ONCOIMMUNOLOGY
2024, VOL. 13, NO. 1, 2324493
https://doi.org/10.1080/2162402X.2024.2324493

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ORIGINAL RESEARCH

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Are tumor-associated carbohydrates the missing link between the gut microbiome and response to immune checkpoint inhibitor treatment in cancer?

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ABSTRACT

Immune checkpoint inhibitor therapy has dramatically improved survival in a significant subset of patients with several solid tumor types. Increasing the number of patients benefitting from this form of therapy is an important translational research goal. Correlations between the composition of the gut microbiome and response to immune checkpoint inhibitor therapy raised the possibility that direct modulation of the gut microbiome may significantly improve the clinical benefit of this treatment. Several lines of observations suggest that tumor-associated carbohydrates, including those recognized as blood group-related glycolipid antigens, such as the Forssman antigen, may be some of the key factors behind this clinical correlation. Such antigens are expressed in human cancer, humans often produce antibodies against those, and they can induce antibody directed cellular cytotoxicity. Importantly, these antibodies are often induced by antigens present in microbes of the gut. If identified, these antibodies could be boosted by appropriate vaccination techniques and thus enhance anti-tumor immunity with minimal side effects.

ARTICLE HISTORY
Received 11 January 2024
Revised 22 February 2024
Accepted 23 February 2024

KEYWORDS
Immune checkpoint inhibitor therapy; gut microbiome; glycolipid antigens; antibody directed cellular cytotoxicity

Introduction

Immune checkpoint inhibitor therapy has dramatically improved survival in several solid tumor types, including non-small cell lung cancer, melanoma, and kidney cancer.[1] The impressive survival benefits have, however, further highlighted the discrepancy between those responsive and those resistant to this form of therapy. Responders often have impressively long term, often several years of clinical benefit. For example, about 20% of melanoma patients treated with checkpoint inhibitors may discontinue further treatment after 6 months of therapy since their risk of relapse is estimated to be less than 10%. Understanding the mechanistic basis of the difference between responders and non-responders holds the promise of extending the benefit of immune checkpoint inhibitor treatment to a larger population and may also identify reliable predictors to this therapy in various tumor types. Interventions that increase the response rates to immune checkpoint inhibitor therapy are of particular importance. One such mechanism emerged while studying the association between response to this form of therapy and the composition of the gut microbiome.

An unexpected clinical association: the impact of the gut microbiome on the efficacy of immune checkpoint inhibitor therapy

A series of landmark studies showed that the composition of the gut microbiome has a significant impact on the response to both anti CTLA-4 and anti PD-1/PD-L1-based immune checkpoint inhibitor therapy.[2–6] These intriguing clinical results have led to the hypothesis that direct manipulation of the gut microbiome by oral administration of bacteria or fecal transplants may improve response to immune checkpoint inhibitor therapy. Recent, early-stage Phase 1 studies indicated that this may, in fact, be the case.[7–9] If these clinical studies are further developed and modulation of the gut microbiome proves to be an effective way to increase the efficacy of immune checkpoint inhibitor treatment, then clarifying the mechanistic basis of this intervention will become an essential starting point for further clinical improvements.

A significant amount of early effort was concentrated on understanding the clinical benefit of immune checkpoint inhibitor therapy in terms of reactivating an HLA-presented peptide antigen induced, cytotoxic CD8 cell-driven antitumor response. Considering the extensive list of potential cancer-associated peptide antigens including mutation induced neoantigens, testicular antigens and aberrant activation of dormant genes such as human endogenous retroviruses, this was a reasonable early research direction. However, PD-1/PD-L1 blockade can also activate anti-tumor immune mechanisms, such as natural killer cells,[10] gamma-delta T lymphocytes,[11] and T follicular helper cells[12] that do not depend on the presentation of tumor associated peptide antigens. Considering such mechanisms is especially relevant when studying the link between the composition of the gut microbiome and anti-tumor immune responses. While it was possible in some cases to identify overlapping antigens between gut microbes and the human peptidome,[13] the mapping of tumor antigens to

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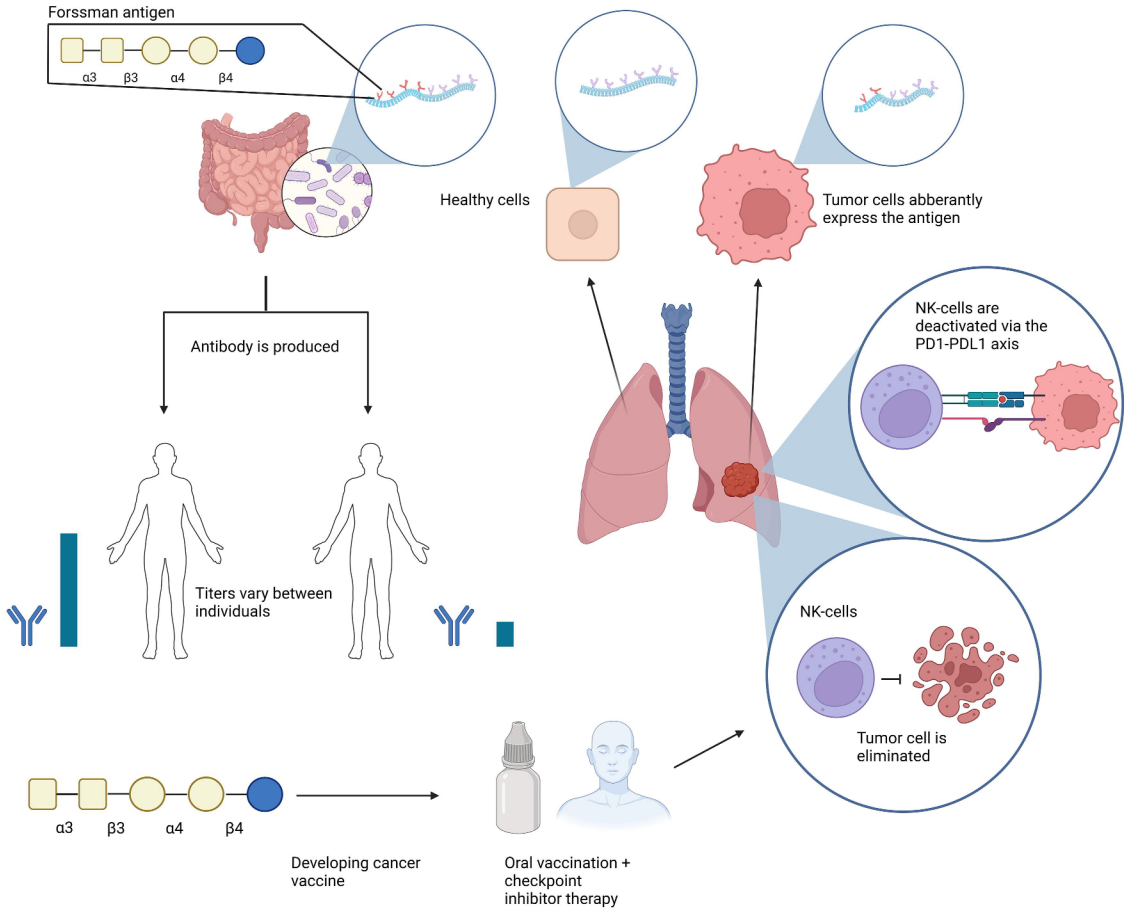

Figure 1. Visual summary of a simplified version of the proposed mechanism by which tumor-associated carbohydrates mechanistically link the gut microbiome and response to immune checkpoint inhibitor treatment in cancer. Tumor cells aberrantly express various glycolipid antigens, such as the Forssman antigen. Humans often produce antibodies against such blood type glycolipid antigens, and these antibodies are expected to produce an anti-cancer immune reaction, which may be turned off by e.g. The activation of the PD-L1/PD-1 axis by tumor cells. Anti-Forssman antibody levels, however, are significantly influenced by the presence or absence of cross-reacting gut bacteria and show a significant range of variation in the population. Patients with low antibody titers would have limited anti-tumor immune reaction but patients with high antibody titers may have a potentially therapeutic anti-tumor immune reaction, which may be turned off by the PD-1/PD-L1 pathway but can be reactivated by appropriate immune checkpoint inhibitor therapy. Boosting the levels of anti-Forssman antibody titers by vaccination, therefore, may increase the efficacy of checkpoint inhibitor therapy.

the gut microbiome in a generalized fashion does not provide a widely applicable mechanistic explanation. Our preliminary analysis did not identify a large number of overlapping peptides between the peptidome of gut microbes associated with improved checkpoint inhibitor therapy and the neoantigen profiles of human cancer.[13] This was not entirely unexpected, since the probability that a wide array of newly arising cancer-associated neoantigens were by chance nearly identical (or identical enough to induce immune recognition) to bacterial peptides was rather low. Therefore, exploring alternative mechanisms, such as antibody directed cellular cytotoxicity, may help to uncover the mechanistic link between the gut microbiome and anti-tumor immune response. This research direction is further supported by the increasing evidence linking the efficacy of immune checkpoint inhibitor therapy to serum IgG levels against commensal bacteria.[14]

The mystery of carbohydrate blood group antibodies

Blood group antigens, such as the AB0 or Forssman blood groups, are glycolipid antigens that, when expressed on the red blood cells or other tissues of an incompatible person, induce severe immune reaction, as experienced, e.g., during incompatible blood transfusion. This immune reaction is initiated by the antibodies already present in the individual, the origins of which constituted a bit of a mystery. These so-called natural antibodies against blood glycans seem to arise in the absence of canonical immunization. For example, a blood group A individual would not encounter the B antigen until an incompatible blood transfusion. The same holds true for the Forssman antigen, which is almost never present in an individual, but most human individuals have an antibody against it. Interestingly, this rather important immunological phenomenon has been somewhat understudied. Nevertheless, a few key studies unambiguously pointed the direction that these antibodies are the result of cross-reactivity induced by commensal, such as gut, microbes (for excellent review see).[15] In some cases, specific microbes could be linked to actual blood group antibodies as well. For example, *E. coli O86* can induce anti-B antibodies when injected into recipient animals.[16] The fact that antibodies to blood group antigens appear in the first few months of life further supports the relevance of some form of cross reactivity driven environmental

exposure mechanism, even if those are not necessarily originated in the gut microbiome.

This correlation between the gut microbiome and cross-reacting serum antibodies offers the intriguing hypothesis whether in some cases the aberrant glycolipid expression on cancer cells may initiate the immune response that is amplified by the appropriate gut microbiome. The naturally occurring anti-blood group antibodies are usually IgM and efficiently activate the complement system, a mechanism which may also contribute to the efficacy of immune checkpoint inhibitor treatment.[17]

Aberrant blood group antigen expression on the surface of cancer cells

Initiating an anti-tumor immune reaction by anti-blood group antibodies requires the presence of a blood group antigen alien to the host on the surface of cancer cells. Due to the chemical structure of blood group antigens, there are multiple mechanisms that can lead to this. There is a well-known, albeit rare phenomenon in transfusion medicine, called "acquired B".[18,19] In such cases, the A blood antigen (of a genetically A blood group person) is converted into blood group B, which is associated with bacterial infection. This is likely mediated by a bacterial deacetylase that modifies α-N-acetyl-D-galactosamine (GalNAc), the immunodominant sugar of blood group A, into α -D-galactosamine. The latter is similar to the immunodominant sugar of the B antigen (α-D-galactose), causing a cross-reaction with human anti-B. A more frequent mechanism with likely relevance to cancer is related to the Forssman antigen. It is a heterophil glycolipid antigen present in a wide variety of species but mostly absent in humans due to inactivating mutations in the GBGT1 gene (Globoside alpha-1,3-N-acetylgalactosaminyltransferase 1), which is coding the human (inactive) form of Forssman glycolipid synthetase. In its active form in other species this enzyme catalyzes the transfer of GalNAc, the last sugar moiety needed for the complete Forssman antigen, to the terminal residue of globoside.[20] Despite the inactivated human GBGT1, the shared similarity between the A antigen and Forssman antigen allows the formation of the latter by "hijacking" the A-transferase. Both the A antigen and the Forssman antigen are glycolipids and the last residue of the immunodominant structure is N-acetyl-D-galactosamine (GalNAc) in both of those antigens. It was demonstrated in experimental model systems that modification (e.g. splice variants), of the A transferase can catalyze the last step, adding a GalNAc to globoside, which is required for the completion of the Forssman antigen.[21,22] Therefore, it is theoretically possible that human cells, especially with aberrant enzymatic activities such as cancer cells, can express the Forssman antigen. Indeed, a few studies reported the presence of the Forssman antigen on the surface of various cancer types.[23,24] Most of these studies used antibodies for detecting the Forssman antigen, and mass-spectrometry-based validation will be required for a definitive proof for the presence of this antigen. Nevertheless, it is notable that an antigen recognized, even by cross-reaction, by anti-Forssman antibodies can often be detected on cancer cells.

The potential relevance of anti-blood group antibody titer levels in human cancer

While the clinical relevance of aberrant expression of blood group antigens in human cancer has not been studied extensively,[25] more information is available about anti-blood group antibody titers. High antibody titers of the anti-blood group A antibody was associated with better survival of prostate cancer patients treated with the PROSTVAC-VF vaccine.[26] Several early studies also reported lower antibody titers against the Forssman antigen in cancer patients.[27–29] These sporadic data gain particular importance in light of the following: Human antibodies against the Forssman antigen, similar to the AB0 blood group antigens, are also likely induced by microbial antigens. The Forssman antigen is present in a number of microbes such as pneumococci,[30–32] which are also present in the gut. Since pneumococci often cause various forms of infections, e.g. pneumonia, antibodies recognizing their surface antigens may be induced during those pathological processes as well. The structural basis for this lies in the structure of Lipoteichoic acids (LTA), which are polymers of alternating units of a polyhydroxy alkane and phosphoric acid, joined to form phosphodiester units.[33] Lipoteichoic acids are found in the envelope of Gram-positive bacteria. Importantly, a subclass of lipoteichoic acid (Type IV LTA) may have terminal GalNAc-GalNAc moieties,[34] which likely provide the molecular basis for the previously detected Forssman antigenicity.[30–32]

Taken all this together, an intriguing hypothesis emerges as follows (Figure 1): The Forssman antigen, usually not present in human tissue, becomes expressed by cancer cells by some promiscuous or mis-directed biochemical mechanism, such as altered A-transferase activity.[21] Antibodies against this antigen are usually present in humans and would most likely induce an anti-tumor immune response, which could be mitigated by, for example, the activation of the PD-L1/PD-1 axis by tumor cells. Anti-Forssman antibody levels, however, are significantly influenced by the presence or absence of cross-reacting gut bacteria, and show a significant range of variation in the population[35] with likely reduced levels in cancer patients.[27–29] Patients with low antibody titers would have limited anti-tumor immune reaction but patients with high antibody titers may have a potentially therapeutic anti-tumor immune reaction, which may be turned off by the PD-1/PD-L1 pathway but may be reactivated by appropriate immune checkpoint inhibitor therapy. In fact, some of clinical trials linking the gut microbiome and immune checkpoint inhibitor response might have reflected the ability of the gut microbiome of a given patient to induce appropriate anti-Forssman antibody levels. Therefore, boosting the levels of anti-Forssman antibody titers by the presence of appropriate microbes, e.g. fecal transplants, may increase the efficacy of checkpoint inhibitor therapy.

A detailed analysis of Forssman antigen expression on cancer cells, anti-Forssman antibody titers and response or

outcome after immune checkpoint inhibitor therapy may provide supportive evidence for this hypothesis. For example, if biological material such as tumor biopsies are still available, it might be worth reanalyzing one of the first clinical cohorts linking the gut microbiome with response to immune checkpoint inhibitor therapy in lung cancer.[13] In this cohort, the presence of Enterococcus hirae in the gut was shown to be one of the main causes of improved response to therapy. Lipoteichoic acids are present in Enterococcus hirae but the exact subclasses and chemical structures of LTA in these bacteria have not been fully elucidated yet. The presence or absence of Forssman like LTA in Enterococcus hirae could be determined by established methods and the presence of Forssman antigen in the tumor biopsies and anti-Forssman antibody titers could also be evaluated. A correlation between those factors, presence of *Enterococcus hirae*, anti-Forssman antibody titers and better response to immune checkpoint inhibitors, would support the hypothesis outlined here.

Establishing a connection between the Forssman antigen and response to immune checkpoint inhibitor therapy in clinical cohorts would, of course, require that this mechanism played a role in most gut microbiome associated response to this therapy. However, there are several other glycolipid antigens,[36] including the Galili antigen, that are present in enteral bacteria and humans also produce significant amounts of antibody against those.[37] Normally human cells do not express the Galili antigen but under pathological conditions, such as Graves' disease, the Galili antibody binds to thyroid cells.[38] If the Galili antigen were expressed on the surface of cancer cells, then that could contribute to increasing the efficacy of cancer immunotherapy. However, if the pathological role of the Galili antibody in thyroiditis is confirmed, then this would also serve as a warning that natural antibodies may also contribute to the well-documented immune-related Adverse Events (irAEs) associated with immune checkpoint blockade.[39]

If such glycolipid antigens were identified, then those could significantly increase the efficacy of the clinical exploitation of the fortuitous observation linking the gut microbiome to response to immune checkpoint inhibitor therapy. Fecal transplants, which are expensive and carry their own risk, would not need to be performed in a manner essentially blinded to the specific nature of the antigens but those could be precisely identified by, for example, immunohistochemistry of the tumor biopsies. Then the relevant antibody titers could be determined and – if found low – those could be boosted by one of the vaccination methods, including enteral vaccination. These vaccinations would probably carry minimal risk since these types of antibodies are often present in high titers in humans without any harmful side effects. While tumor-associated carbohydrate vaccines often proved to be poorly immunogenic,[40] antibodies targeting blood-type antigens are expected to elicit a stronger immune reaction as experienced, e.g., during mismatched blood transfusion.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

Z.S. was supported by the Department of Defence, Congressionally Directed Medical Research Programs (award number is W81XWH-18-1-0751 and W81XWH-22-1-0089) and the Breast Cancer Research Foundation (BCRF-22-159). J.M. was supported by the Hungarian National Research, Development and Innovation Office, K-147226. The figure was created with BioRender.com.

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