

Vitamin A: The Key to Immune Tolerance in the Gut

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Abstract *The reason humans survive and thrive is because we have developed the ability to eat and utilize a wide range of foods and this has facilitated foraging and mobility. We are able to do this because our mucosal immune system is capable of maintaining and developing tolerance to a wide range of food components that are not us. Part of the intricate responsibility for achieving this is under the control—rather serendipitously as it is collected from our diet—the nutrient vitamin A or retinoic acid. Other aspects of energy harvesting are assigned to our bacterial bedfellows and these organisms work in collaboration with essential nutrients to support tolerance. Our recent fear of retinoic acid, based on overconsumption of vitamin A-rich liver, has suppressed the immense value that this nutrient provides to our local and systemic health. Its relevance in immune tolerance and its role in mucosal tissue health is described here.*

Introduction

Vitamin A is essential to immunological and bone health. Just as vitamin D has attracted attention for its ability to increase antimicrobial peptides and help us defeat pathogens, vitamin A is essential for the very tissues that protect us from the same pathogens.^{1,2}

The availability of vitamin A in our food is a key factor in a tolerant, highly functional immune system. To quote from the title of a commentary in the March 2008 issue of *Nature's Mucosal Immunology*, "Vitamin A rewrites the ABCs of oral tolerance."³

Vitamin A is crucial to a very sophisticated bi-directional mechanism that takes place in the digestive system and leads to immune tolerance across the entire gut lining. Immune tolerance is the essence of good health. An intolerant immune system will lead to a wide range of illnesses, and the gut is where many people first lose immune tolerance. Vitamin A is key to our ability to consume a wide range of antigens (food) and yet not react adversely, and it's quite fascinating.⁴

Vitamin A is required for innate and adaptive immunity and is an immune en-

hancer that potentiates the antibody response, maintains and restores the integrity and function of all mucosal surfaces. When we speak of vitamin A, we are usually speaking of three essential fat-soluble molecules, retinol, retinal and retinoic acid. Retinol is the form in which vitamin A is stored. Retinal is crucial for vision and retinoic acid actually functions like a hormone, binding to two receptors (retinoic acid receptor/RAR and retinoid X receptor/RXR) and impacting over 500 different genes.⁵

Vitamin A is of fundamental importance for energy homeostasis. New research finds that retinol is essential for the metabolic fitness of mitochondria. When cells are deprived of retinol, respiration and adenosine triphosphate synthesis fall. They recover energy output as soon as retinol is restored to physiological concentration. This may answer the nearly 100-year-old question of why vitamin A deficiency causes so many pathologies that are independent of retinoic acid action. Most important of all, vitamin A directs immune tolerance in the body through the cooperative interactions of gut-associated lymphoid tissues, secretory immunoglobulin A (IgA), bacterial

communities and dendritic cells.

Vitamin A cannot be synthesized by the human body; it must be absorbed by the intestine from the diet. In the presence of innate danger signals vitamin A effects can diminish or synergize with innate responses to promote or enhance protective immunity, ensuring suitable plasticity.⁶

Vitamin A and Mucosal Tolerance

Mucosal tolerance is a necessity for us to survive; without it we would not live a single day. The cells along the vast mucosal surfaces of the body are constantly in contact with foods, microbes and toxins. As the gut makes innumerable immunological decisions, it relays information from the innate to the adaptive, systemic immune system.

Vitamin A is the key to the gut making the right decisions. A deficiency in vitamin A skews the body toward a type of effector T cell called TH17 and its production of IL-17, a pro-inflammatory cytokine with propensity to causing autoimmune disease. In contrast, when stores of vitamin A are sufficient, there are sufficient peripheral naïve T cells converted to T regulatory cells (Tregs) to help maintain tolerance across the immune system. While T cell production of inflammatory chemicals such as cytokines is relevant during infectious events, it can become problematic when it continues unabated or at inappropriate levels. This background inflammation, known as para inflammation, is closely linked with a number of diseases.⁷

Inappropriate inflammation is quenched, that is inflammation derived from the effector T cells TH17, TH1 and TH2, is brought under control in a healthy patient through the cooperative use of retinoic-dependent regulatory T cells and other inhibitory mechanisms.⁸

The discovery of T cells that secrete IL-17 and other inflammatory cytokines is profoundly important. The TH17 subset is centrally involved in autoimmune disease and is important in host defense on mucosal surfaces.⁹

Tregs can help control excess IL-17, and retinoic acid is essential to promote Tregs. New research also implicates IL-17 in rheumatoid

arthritis; IL-17 may drive the production of harmful auto-antibodies (antibodies to our own tissue) and may trigger and support an inflammatory cascade. We now have a fascinating and emerging area of clinical investigation: finding out if it is possible to use vitamin A to actually convert T cells already polarized to an inflammatory subset, back to tolerance. This would allow a restorative use of this nutrient rather than preventive only.

In addition to self-tolerance, a functional immune system also needs to be able to tolerate non-self antigens that do not pose a threat. Such harmless non-self antigens are abundant in the intestine where trillions of commensal bacteria colonize the colon and where digested food is continuously absorbed via the small intestine epithelium. Effective immune-regulation is the *sine qua non* of healthy gut physiology. The importance of Treg cells to control and prevent aberrant immune responses directed towards self- or non-self antigens and to establish tolerance has already been demonstrated.¹⁰

An important molecule in this context is transforming growth factor beta (TGF- β), abundantly produced in the gut through the gut microbes. TGF- β is a multifunctional peptide that controls proliferation, differentiation, and other functions in many cell types, promoted by commensal organisms in the gut. This is one of the roles where suitable probiotics can really add health benefits, as certain strains are known to increase human originating TGF- β .¹¹ Effector T cells responsible for the adaptive immune responses can have a long life, sometimes years. That's why regulatory cell formation is a powerful element of human health.¹² Since TH17 cells reside mainly in the mucosa of the gut, it is an elegant serendipity that our food (nutrient) choice should have such a potentially powerful effect on our local and systemic immune plasticity.

The achievement of oral tolerance requires the availability of retinoic acid by enhancing a gut-specific mechanism of retinoic acid-enhanced, TGF- β -dependent conversion of T cells into Treg cells. In addition to their crucial roles in development, TGF- β and retinoic acid are involved at almost every level of immune

differentiation and function, affecting passive immunity as well as innate and adaptive immunity. Both TGF- β and retinoic acid are actively produced by the intestinal epithelium and play important roles in maintaining the integrity of its barrier function, vital for systemic health. The use of probiotics and suitable vitamin A supplementation provides a combination of TGF- β and retinoic acid that will support immune tolerance in the immune compromised patient.

Vitamin A and Infections

Vitamin A has been well known for its protective roles against infections. An important part of the protective roles might be through its ability to enhance antibody responses, especially IgA antibody responses in mucosal tissues.¹³

IgA is secreted into the gut lining where it provides protection against harmful pathogens. It thus helps maintain a healthy flora. Retinoic acid, derived from vitamin A in the diet, exerts a positive impact on the precursors for IgA-producing plasma cells.

In the intestine, induction and regulation of mucosal immunity takes place primarily in Peyer's patches, together with other parts of gut-associated lymphoid tissue (GALT) and the gut-draining mesenteric lymph nodes. Every hour of every day your Peyer's patches, clusters of cells in the lining of the small intestine, are a hotbed of signaling and conversation about the food you're eating. Their job is to help us share our gut with trillions of bacteria in a reasonably diplomatic manner, so we have friendly handshakes at the dinner table, not food fights and drunken brawls. With adequate vitamin A our gut is less likely to be chronically inflamed by inappropriate T-cell conversion leading to a myriad of inflammatory diseases.¹⁴

Our diets have changed dramatically over time, and to try to compensate for what we've lost in fresh, farm grown produce and pastured dairy and meat, we've fortified our foods. If people don't tolerate fortified milk, wheat and cereals, which are common allergens, and if they don't eat organ meats and are poor converters of carotene, they may well be

deficient in vitamin A.¹⁵ The more deficient in retinoic acid they are, the greater their risk of loss of immunological tolerance.

Carotenoids

Carotenoids have been called the colors of nature. Over 600 have been identified, and they give vegetables their gorgeous rainbow of hues, from green to orange to red to purple. About 50 can be converted into vitamin A. The major carotenoids in humans are beta-carotene, alpha-carotene, lycopene, lutein, and beta-cryptoxanthin.

The conversion of carotenoids to vitamin A is not as efficient or perfect as we've been led to believe. They can be difficult to convert, and a recent study from Newcastle University in England found that as many as 50% of women studied were unable to efficiently convert carotenoids into vitamin A, and thus may be retinoic acid deficient. The lead researcher, Dr. George Lietz, told *Science News*, "What our research shows is that many women are simply not getting enough of this vital nutrient because their bodies are not able to convert the beta-carotene."¹⁵

Other studies echo Lietz's. Research reported in the *American Journal of Clinical Nutrition* in 2000 found no evidence of benefit on vitamin A status from the increased consumption of dark-green or yellow vegetables. Beta-carotene from vegetables provided an estimated vitamin A equivalence of 25 to 1 (beta-carotene to vitamin A), not the reported 6 to 1 for beta-carotene and 12 to 1 for other carotenes. In addition, up to 50% of beta-carotene is highly dependent on fat consumption at the same time, and cooked carotenoids are better absorbed than raw. Poor protein status or zinc deficiency also affects beta-carotene uptake, and its conversion to retinol.¹⁶

Carotenoids may not always be beneficial. It appears that high doses of beta-carotene under highly oxidative conditions lead to breakdown products that have toxic biological activity. Beta-carotene molecules *in vitro* can split into carotenoic acids that can lead to toxic cleavage products. "What happens when these eccentric cleavage products accumulate in large amounts?" asks Robert

Russell in an article from the *American Journal of Clinical Nutrition*. He pointed out that beta-carotene likely interferes with the action of retinoic acid, which probably explains the results from two carotene intervention trials.¹⁷ These studies showed a higher incidence of lung cancer in smokers who consumed high doses of beta-carotene. Although carotenoids offer a rainbow of important nutrition, they are not reliable sources of vitamin A.

Conclusion

Vitamin A may also decrease bone mineral density and increase the risk of fracture when vitamin D stores are not adequate.¹⁸ The Council for Responsible Nutrition reviewed all the evidence on vitamin A and fracture risk in a 2004 report, and concluded that “the overall database remains...conflicted and unresolved...if anything, the preponderance of evidence may have moved away from the suggestion that vitamin A might increase the risk of hip fracture.” The council considers supplements of 10,000 IU daily of preformed vitamin A (retinol) to be generally safe. They note a long history of safe use of supplements containing up to 10,000 IU daily. Those who regularly consume liver or organ meats may be getting enough from their diet and may exercise more caution about vitamin A supplements.

Competing Interests

Apart from a long clinical life and research obsession, the author is the Managing Director of Nutri-Link Ltd, a food supplement distribution company in the UK. Nutri-Link Ltd also provides extensive continuing professional development approved post-graduate education services. The author is also Managing Director of Integrative Health Consulting Ltd, a specialist research-orientated company in the UK that provides support to the food and medicines industry seeking to find health solutions through food substrates.

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