancer and allergy is well explained by this hypothesis. But there is another class of allergic reactions which is manifested only after hours instead of minutes and these types of allergies could not have the preventive function mentioned by Profet. How can we resolve this paradox?

Here we propose a hypothesis that in the case of delayed allergy, the reaction is not prevention but a direct attack against cancer cells to destroy them. It has been a long-time controversy that allergy has direct effects against tumor cells but the exact mechanisms are unknown. Beside the theories that try to explain the negative relationship between allergy and cancer there is another called immune surveillance hypothesis. This states that the allergy makes the immune system hypersensitive but the exact molecular mechanism needs clarification.^[16] In this hypothesis article we argue through the lens of tick bite induced AGS that allergic reaction can also target cancer tissue and we can propose a plausible molecular mechanism for this.

Allergy, α -gal, pathogens, and tumors are interconnected

The prophylaxis theory of allergy has gained momentum and become very popular.^[17] It explains well the immediate form of allergy but struggled to clear the delayed late-phase 1. If a toxin enters into the host body the immune system must react very quickly because any delay could be fatal. In the case of tick bite induced AGS developing after the consumption of mammalian meat, even the life-threatening food allergy reaction manifests only after 3–6 h^[18] which is paradoxical in terms of the prophylaxis theory. We theorize that there is another specific target for this reaction: to directly attack and destroy tumor cells inside the host body.

In the mainstream scientific literature most articles mentioned α -gal as the central molecule in the pathogenesis of the AGS allergic reaction. However, there are many examples where the suspect is a different kind of protein instead of the sugar molecule.^[5] After mosquito bites, e.g., a tick α -gal-like molecule can induce hypersensitivity reaction in the host organism. However, not only this molecule can be allergic but many proteins play role in the development of the hypersensitivity reactions. Interestingly, many of them have delayed allergy-like responses similarly to the case of tick bite induced AGS developing after the ingestion of mammalian meat.^[19] Moreover, the levels of anti- α -gal antibodies produced show inconsistent patterns when we try to find correlation with the severity of symptoms.^[20] We hypothesize that these differences mainly depend on the size and prevalence (metastases) of cancer present in the individual. There are two key molecules in the anticancer effect of AGS. One of them is α -gal which is a trigger of the virulence for cancer-causing pathogens by highlighting the presence of competing tick-transmitted pathogens. As a result, tumor size can increase. The other key molecule is N-Glycolylneuraminic acid (Neu5Gc), which is actually responsible for the anti-cancer effect. Neu5Gc, that is also absent from humans, is taken up by consuming mammalian meat. The increased size of tumor leads to an increased amount of Neu5Gc incorporated. This leads to a more aggressive anti-

Neu5Gc immune reaction targeting cancer cells. We argue that the α -gal molecule in the tick saliva is a trigger (there could be many others) which increases the aggressiveness of tumor cells because, as previously mentioned, most pathogens harbor α -gal^[21] and cancer causing ones might also do so like Human Papilloma virus, Epstein-Barr virus, *Helicobacter pylori*, etc. Therefore, in this case these molecules are indicators of appearance of potential tick-transmitted rival viruses, bacteria and protists as competitors for carcinogenic pathogens inside the host body. There is strong evidence that in a lot of cases multiple infections with different strains or species of pathogens lead to increase in virulence of all of the participants.^[22, 23] Because many cancers have infectious etiology,^[12] they probably function according to the previously mentioned rule. Tumors caused by viruses, bacteria, and parasites are frequent cause of morbidity and mortality in the reproductive age too.^[24-28] The most important cause of cervical cancer, HPV (Human Papilloma Virus) significantly affects women under 30.^[26] The cause adult T-cell leukemia/lymphoma, HTLV (Human T-lymphotropic Virus), has been reported frequently in patients within the reproductive age.^[27] Epstein-Barr virus- (EBV) is associated with lymph proliferative diseases such as Burkitt lymphoma which is typical in children in malaria-endemic parts of Africa.^[28] In addition, brain cancer and leukaemia are also typical tumors during childhood.^[24, 25] Consequently, pathogen-induced cancers can exert a strong selective pressure onto the reproductive human population. There are two ways for reaching higher virulence: the first is increasing the level of free virions of carcinogenic viruses, the second is increasing the replication of integrated viruses inside of the dividing cancer cells. Because the integrated type is invisible for the immune system, only the free virion type, probably containing α -gal, induces the production of anti- α -gal antibodies.

We hypothesize that, by introducing pathogens, the tick bite may increase aggression of tumor cells and this can lead to more severe allergic symptoms. There are many examples in the medical literature supporting this notion. The occurrence of Burkitt-lymphoma which appears on the head and neck of children in Africa strongly correlates with the geographical distribution of the endemic malaria parasites. There is a more direct evidence when, after mosquito bite, the Epstein-Barr virus-infected lymphocytes begin to proliferate extensively.^[29] After tick bite the same reaction has been reported in connection with transmitted *Borrelia* infections but in this case the links with Epstein-Barr virus is unclear.^[30] According to a hypothesis, the complex phenomena of tick bite allergy (not the mammalian meat allergy) are a kind of protection against tick salivary molecules and tick-transmitted infections. The reactions include epidermal hyperplasia and increase in thickness of the skin. This can be an alternative of our pathogen harboring cancer cell argument but the fact that this allergic reaction is systemic and not a localized one strengthens our hypothesis.^[31]

Anthropogenic evidences show selective advantages of allergy

N-Glycolylneuraminic acid (Neu5Gc) molecule similarly to α -gal has been lost from humans but unlike α -gal it exists in our close relatives like chimpanzees. The α -gal was lost nearly 30 million years ago but Neu5Gc disappeared only 2 million years ago. In the case of α -gal it is

supposed that reason of loss was a dangerous pathogen^[32] but it is implausible for Neu5Gc. There is a very interesting co-occurrence of an important event in the history of early human evolution with the loss of the molecule Neu5Gc namely the control and use of fire.^[33] There is a solid consensus agreement that eating processed meat and developing cancer are closely linked.^[34] We argue that the reason for the loss of Neu5Gc is to protect humans from various cancers induced by this dietary shift. To show connection between the loss of Neu5Gc and cancer we have to find similar patterns in domesticated carnivores like dogs, cats, and ferrets because humans share the processed meat with these animals. Interestingly, this is really the case.

In dogs there are regional differences. In Europe, where processed meat is common, dogs lost their Neu5Gc universally but in Asia, where the dietary habits are mixed, the genetic composition of Neu5Gc positive and negative dogs is mixed too. In the case of ferrets the purely wild type has Neu5Gc but in the derived domesticated one it is missing.^[35] Furthermore, when we artificially knock out the Neu5Gc gene in laboratory mice we experience similar targeted accumulation of Neu5Gc molecules inside the cancer cells of these animals as in the case of humans.^[32] Tumors were induced by a mouse mammary tumor virus oncogene.^[36] Based on our hypothesis, this trait could be used for tumor localization in the future. This experiment confirms that the function of Neu5Gc is universal and its loss is not a by-product but a case of adaptation in all of the participants probably for the same reason: to fight cancer. The fact that mice as independent model organisms physiologically behave like humans after knocking out Neu5Gc strengthens the suspicion that the same had happened to humans and domesticated carnivores for similar evolutionary reasons in the past.

Neu5Gc pathogenesis of allergy: An anticancer mechanism

The 3–6 h delay in the tick bite induced mammalian meat allergy is hard to explain mechanistically. We suggest that after eating mammalian meat the process is slow because the prolonged process of digestion, absorption, and intake of Neu5Gc and its expression on the surface of cancer cells takes a lot of time. Interestingly, mainly placenta and tumors accumulate Neu5Gc and express them on the cell surface.^[37] These two tissues are not as dissimilar as we think at first sight because placental cells structurally and behaviorally are essentially cancerous.^[38] We hypothesize that after cancer cells express Neu5Gc on their surface the produced anti-Neu5Gc antibodies bind to them and destroy them very effectively in a form of allergic reaction (Figure 1). According to some speculations, the resulting inflammation would not stop but help the progression of tumors.^[37] We find many contradicting evidence for this. First, we know that pathogenic microorganisms incorporate Neu5Gc on their surface and anti-Neu5Gc kills them effectively on many occasions.^[37] Second, many tumors have infectious etiology.^[12] Moreover, there is an observed negative correlation between many cancers and allergy.^[13, 14] There is general consensus that mammalian meat consumption leads to development of cancer, however, there are three cancers that, as an exception, are negatively connected to mammalian meat consumption,

namely lymphoma, melanoma, and endometrial cancer.^[39] Further clinical and experimental data need to be available to find out which specific cancers are negatively connected to mammalian meat allergy and why.

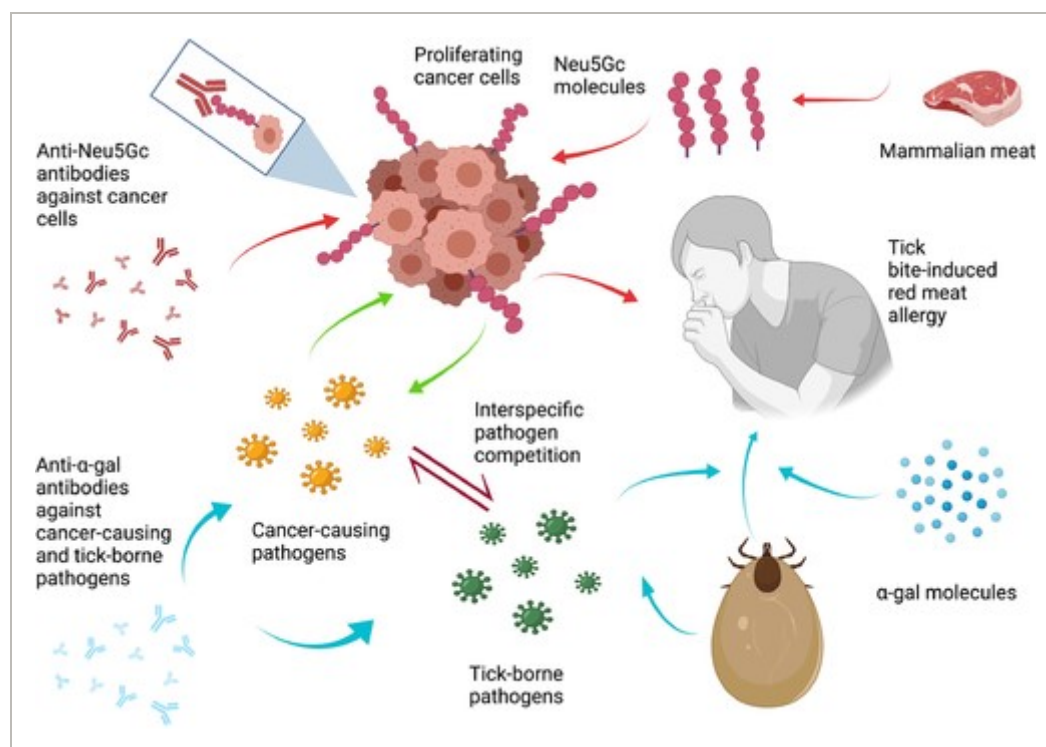


FIGURE 1

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Putative anticancer mechanism of the delayed allergic reaction after consumption of mammalian meat. Red arrows indicate the processes triggered by Neu5Gc molecule. Blue arrows indicate the processes triggered by α -gal molecule. Green arrows show the alternation of cancer-causing pathogens between the states of free virions and the integrated form inside the cancer cell genome. Created with BioRender.com

Besides mammalian meat allergy, tick bite can induce anaphylaxis in cancer patients treated with the drug called Cetuximab.^[40] This medicine is a human-murine hybrid monoclonal antibody containing both α -gal and Neu5Gc.^[41, 42] The originally planned mechanism of action of these antibodies is to bind and block the epidermal growth factor receptors and stop the progress of cancer. However, it seems that the drug is primarily working because of its secondary cytotoxic effect not by the direct inhibition of the epidermal growth factor molecules. Interestingly, the other monoclonal antibody drug, the purely human Panitumumab, is weaker because of the poor cancer cell killer effect.^[43] In the case of mammalian meat allergy the anaphylaxis appears after 3–6 h but for Cetuximab it is only 15 min.^[40] The reason for this could be the fact that Cetuximab is an intravenous drug and this direct route speeds up the manifestation of Neu5Gc and α -gal induced allergic symptoms and reaction.

LDL cholesterol parallels with Neu5Gc

The anti-cancer effect of tick bite induced AGS can probably be extrapolated to other types of delayed late-phase allergies. If our reasoning is correct, we have to find other molecules that have very similar characteristics to Neu5Gc. LDL-cholesterol was shown to induce the production of anti-cholesterol antibodies and is linked to allergic reactions.^[44] Moreover, microorganisms cannot synthesize LDL-cholesterol but can incorporate it into the cell wall in case of bacteria.^[45] The higher blood level of cholesterol is inversely connected to infection level^[46] and many microorganisms are directly linked to cancer.^[12] There are widespread data that statins (molecules that lower blood cholesterol) increase the severity of infections and boost tumor.^[47] Tumors can accumulate significant amounts of LDL-cholesterol and express it on their cell membrane.^[48] There is experimental evidence that higher levels of cholesterol decrease the severity and extension of hepatocarcinoma^[49] but there is no explanation for the phenomenon. We expect a similar molecular mechanism here as in the case of Neu5Gc-mediated anti-tumor reaction. As cancer cells accumulate cholesterol and express it on their cell surface the production of anti-cholesterol antibodies will be induced leading to an anti-tumor immune reaction as detailed above for Neu5Gc.

Interestingly, many cancers have an inverse relationship with atherosclerosis^[50] which is the result of inflammatory reaction to the LDL-cholesterol sticking on the cell membrane. Atherosclerosis is solely a human disease and we cannot find it in our closest relatives, chimpanzees.^[51] Moreover, there is an intriguing synergistic effect between the amount of fat in mammalian meat and the tick-bite induced AGS. The higher fat content leads to more severe allergic symptoms.^[52] There is published evidence indicating that allergy can promote the development of atherosclerosis.^[53] This is in line with our above hypothesis concerning the Neu5Gc-mediated anti-tumor reaction.

How to test our hypotheses?

The proposed negative correlation between allergy and cancer should be reflected in clinical data. We predict a significantly lower occurrence of tumors among individuals with allergic conditions, especially among those who have mammalian meat-related allergies. This could be tested by quantifying allergic diseases in large clinical datasets of patients with diagnosis of cancer in comparison to the healthy population. Large-scale retrospective studies of this kind could help to shed light on other candidate molecules with anti-cancer effects that are currently unknown.

In the case of allergy to the cancer drug Cetuximab we need to focus on cases with the most radical symptoms. We predict that in patients with high occurrence of anaphylaxis the prognosis of cancer is very good compared to those who do not develop any symptoms. The other option is to experimentally observe ferrets where the purely wild type has Neu5Gc but in the derived domesticated one it is missing.^[35] The susceptibility to cancer after consuming processed meat could be compared under laboratory conditions between the wild type ferrets and the domesticated ones that do not harbour Neu5Gc.

CONCLUSIONS AND PROSPECTS

Published evidence summarized above convincingly support our hypothesis that the delayed late phase allergy is an adaptive and effective defence mechanism against cancer. We used an interdisciplinary approach to prove our concept. First, we found anthropogenic data that humans lost their innate Neu5Gc but, after consumption of mammalian meat as an external source, this molecule accumulates inside cancer cells. Surprisingly, the situation can be experimentally reproduced in a non-human host. When we knock out the Neu5Gc gene in laboratory mice targeted accumulation of Neu5Gc molecules inside the cancer cells occurs which indicates that this is a universal phenomenon. Moreover, in domesticated carnivores this gene has been lost too because, we suppose, humans share processed meat with their pets. Interestingly the time of the first use of fire by humans is very close to loss of Neu5Gc, approximately 2 MYA.^[33] Secondly, the cancer drug Cetuximab harbors both α -gal and Neu5Gc and binds to the epidermal growth factor receptors. It can destroy cancer cells while the purely human Panitumumab cannot. This highlights the possibility that Neu5Gc directs an allergic immune attack against cancer cells. Thirdly, Neu5Gc induced anti-cancer effect is probably not unique but part of a more general mechanism. For this reason, scientific efforts need to be directed to find other molecules with similar behavior. A probable next suspect is LDL cholesterol which is as immunogenic as Neu5Gc and shares many similarities with this molecule. In the future we need to search for more candidates in these classes of molecules which open a new way to not only treat but cure different kinds of deadly cancers.

In conclusion we highlighted a new kind of natural anticancer adaptation, namely the loss of some genes encoding α -gal and Neu5Gc from our genome to protect us from cancer. Probably we have been losing a lot of innate molecules for this reason during human evolution. We acquire these molecules from external sources like tick bite in case of α -gal and mammalian meat consumption in case of Neu5Gc, the latter accumulating in tumor tissues, that induces antibody production. By this specific immune response humans have developed a new molecular weapon to fight against deadly tumors. By further testing and practical application of our hypothesis new avenues in cancer research and therapy will open that might save lives and decrease human suffering.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

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