Naturopathic Doctor News & Review

IMMUNE MODULATOR FOR AUTOIMMUNE DISEASE?
The Case for Active Hexose Correlated Compound (AHCC)

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Although the naming of the phenomenon of autoimmune disease is simple and reflects a self-triggered immune response, factors leading to the development of this state are complex and many. The immune system has many levels of function, and communication between immune responders involves a complex milieu of cytokines. The innate immune response is considered more primitive in function, and includes responders known as macrophages, dendritic cells, mast cells, eosinophils, basophils, and natural killer cells. The responders of the innate immune system are more of a surveillance system, which upon invasion send cytokines to trigger further immune responses upstream. The adaptive immune response, on the other hand, is slightly more complex and involves B-cell and T-cell recognition of antigens or infectious microbes. These potential threats to the body trigger a more focused immune response designed to clear the infection or protect the body from antigens. However, the innate and adaptive immune responses, and the players within them, do not reflect a dichotomy of either one or the other; rather, there is a complex interplay between them.

THE INNATE IMMUNE SYSTEM IN AUTOIMMUNITY

Natural killer (NK) cells – very lethal sounding in name – do just that. They recognize and destroy cells which are missing the normal flag to identify them as "self." The primary settings in which NK cells play a role are viral infections and cancer, as these situations lead to a low level of self-protein being expressed. NK cells are being increasingly recognized as more complex in function, playing a role in the adaptive immune response and regulating the autoimmune response as well.[1] By the production of the anti-inflammatory cytokine interleukin (IL)-10, NK cells can also modulate inflammation more directly.[2]

Dendritic cells are found on skin-type surfaces of the body, including the mucosa of the intestinal tract and respiratory system, and serve the function of presenting antigens to the adaptive immune system. Serving this interface, they have been recognized to play a possible role in the immune response to self-antigens, inducing immune tolerance in some situations but autoimmunity in others.[3]

NK cells communicate with dendritic cells and can promote maturation, but also are capable of killing immature or mature

dendritic cells that lack expression of high levels of "self" protein.[4] Conversely, dendritic cells can promote NK cell proliferation via secretion of the cytokine IL-12. Immature dendritic cells circulate in the periphery, capturing self-antigens and environmental proteins, and their effect on T-cells depends on whether the antigen is present with or without stimulus for dendritic cell maturation. This either leads to deletion of self-reactive T cells or the development of effector T cells, memory T cells, and an activated immune response.[5]

Low levels and impaired function of NK cells have been observed in individuals with a variety of autoimmune diseases.[6] This includes autoimmune thyroid disease,[7] psoriasis,[8] rheumatoid arthritis,[9] and others.[10] It is theorized that this may play a role in the disease pathogenesis or may occur secondary to the disease and its treatments. However, the fact that NK cell defects and reduced levels have been observed early in the course of disease in treatment-naïve persons suggests that, at least for a subset of patients, this may contribute to the disease development.[11-13] For the aforementioned reasons, therapies that support the body's production and function of NK cells may offer benefit for autoimmune disease.

In the setting of autoimmune disease, it is important to not overly stimulate the immune system, as stimulating it may worsen the response to self-antigens as well. For this reason, many nutraceuticals with known immune-stimulating potential may be contraindicated or, at the very least, should be used with caution. On the other hand, substances known as immunomodulators serve to regulate or normalize the immune system response. Immunomodulators are not contraindicated

in settings of autoimmune disease, and furthermore may be beneficial. Immunomodulating nutritional supplements include, but are not limited to, vitamin A,[14] Saccharomyces boulardii,[15] vitamin D,[16] and zinc.[17]

Modulation of the gut microbiome also may have implications for autoimmune disease, as well as many chronic diseases with an inflammatory component.[18,19] Although this may be the case for all conditions of autoimmunity, one in which it is most recognized is the condition of inflammatory bowel disease (IBD).[20,21] Therapeutic strategies for IBD, including antibiotics, probiotics, prebiotics, and short-chain fatty acids, all have potential to modify the gut microbiota, and have been studied as therapeutic strategies in conditions such as Crohn's disease, ulcerative colitis, and other autoimmune diseases. Additionally, other supplements, such as vitamin A or D, which are not commonly thought of as modifiers of the gut microbiota, have been found to impact flora balance and disease-related markers.[22,23]

ACTIVE HEXOSE CORRELATED COMPOUND

A compound called Active Hexose Correlated Compound (AHCC) has been studied extensively for its effects on the immune system. AHCC, which is a mixture of polysaccharides, amino acids, and minerals derived from Basidiomycetes mushrooms, has a long history of use by alternative medicine practitioners in the realm of oncology.[24] The production of AHCC from Basidiomycetes mushrooms is a proprietary process that includes the culturing of mycelia and hot water extraction – the traditional technique utilized to extract polysaccharides from mushrooms. Basidiomycetes spp of fungi, which include shiitake and ganoderma, are known for their effects on the immune system.[25]

AHCC & CANCER

An increased response or amount of NK cells has been observed to be one mechanism by which AHCC affects the immune system. This mechanism has been explored in patients with solid malignancies and response to viral infection. Cancer patients have been observed to have lowered numbers and activity of NK cells, which may adversely affect their prognosis, thus the importance of healthy levels both for cancer prevention and during therapies.[26,27] In patients with solid tumors who were shown to have lowered NK cell activity, supplementation with AHCC was found to increase NK activity to normal levels.[28] It was also observed to increase secretion of the cytokines IL-12 and IFN-γ, which were also depressed.[28] In a comparison study with other known natural substances with immune-modulating effects (modified arabinoxylane, the mushroom Coriolus versicolor, and antigen-infused bovine colostrum/whey extract), AHCC was the only supplement that consistently and statistically increased NK cell activity in cancer patients.[29] The average observed increase in NK activity was 2.5-fold in 9 out of 11 cancer patients after 2 weeks of therapy with 3 g of AHCC daily.

AHCC & VIRAL INFECTION

In the setting of viral infection, AHCC was observed to increase the percentage and number of NK cells in the lungs, as well as NK activity in both the lungs and spleen in mice subject to influenza A infection.[30] Although not all studies pertaining to the use of AHCC in the setting of viralinfection have investigated or shown direct impact of AHCC on NK function, results consistently show improved response to infection.[31,32] This includes studies of animals with avian influenza virus,[33] Klebsiella pneumoniae,[34] Candida albicans,[35] Pseudomonas aeruginosa, and methicillin-resistant Staphylococcus aureus.[36]

Additionally, AHCC has been studied in clinical settings of human papillomavirus (HPV) infection, and was shown in a small pilot study to improve eradication of persistent HPV infection.[37] In healthy adults taking AHCC, it was observed that the CD4(+) and CD8(+) T-cell response and production of IFN-γ and/or tumor necrosis factor (TNF)-α was enhanced.[38] Given the effects observed with AHCC in response to viruses and altered cytokine profiles, AHCC may one means of addressing latent or active viral infections, as well as the state of immune imbalance that can contribute to autoimmunity.

AHCC & AUTOIMMUNITY

A variety of studies have investigated the potential impact of AHCC in the setting of autoimmune disease. AHCC was observed to exert a protective effect in streptozotocin (STZ)-induced diabetes, the standard animal model of type-1 diabetes.[39] Treatment of rats with STZ led to increased blood glucose, decreased serum insulin, and an increase in serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Daily supplementation with AHCC for 1 week prior to and 2 weeks after STZ treatment significantly decreased or normalized STZ-induced changes in blood glucose, serum insulin, and serum AST and ALT levels.[39]

As many polysaccharides, such as fructooligosaccharide and xylooligosaccharide, act as prebiotics, ie, promoting strains of intestinal bacteria with health benefits,[40,41] the possible effects of the oligosaccharide-containing AHCC also has been investigated with regards to intestinal health, including

diseases of autoimmunity that affect the intestines. Multiple studies have assessed the potential impact of AHCC in animal models of colitis.

In rats with trinitrobenzene sulfonic acid (TNBS)-induced colitis, AHCC was found to attenuate colonic inflammation, reduce the extension of necrosis and expression of proinflammatory cytokines and chemokines, and improve glutathione concentration.[42] Markers of neutrophil infiltration and inflammation (myeloperoxidase [MPO] and alkaline phosphatase [AP] activity) were also improved with AHCC treatment. The normalization of many of the markers of damage and inflammation observed with AHCC treatment was similar to the anti-inflammatory effect observed in animals treated with sulfasalazine, a standard pharmaceutical treatment for IBD. Rats treated with AHCC also had higher bifidobacteria and lactic acid bacteria counts. Overall markers of animal health, such as weight and food intake, were also improved.[42]

In a CD4+ CD62L(+) T-cell transfer model of colitis, considered to be the animal model closest to the human disease state, AHCC was found to improve colitis, reducing MPO and AP activity and genetic transcription of many proinflammatory cytokines, most notably that of TNF-α and IL-1β.[43] The increased production of the cytokines IL-6, IL-17, and IL-10 in mesenteric lymph node cells in the disease state was also restored to a normal level in animals treated with AHCC.

Another rat study examined the possible symbiotic impact that a combination of AHCC – serving as a prebiotic – and the probiotic Bifidobacterium longum BB536 had on the TNBS model of colitis.[44] Prebiotics combined with probiotics are often observed to have synergism, and are thus noted as synbiotics.[45] Such was observed to be the case for the combination of AHCC with B longum BB536, as the combination had a greater anti-inflammatory effect compared to either agent alone, although an anti-inflammatory effect was also observed for each individually. Interestingly, the combination of a lower dose of AHCC with B longum BB536 was observed to have the greatest anti-inflammatory activity. Other markers, including weight gain and MPO activity, were also improved with AHCC and B longum BB536 treatments.[44]

The potential impact of AHCC on the intestinal immune response was also assessed in a non-disease state. It was found that treatment with AHCC increased immunoglobulin A (IgA)-secreting cells in the intestine, as well as levels of secretory IgA, IL-10, and IFN-γ in the intestinal fluid.[46] In a cell culture of intestinal epithelial cells, contact with AHCC increased secretion of IL-6, while the blocking of toll-like receptor (TLR)-2 and TLR-4 reduced IL-6 secretion, suggesting that these innate receptors are involved in the immune response to AHCC. Interestingly, a similar pathway of response has been demonstrated with treatment with bovine colostrum, another agent known to enhance NK activity.[47]

HUMAN STUDIES OF AHCC

One autoimmune condition in which AHCC has been studied in a clinical setting is Sjögren's syndrome, a condition in which the immune system attacks the glands that make tears and saliva, consequently causing dryness of the eyes, mouth, and other body organs.[48] In a population of 10 individuals, AHCC was supplemented at a dosage of 1 g TID as the focus of therapy. Clinical symptoms which were evaluated included oral and vaginal moisture, tear production, swallowing ability, appetite, weight, and mood; lymphocyte count and salivary gland scintigraphy were also assessed. Within a month, improvements were seen in vaginal and oral moisture, tear production, and mood and appetite. With ongoing therapy (continuous clinical management), improvements were observed in salivary gland scintigraphy as well as lymphocyte CD3, CD4, and CD8 levels.

The use of AHCC has also been investigated in clinical settings with individuals with IBD. With ongoing use of AHCC in patients with IBD, long periods of remission and milder relapses were seen.[49]

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REFERENCES

1. Vivier E, Tomasello E, Baratin M, et al. Functions of natural killer cells. *Nat Immunol.* 2008;9(5):503-510.
2. Perona-Wright G, Mohrs K, Szaba FM, et al. Systemic but not local infections elicit immuno suppressive IL-10 production by natural killer cells. *Cell Host Microbe*. 2009;6(6):503-512.
3. Steinman RM, Nussenzweig MC. Avoiding horror autotoxicus: the importance of dendritic cells in peripheral T cell tolerance. *Proc Natl Acad Sci U S A.* 2002;99(1):351-358.
4. Moretta A. Natural killer cells and dendritic cells: rendezvous in abused tissues. *Nat Rev Immunol.* 2002;2(12):957-964.
5. Steinman RM, Hawiger D, Nussenzweig MC. Tolerogenic dendritic cells. *Annu Rev Immunol.* 2003;21:685-711.
6. Fogel LA, Yokoyama WM, French AR Natural killer cells in human autoimmune disorders. *Arthritis Res Ther.* 2013;15(4):216.
7. Ciampolillo A, Guastamacchia E, Amati L, et al. Modifications of the immune responsiveness in patients with autoimmune thyroiditis: evidence for a systemic immune alteration. *Curr Pharm Des*. 2003;9(24):1946-1950.
8. Cameron AL, Kirby B, Griffiths CE. Circulating natural killer cells in psoriasis. *Br J Dermatol.* 2003;149(1):160-164.
9. Aramaki T, Ida H, Izumi Y, et al. A significantly impaired natural killer cell activity due to a low activity on a per-cell basis in rheumatoid arthritis. *Mod Rheumatol*. 2009;19(3):245-252.
10. Popko K, Górska E. The role of natural killer cells in pathogenesis of autoimmune diseases. *Cent Eur J Immunol*. 2015;40(4):470-476.
11. O'Gorman MR, Smith R, Garrison A, et al. Lymphocyte subsets in peripheral blood from newly diagnosed, untreated patients with juvenile dermatomyositis (JDM) are associated with disease activity scores (DAS). *Arthritis Rheum*. 2002;15:S490.
12. Yabuhara A, Yang FC, Nakazawa T, et al. A killing defect of natural killer cells as an underlying immunologic abnormality in childhood systemic lupus erythematosus. *J Rheumatol.* 1996;23(1):171-177.
13. Rodacki M, Svoren B, Butty V, et al. Altered natural killer cells in type 1 diabetic patients. *Diabetes.* 2007;56(1):177-185.
14. Rumore MM. Vitamin A as an immunomodulating agent. *Clin Pharm*. 1993;12(7):506-514.
15. Pothoulakis C. Review article: anti-inflammatory mechanisms of action of Saccharomyces boulardii. *Aliment Pharmacol Ther*. 2009;30(8):826-833.
16. Kamen DL, Tangpricha V. Vitamin D and molecular actions on the immune system: modulation of innate and autoimmunity. *J Mol Med*(Berl). 2010;88(5):441-450.
17. Goswami TK, Bhar R, Jadhav SE, et al. Role of dietary zinc as a nutritional immunomodulator. *Asian-Aust J Anim Sci.* 2005;18:439-452.
18. Zhang X, Zhang D, Jia H, et al. The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment. *Nat Med.* 2015;21(8):895-905.
19. Richards JL, Yap YA, McLeod KH, et al. Dietary metabolites and the gut microbiota: an alternative approach to control inflammatory and autoimmune diseases. *Clin Transl Immunology.* 2016;5(5):e82.
20. Manichanh C, Borruel N, Casellas F, Guarner F. The gut microbiota in IBD. *Nat Rev Gastroenterol Hepatol*. 2012;9(10):599-608.
21. Round JL, Mazmanian SK. The gut microbiota shapes intestinal immune responses during health and disease. *Nat Rev Immunol*. 2009;9(5): 313-323.
22. Amit-Romach E, Uni Z, Cheled S, et al. Bacterial population and innate immunity-related genes in rat gastrointestinal tract are altered by vitamin A-deficient diet. *J Nutr Biochem*. 2009;20(1):70-77.
23. Ooi JH, et al. Vitamin D regulates the gut microbiome and protects mice from dextran sodium sulfate-induced colitis. *J Nutr*. 2013;143(10): 1679-1686.
24. Ritz BW. Active hexose correlated compound (AHCC) and immune outcomes in humans: a review. *Nat Med J*.2011;3:3-7.
25. Lu CC, Hsu YJ, Chang CJ, et al. Immunomodulatory properties of medicinal mushrooms: differential effects of water and ethanol extracts on NK cell-mediated cytotoxicity. *Innate Immun.* 2016;22(7):522-533.
26. Takeuchi H, Maehara Y, Tokunaga E, et al. Prognostic significance of natural killer cell activity in patients with gastric carcinoma: a multivariate analysis. *Am J Gastroenterol*. 2001;96(2):574-578.
27. Levy S, Herberman R, Lippman M, d'Angelo T. Correlation of stress factors with sustained depression of natural killer cell activity and predicted prognosis in patients with breast cancer. *J Clin Oncol*. 1987;5(3):348-353.
28. Uno K, Kosuna K, Sun B, et al. Active hexose correlated compound (AHCC) improves immunological parameters and performance status of patients with solid tumors. *Biotherapy*(Japan). 2000;14:303-309.
29. Belanger J. An in-office evaluation of four dietary supplements on natural killer cell activity. *Townsend Letter for Doctors and Patients*. May 2005:88-93.
30. Ritz BW, Nogusa S, Ackerman EA, Gardner EM. Supplementation with active hexose correlated compound increases the innate immune response of young mice to primary influenza infection. *J Nutr*. 2006;136(11):2868-2873.
31. Nogusa S, Gerbino J, Ritz B. Low-dose supplementation with active hexose correlated compound improves the immune response to acute influenza nfection in C57BL/6 mice. *Nutr Res*. 2009;29:139-143.
32. Ritz BW. Supplementation with active hexose correlated compound increases survival following infectious challenge in mice. *Nutr Rev*. 2008;66(9):526-531.
33. Roman BE, Beli E, Duriancik DM, Gardner EM. Short-term supplementation with active hexose correlated compound improves the antibody response to influenza B vaccine. *Nutr Res*. 2013;33(1):12-17.
34. Aviles H, Belay T, Fountain K, et al. Active hexose correlated compound enhances resistance to Klebsiella pneumoniae infection in mice in the hindlimb-unloading model of spaceflight conditions. *J Appl Physiol* (1985). 2003;95(2):491-496.
35. Ikeda T, Ishibashi H, Fujisaki R, et al. [Prophylactic efficacy of a basidiomycetes preparation AHCC against lethal Candida albicans infection in experimental granulocytopenic mice]. *Niho Ishinkin Gakkai Zasshi*. 2003;44(2):127-131. [Article in Japanese]
36. Aviles H, O'Donnell P, Sun B, Sonnenfeld G. Active hexose correlated compound (AHCC) enhances resistance to infection in a mouse model of surgical wound infection. *Surg Infect*(Larchmt). 2006;7(6):527-535.
37. Nelson R. Japanese Mushroom Extract Could Help Treat HPV Infections. October 31,2014. Medscape Web site. http://www.medscape.com/viewarticle/834183. Accessed December 15, 2016.
38. Yin Z, Fujii H, Walshe T. Effects of active hexose correlated compound on frequency of CD4+ and CD8+ T cells producing interferon-γ and/or tumor necrosis factor-α in healthy adults. *Hum Immunol*. 2010;71(12): 1187-1190.
39. Wakame K. Protective effects of active hexose correlated compound (AHCC) on the onset of diabetes induced by streptozotocin in the rat. *Biomed Res*. 1999;20:145-152.
40. Sabater-Molina M, Larqué E, Torrella F, Zamora S. Dietary fructooligosaccharides and potential benefits on health. *J Physiol Biochem*. 2009;65(3):315-328.
41. Lin SH, Chou LM, Chien YW, et al. Prebiotic Effects of Xylooligosaccharides on the Improvement of Microbiota Balance in Human Subjects. *Gastroenterol Res Pract*. 2016;2016:5789232.
42. Daddaoua A, Martínez-Plata E, López-Posadas R, et al. Active hexose correlated com pound acts as a prebiotic and is antiinflammatory in rats with hapten-induced colitis. *J Nutr.* 2007;137(5):1222-1228.
43. Mascaraque C, Suárez MD, Zarzuelo A, et al. Active hexose correlated compound exerts therapeutic effects in lymphocyte driven colitis. *Mol Nutr Food Res*. 2014;58(12):2379-2382.
44. Ocón B, Anzola A, Ortega-González M, et al. Active hexose-correlated compound and Bifidobacterium longum BB536 exert symbiotic effects in experimental colitis. *Eur J Nutr*. 2013;52(2):457-466.
45. de Vrese M, Schrezenmeir J. Probiotics, prebiotics, and synbiotics. *Adv Biochem Eng Biotechnol*. 2008;111:1-66.
46. Mallet JF, Graham É, Ritz BW, et al. Active Hexose Correlated Compound (AHCC) promotes an intestinal immune response in BALB/c mice and in primary intestinal epithelial cell culture involving toll-like receptors TLR-2 and TLR-4. *Eur J Nutr*. 2016;55(1):139-146.
47. Wong EB, Mallet JF, Duarte J, et al. Bovine colostrum enhances natural killer cell activity and immune response in a mouse model of influenza infection and mediates intestinal immunity through toll-like receptors 2 and 4. *Nutr Res*. 2014;34(4):318-325.
48. Karkow F. Chapter 14: Sjögren's Syndrome. In: Kulkarni AD, Calder P, Ito T, eds. *Clinician's Guide to AHCC*. In press.
49. Karkow F. Chapter 12: Inflammatory Bowel Diseases: Crohn's Disease and Ulcerative Colitis. In: Kulkarni AD, Calder P, Ito T, eds. *Clinician's Guide to AHCC*. In press.