BY SARA ADÃES, PH.D. , JULY 8, 2019

HOW THE GUT MICROBIOTA INFLUENCES OUR IMMUNE SYSTEM

HOW THE GUT MICROBIOTA INFLUENCES OUR IMMUNE SYSTEM

Key Learning Objectives

- Understand the importance of gut microbiota-immune system interactions
- Acquire basic concepts of the immune system and its cells
- Find out how the gut microbiota influences immune response
- Discover how diet impacts gut microbiota-immune system interactions
- Appreciate the impact of the gut microbiota on our health

INTRODUCTION TO THE GUT MICROBIOTA

Our gut is home for a very large number of microbes collectively known as the gut microbiota. They're around 38 trillion microbes—at least as many cells as we have in our whole body. Their collective genome, known as the gut microbiome, contains 150 times more genes than the human genome.[1,2]

Naturally, our body had to find a way to cope with so many guests. Beyond just dealing with their presence, our body actually developed a mutually beneficial relationship with our microbes, what is known in biology as *symbiosis*—a term that describes any type of close biological interaction between two different species that live together.

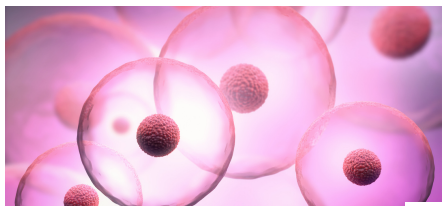
Science is only beginning to unravel the extent of this mutual influence, but it's already clear that it's massive and has a huge impact on our health and the body's homeostasis—the state of balance, of dynamic equilibrium that is fundamental for our survival.

The gut microbiota influences many aspects of human physiology, from metabolism, to the cardiovascular system or the nervous system, for example. In this article, we focus on the interaction between the gut microbiota and our immune system.

CATEGORIES

Learning & Development
Nutrition & Supplementation
Brain Health
Neurotechnologies
Mind & Psychology
Body & Movement
Sleep
Tips & Practices
Core Concepts
Managing Stress
Neurology
Healthspan

FEATURED POSTS



THE CROSSTALK BETWEEN THE GUT AND THE IMMUNE SYSTEM

The immune system is the group of cells and molecules that protect us from disease by monitoring our body and responding to any foreign (non-self) substances they perceive as threats, particularly infectious microbes. Our immune system has co-evolved along with a diverse gut flora, not only to create defenses against pathogens, but also to develop tolerance for beneficial microbes.[3] As a consequence, the immune system and the gut microbiota developed a mutualistic relationship, regulating one another and cooperating to support each other. The importance of this interaction is clearly highlighted by the fact that 70–80% of the body's immune cells are found in the gut.[4]

The dialogue between the immune system and the microbiota starts the moment our body gets in contact with microbes—at birth. As we grow, the microbiota shapes the development of our immune system, and the immune system shapes the composition of the microbiota.[5] This communication and mutual regulation is maintained throughout life and is the key for a healthy interaction between the microbiota and the immune system.

In normal conditions, the immune system promotes the growth of beneficial microbes and helps maintain a stable microbial community, while in return, a healthy microbiota produces molecular signals that support the development of immune cells and contribute to the fine tuning of immune responses.[6,7] A healthy crosstalk between the gut microbiota and the immune system supports protective responses against pathogens, promotes tolerance to harmless microbes and their products, and helps maintain self-tolerance (the ability of our immune system to not react harmfully to our own body).

> ❝ Our immune system co-evolved with the gut microbiota. Both work together to keep us healthy and protect us against unwanted microbes. ❞

A QUICK OVERVIEW OF OUR IMMUNE SYSTEM

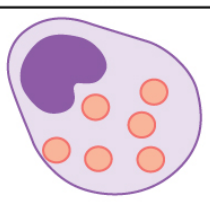
Before we go any further in this exploration of gut microbiota-immune system interactions, it may be useful to review some basic concepts of the immune system.

The immune system is divided into two types of coordinated responses: (1) innate immunity, and (2) adaptive immunity. The innate immune system is our first line of defense.[4] It is composed of physical and chemical barriers, immune cells, and blood proteins that mediate inflammation (e.g., cytokines).

Physical and chemical barriers include the cells that line the outer surfaces and cavities of organs and blood vessels, as well as the antimicrobial chemicals they produce. These cells are called epithelial cells and they create what is known as epithelial barriers.

The cells of the innate immune system patrol our body looking for threats (e.g., microbes, microbial proteins) and devise quick immune responses when they find them that aim to destroy the foreign, damaged, or infected cells.[4] These responses are nonspecific, but they influence subsequent specific adaptive immune responses.

> ❝ The innate immune system, our first line of defense, devises a quick nonspecific response to threats. ❞

Cell type	Characteristics	Location	Image
Mast cell	Dilates blood vessels and induces inflammation through release of histamines and heparin. Recruits macrophages and neutrophils. Involved in wound healing and defense against pathogens but can also be responsible for allergic reactions.	Connective tissues, mucous membranes	
Macrophage	Phagocytic cell that consumes foreign	Migrates from blood	

HOW TO INTERMITTENT FAST: AN EXPLORATION OF FASTING PROTOCOLS

WHAT IS GLUTAMATE?

WHAT IS DOPAMINE?

BOX BREATHING: A BREATHING TECHNIQUE TO FOCUS THE MIND

POPULAR TAGS

ACETYLCHOLINE
ACETYLCHOLINE
ACETYL-L-CARNITINE
ADAPTOGEN
ADAPTOGENS
ADDERALL
ADDICTION
ADVANCED MEDICINE
ADVANCING MEDICINE
AGENCY
AGING
AGING
AGING SUPPORT
A HEAD ABOVE
AMINO ACID
AMINO ACIDS

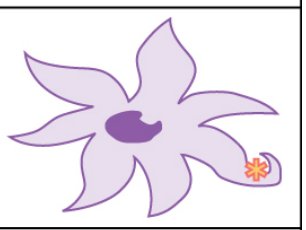
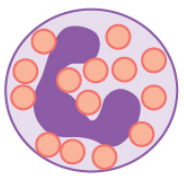
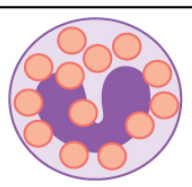
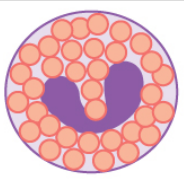
			
Dendritic cell	Presents antigens on its surface, thereby triggering adaptive immunity.	Present in epithelial tissue, including skin, lung and tissues of the digestive tract. Migrates to lymph nodes upon activation.	
Monocyte	Differentiates into macrophages and dendritic cells in response to inflammation.	Stored in spleen, moves through blood vessels to infected tissues.	
Neutrophil	First responders at the site of infection or trauma, this abundant phagocytic cell represents 50-60 percent of all leukocytes. Releases toxins that kill or inhibit bacteria and fungi and recruits other immune cells to the site of infection.	Migrates from blood vessels into tissues.	
Basophil	Responsible for defense against parasites. Releases histamines that cause inflammation and may be responsible for allergic reactions.	Circulates in blood and migrates to tissues.	
Eosinophil	Releases toxins that kill bacteria and parasites but also causes tissue damage.	Circulates in blood and migrates to tissues.	

Image 1: Cells of the innate immune system (Source: Innate Immune Response by Charles Molnar and Jane Gair. License: CC BY 4.0)

The adaptive immune system is responsible for the more complex immune responses that develop when innate immunity is insufficient to manage a threat.[4] Adaptive immunity is mediated by cells called lymphocytes.

There are two major populations of lymphocytes called B cells and T cells. B cells are involved in humoral immunity mediated by the production of antibodies. Antibodies in the blood and mucosal secretions recognize microbial antigens (i.e., molecules recognized by antibodies or lymphocyte receptors that may trigger an immune response), neutralize the microbes, and target them for elimination by immune cells.

T cells are involved in cell-mediated immunity, which acts to destroy any microbes that are not accessible to antibodies—microbes that have infected our cells or that have survived within other immune cells. Cell-mediated immunity destroys those infected cells and eliminates infections.[4]

At the surface of their cell membrane, lymphocytes express a very diverse repertoire of receptors that recognize specific portions of antigens called epitopes. Lymphocyte receptors may detect up to 1 billion different antigens. Lymphocytes survey our body continuously, looking for potential pathogens. When they come across an antigen they recognize, lymphocytes are activated, trigger a specific immune response, and proliferate, creating a pool of new lymphocytes with the same specificity. Some of these new lymphocytes will remain in our body after the threat is eliminated. They are called memory B cells because they act as the memory of our immune system, ensuring that if it ever encounters the same antigen, the response will be faster, greater, and more effective—we thus become immune to that specific threat. [4]

> “ The adaptive immune system is what remembers past infections and vaccines, allowing the immune system to respond quickly when we encounter something similar again. ”

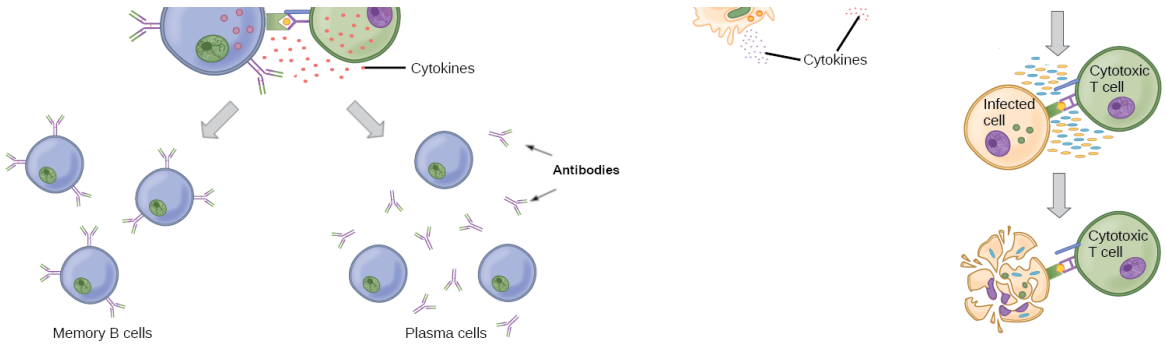


Image 2: The Adaptive immune system (Adapted from Adaptive Immune Response by Charles Molnar and Jane Gair. License: CC BY 4.0)

HOW INTESTINAL BARRIER FUNCTIONS WORKS

The intestinal wall is the primary interface between the gut microbiota and our body. It acts as a dynamic barrier that isolates our body from gut microbes but allows desirable interactions to take place. The intestinal barrier is made up of physical and chemical elements. The physical barrier is created by the epithelial cells that line the gut, the molecules on their surface, and the mucus they produce; the chemical barrier is created by inflammatory molecules (cytokines), antibodies, and antimicrobial substances produced by epithelial and immune cells.

Epithelial cells recognize microbial products via immune receptors known as pattern-recognition receptors (PRRs).[8] Activation of PPRs enables a dynamic adjustment of epithelial activity based on chemical signals from the microbiota. This allows epithelial cells to adjust their antimicrobial response to eliminate pathogenic infections, destroy infected cells, and influence the composition of the gut flora. Proper PRR signaling is important for the maintenance of tolerance to good microbes, for the elimination of intestinal infections, and consequently, for the maintenance of a balanced gut microbiota.[9]

Epithelial cells also respond to metabolites produced by the gut microbiota, such as short-chain fatty acids (SCFAs), polyamines, and amino acids. SCFAs, for example, serve as energy sources for epithelial cells, modulate their metabolism and their secretions, and help support the integrity of the epithelial barrier.[10]

Many microbial metabolites cross the epithelial barrier and are absorbed into the blood, through which they can reach other tissues in our body. Microbial metabolites can influence the development, maturation, and function of circulating and tissue-resident immune cells in different organs, including the brain.[11] Through these metabolites, the gut microbiota is able to fine-tune innate immune responses throughout the body.[10]

The barrier function of the intestinal wall is also maintained by immune cells. For example, microfold cells (M cells) are cells of the immune system found among epithelial cells that transport microbes and microbial antigens across the epithelial layer and deliver them to antigen-presenting cells to initiate immune responses.[12] Found within the intestinal wall are also dendritic cells, whose extensions protrude from between epithelial cells into the intestinal lumen, where they probe the microbiota environment, searching for potential threats and devising adequate responses.[13] T and B cells located in the intestinal wall participate in adaptive immune responses that contribute to the maintenance of the epithelial barrier and to the suppression of responses to harmless microbes, thereby promoting immune homeostasis.[14,15]

> “ Healthy intestinal barrier function allows certain gut-derived molecules to get into the body, while keeping others out. This supports better immune and brain performance. ”

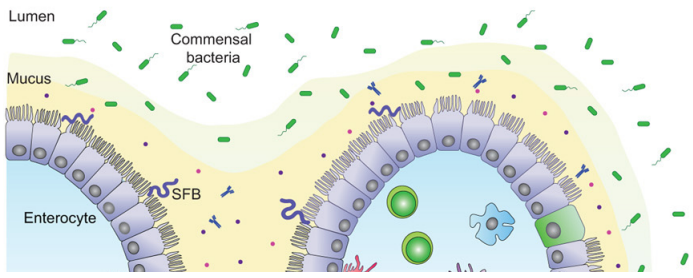


Image 3: Intestinal epithelial barrier and immune cells (Adapted from Muniz et al, 2012; 10.3389/fimmu.2012.00310. License: CC BY 4.0)

HOW INTESTINAL BARRIER DYSFUNCTION LEADS TO LEAKY GUT

The integrity of the intestinal barrier is fundamental for a healthy relationship with the gut microbiota. A healthy intestinal barrier will keep pathogens and harmful microbial products away from our body, while being selectively permeable to microbial signaling molecules and metabolites that contribute to the health of our biological processes.

Dysfunctions in the intestinal barrier alter its permeability and lead to what is commonly known as “leaky gut.” Leaky gut is fundamentally about two things: (1) macromolecules being allowed to pass through intact cell membranes due to changes in the transport mechanisms and (2) loosening of the tight junctions between epithelial cells. This means that the intestinal barrier becomes permeable to things to things we don’t want to get in.

Changes in the permeability of the intestinal barrier compromises its ability to block the access of undesired microbes and microbial products to our body. This may result in chronic inflammatory reactions and altered immune responses that can undermine our physiological processes.[16]

> “ Leaky gut can show up as a variety of signs and symptoms, which have in common aspects of chronic inflammation and immune system issues (e.g., autoimmunity, allergies). ”

WHY IMMUNOGLOBIN A IS IMPORTANT FOR GUT IMMUNITY

One of the most important molecules involved in the crosstalk between the immune system and the microbiota is immunoglobulin A (IgA). IgA is a type of antibody produced by specific B cells known as plasma cells. IgA can bind and coat specific microbes, microbial components, dietary components, and other antigens in the intestine. This creates an additional physical barrier that prevents potentially harmful interactions with the immune system.[17]

IgA supports the establishment of a balanced microbiota by regulating its composition, controlling microbial gene expression, increasing microbial diversity, and enhancing mutualism between the gut microbiota and the host.[18,19] In turn, the gut microbiota affects the production of IgA by influencing the accumulation of plasma cells, as well as the diversity and magnitude of IgA responses. The IgA repertoire in the gut is constantly adjusted in response to changes in microbial composition, with increases in microbial diversity leading to increases in the diversity of the IgA pool.[20]

In the crosstalk between the gut microbiota and the immune system, there is another type of cell that plays a significant part: TH17 cells, a type of helper T cell. TH17 cells located in the intestinal wall stimulate the production of antimicrobial proteins, including IgA, and enhance the integrity of the intestinal mucosal barrier, thereby having a beneficial role in preventing infection and promoting homeostasis.

But TH17 cells are a bit of a double-edged sword. Under some circumstances the gut microbiota can make TH17 cells produce pro-inflammatory cytokines, essentially shifting TH17 cells towards becoming harmful to healthy function. Harmful TH17 cells can migrate to the lymph nodes found throughout the body, where they promote immune reactions to self-antigens. Through this action, TH17 cells may promote or exacerbate autoimmune and inflammatory reactions.[14,21,22]

WHY PLANT FIBERS ARE CRITICAL FOR BRAIN AND IMMUNE HEALTH

Gut microbes get most of their nutrients from our diet and help us digest much of the food we ingest. Therefore, it should come as no surprise that diet has a huge impact on the composition of gut microbiota and, consequently, on our immune system.[23] Diet influences many aspects of the microbiota-immune system crosstalk, including, for example, the permeability of the intestinal barrier,[24] the types of microbes targeted by IgA, [25] or whether TH17 cells become beneficial or harmful.[22,26]

Modern diets, particularly those of the Western world, are characterized by an excessive intake of highly palatable energy-dense foods, including high levels of animal protein, saturated fats, simple sugars and salt, but low amounts of plant-derived fibers. And this is exactly the dietary pattern that is being increasingly linked to immune dysfunctions associated with the gut microbiota. For example, high dietary intake of salt or of long-chain and saturated fatty acids may stimulate the harmful actions of TH17 cells, which, in turn, may increase the risk of autoimmune reactions.[27,28]

On the other hand, short-chain fatty acids (SCFAs), which are produced from insoluble dietary fibers by certain microbial species, promote the activity of regulatory T cells (Treg).[29,30] Treg cells prevent inflammatory reactions against harmless intestinal microbes by suppressing the abnormal activation of other immune cells, including TH17 cells. Treg cells therefore play a very important part in maintaining immune tolerance to the gut microbiota, dietary components, and self-antigens.[14,31,32]

SCFAs also support the integrity of the epithelial barrier, increase the production of IgA, and promote gut homeostasis by increasing intestinal secretions and decreasing inflammatory responses. SCFAs can reach other organs, such as the brain, for example, where they also decrease neuroinflammatory responses that are known to underlie many neurodegenerative diseases.[7] SCFAs are one of the reasons why fiber-rich diets support our immune system.[33]

> “ SCFA, like acetate and butyrate, are made when gut microbes ferment insoluble fiber and carbohydrates (e.g., resistant starches, oat bran, pectins, fructooligosaccharides). Eating a diet rich in plant foods that can be converted into SCFA helps keep the brain and immune system healthy. ”

THE IMPACT OF THE GUT MICROBIOTA ON HEALTH

Microbes produce a vast number of metabolic products and other compounds that can directly interact with our physiological pathways. The immune system monitors the metabolic state of the gut microbiota and relays that information to other tissues in the body to adjust their physiological processes.

The set of compounds produced by the gut microbiota depends on the composition of the gut flora. Therefore, microbial imbalances in the gut (referred to as dysbiosis) can affect the production of the molecular signals that underlie the crosstalk between the gut microbiota and our physiological pathways and have a significant impact on those processes. Metabolic changes in the microbiota can even lead to the production of toxic products.

> “ Many people are affected by health challenges related to poor immunity and inflammation. Diet can play a large role in worsening or improving these issues, because of interactions between the gut microbiota and immune system. ”

Dysbiosis can be caused by multiple environmental factors, such as the use of antibiotics and psychological and physical stress, for example. However, diet stands out as one of the most impactful factors.[34]

IMAGE

A healthy interaction between our immune system and the gut microbiota is crucial for the maintenance of our body's homeostasis and health. Imbalances in the gut microbiota may dysregulate immune responses and lead to the development of chronic inflammatory and autoimmune dysfunctions. This is why it is important to take good care of our gut. And this starts with what we eat.

References

[1] J. Qin, R. Li, J. Raes, M. Arumugam, K.S. Burgdorf, C. Manichanh, T. Nielsen, N. Pons, F. Levenez, T. Yamada, D.R. Mende, J. Li, J. Xu, S. Li, D. Li, J. Cao, B. Wang, H. Liang, H. Zheng, Y. Xie, J. Tap, P. Lepage, M. Bertalan, J.-M. Batto, T. Hansen, D. Le Paslier, A. Linneberg, H.B. Nielsen, E. Pelletier, P. Renault, T. Sicheritz-Ponten, K. Turner, H. Zhu, C. Yu, S. Li, M. Jian, Y. Zhou, Y. Li, X. Zhang, S. Li, N. Qin, H. Yang, J. Wang, S. Brunak, J. Doré, F. Guarner, K. Kristiansen, O. Pedersen, J. Parkhill, J. Weissenbach, MetaHIT Consortium, P. Bork, S.D. Ehrlich, J. Wang, Nature 464 (2010) 59–65.
[2] R. Sender, S. Fuchs, R. Milo, PLoS Biol. 14 (2016) e1002533.
[3] R.E. Ley, D.A. Peterson, J.I. Gordon, Cell 124 (2006) 837–848.
[4] A.K. Abbas, A.H.H. Lichtman, S. Pillai, Cellular and Molecular Immunology E-Book, Elsevier Health Sciences, 2017.
[5] J.K. Nicholson, E. Holmes, J. Kinross, R. Burcelin, G. Gibson, W. Jia, S. Pettersson, Science 336 (2012) 1262–1267.
[6] M. Levy, C.A. Thaiss, E. Elinav, Genome Med. 7 (2015) 120.
[7] M.G. Rooks, W.S. Garrett, Nat. Rev. Immunol. 16 (2016) 341–352.
[8] J. Pott, M. Hornef, EMBO Rep. 13 (2012) 684–698.
[9] D. Fawkner-Corbett, A. Simmons, K. Parikh, Best Pract. Res. Clin. Gastroenterol. 31 (2017) 683–691.
[10] C.A. Thaiss, N. Zmora, M. Levy, E. Elinav, Nature 535 (2016) 65–74.
[11] D. Erny, A.L. Hrabě de Angelis, D. Jaitin, P. Wieghofer, O. Staszewski, E. David, H. Keren-Shaul, T. Mahlakoiv, K. Jakobshagen, T. Buch, V. Schwierzeck, O. Utermöhlen, E. Chun, W.S. Garrett, K.D. McCoy, A. Diefenbach, P. Staeheli, B. Stecher, I. Amit, M. Prinz, Nat. Neurosci. 18 (2015) 965–977.
[12] N.A. Mabbott, D.S. Donaldson, H. Ohno, I.R. Williams, A. Mahajan, Mucosal Immunol. 6 (2013) 666–677.
[13] E.A. Mayer, Nat. Rev. Neurosci. 12 (2011) 453–466.
[14] K. Honda, D.R. Littman, Nature 535 (2016) 75–84.
[15] L.M. Kato, S. Kawamoto, M. Maruya, S. Fagarasan, Immunol. Rev. 260 (2014) 67–75.
[16] M. Camilleri, Gut (2019).
[17] O. Pabst, Nat. Rev. Immunol. 12 (2012) 821–832.
[18] D.A. Peterson, N.P. McNulty, J.L. Guruge, J.I. Gordon, Cell Host Microbe 2 (2007) 328–339.
[19] S. Kawamoto, M. Maruya, L.M. Kato, W. Suda, K. Atarashi, Y. Doi, Y. Tsutsui, H. Qin, K. Honda, T. Okada, M. Hattori, S. Fagarasan, Immunity 41 (2014) 152–165.
[20] C. Lindner, I. Thomsen, B. Wahl, M. Ugur, M.K. Sethi, M. Friedrichsen, A. Smoczek, S. Ott, U. Baumann, S. Suerbaum, S. Schreiber, A. Bleich, V. Gaboriau-Routhiau, N. Cerf-Bensussan, H. Hazanov, R. Mehr, P. Boysen, P. Rosenstiel, O. Pabst, Nat. Immunol. 16 (2015) 880–888.
[21] K. Hirota, J.-E. Turner, M. Villa, J.H. Duarte, J. Demengeot, O.M. Steinmetz, B. Stockinger, Nat. Immunol. 14 (2013) 372–379.
[22] C.T. Weaver, C.O. Elson, L.A. Fouser, J.K. Kolls, Annu. Rev. Pathol. 8 (2013) 477–512.
[23] M.A. Conlon, A.R. Bird, Nutrients 7 (2014) 17–44.
[24] M. Vancamelbeke, S. Vermeire, Expert Rev. Gastroenterol. Hepatol. 11 (2017) 821–834.
[25] A.L. Kau, J.D. Planer, J. Liu, S. Rao, T. Yatsunenko, I. Trehan, M.J. Manary, T.-C. Liu, T.S. Stappenbeck, K.M. Maleta, P. Ashorn, K.G. Dewey, E.R. Houpt, C.-S. Hsieh, J.I. Gordon, Sci. Transl. Med. 7 (2015) 276ra24.
[26] I.I. Ivanov, R. de L. Frutos, N. Manel, K. Yoshinaga, D.B. Rifkin, R.B. Sartor, B.B. Finlay, D.R. Littman, Cell Host Microbe 4 (2008) 337–349.
[27] M. Kleinewietfeld, A. Manzel, J. Titze, H. Kvakan, N. Yosef, R.A. Linker, D.N. Muller, D.A. Hafler, Nature 496 (2013) 518–522.
[28] A. Haghikia, S. Jörg, A. Duscha, J. Berg, A. Manzel, A. Waschbisch, A. Hammer, D.-H. Lee, C. May, N. Wilck, A. Balogh, A.I. Ostermann, N.H. Schebb, D.A. Akkad, D.A. Grohme, M. Kleinewietfeld, S. Kempa, J. Thöne, S. Demir, D.N. Müller, R. Gold, R.A. Linker, Immunity 43 (2015) 817–829.
[29] P.M. Smith, M.R. Howitt, N. Panikov, M. Michaud, C.A. Gallini, M. Bohlooly-Y, J.N. Glickman, W.S. Garrett, Science 341 (2013) 569–573.
[30] N. Arpaia, C. Campbell, X. Fan, S. Dikiy, J. van der Veeken, P. deRoos, H. Liu, J.R. Cross, K. Pfeffer, P.J. Coffer, A.Y. Rudensky, Nature 504 (2013) 451–455.
[31] A.M. Bilate, J.J. Lafaille, Annu. Rev. Immunol. 30 (2012) 733–758.
[32] K.S. Kim, S.-W. Hong, D. Han, J. Yi, J. Jung, B.-G. Yang, J.Y. Lee, M. Lee, C.D. Surh, Science 351 (2016) 858–863.
[33] A. Trompette, E.S. Gollwitzer, C. Pattaroni, I.C. Lopez-Mejia, E. Riva, J. Pernot, N. Ubags, L. Fajas, L.P. Nicod, B.J. Marsland, Immunity 48 (2018) 992–1005.e8.
[34] L.A. Hawrelak, S.P. Myers, Altern. Med. Rev. 9 (2004) 180–197.

NEUROHACKER®
COLLECTIVE

NO COMMENTS YET

Sign in or Register to Comment

NEUROHACKER®
COLLECTIVE

We are focused on making groundbreaking products for health and well-being through complex systems science.

COMPANY

About
Affiliate
Press Releases
Press Inquiries
Careers
Investors
Wholesale

SUPPORT

My Account
FAQ
Store Locator
Pilot Study
Money Back Guarantee
Score Better Guarantee

COLLECTIVE INSIGHTS

Podcast
Healthspan
Nootropics
Brain
Fitness
Glossary

CONTACT

5938 Priestly Dr., Suite 200
Carlsbad, CA 92008

Email Customer Service

(855) 281-2328

Privacy Policy Terms & Conditions Secure Shopping with 100% industry Standard SSL

* These statements have not been evaluated by the Food and Drug Administration. The products and information on this website are not intended to diagnose, treat, cure or prevent any disease. The information on this site is for educational purposes only and should not be considered medical advice. Please speak with an appropriate healthcare professional when evaluating any wellness related therapy. Please read the full **medical disclaimer** before taking any of the products offered on this site.

† note offer applies to first-time subscription orders only