The Microbiome Theory of Aging (MTA)

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Abstract

The Microbiome Theory of Aging (MTA) explains how microbial imbalance in the intestinal tract, which is also referred to as dysbiosis, causes health problems that accelerate biological aging. The underlying mechanisms involved include increased inflammation, elevated levels of zonulin, destruction of intestinal tight junctions, and intestinal permeability, which allow lipopolysaccharides (LPS) to leak into systemic circulation. LPS is a powerful endotoxin that causes chronic inflammation throughout the body. Chronic inflammation is associated with chronic diseases and the acceleration of biological aging. Postbiotic metabolites are compounds that are created by probiotic bacteria in the colon. Postbiotic metabolites have been called the new frontier in microbiome science due to their key roles in regulating the structure and function of the gut microbiome and many aspects of human health.

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Revolutionary advancements in technology, especially next-generation gene sequencing (NGS), have resulted in a new understanding of the structure and function of the human gut microbiome and its fundamental role in regulating health and aging.[1]

#1 Game Changer

The Cleveland Clinic is a highly respected medical institution. It was ranked the second hospital in the nation and the first hospital for heart care in U.S. News & World Report's 2021-22 Best Hospitals rankings.[2]

In 2016, the Cleveland Clinic assembled a panel of top doctors and scientific researchers to create a list of medical innovations that they expect to be major game changers in the coming years. When the panel of medical and scientific experts announced their list of the top 10 medical innovations that are most likely to transform healthcare in 2017 and beyond, topping the list as the #1 Game Changer expected to transform healthcare was using the microbiome to prevent, diagnose, and treat disease.[3]

A wide range of diet, lifestyle, and environmental factors influence the aging process, and over time, numerous theories of aging have been proposed. The microbiome theory of aging (MTA) isn't intended to dislodge or negate previous theories. The theory's purpose is to emphasize the critical role that the gut microbiome plays in regulating many aspects of human health, which directly influence people's rate of physical decline and biological aging.

The Gut-Immune System

From 70-80% of the immune cells in the human body are located in the gastrointestinal (GI) tract.[4] Many factors are capable of upsetting the microbial balance in the GI tract. Regardless of the cause, the MTA explains how dysbiosis, which refers to microbial imbalance in the GI tract, causes changes that weaken the immune system, which then increase the likelihood of developing chronic degenerative diseases.

Studies have been published linking dysbiosis with virtually all chronic degenerative diseases, including inflammatory,[5] metabolic,[6] neurological,[7] immunological,[8] and cardiovascular diseases.[9] Although an association exists between dysbiosis and most of our common diseases, association isn't causation. The purpose of this article is to discuss a fundamental mechanism that explains why dysbiosis is associated with the development of age-related diseases.

Microbiome Science

The first study with the term microbiome in the title was published in April 2006.[10] Although microbiome science is a relatively new field of study, the microbiome's

critical importance in regulating human health is reflected in the amount of scientific research that is being conducted on it. Since April 2006, over 48 000 citations have been indexed in PubMed with the term microbiome in the title or abstract.

The Human Gut Microbiome

The gut microbiome ecosystem includes three main components: (1) the microbiota, which are the inhabitants of the gut microbiome—an estimated 100 trillion bacteria—but also viruses, yeast, fungi, and archaea; (2) epithelial cells, which are a single-layer cells that line the GI tract; and (3) the mucus layer, which forms a barrier that protects epithelial cells from exposure to bacteria and other harmful substances.[11] Over 99.9% of the bacteria in the GI tract reside in the outer mucosal layer in the colon.[12,13]

If any of these parts of the microbiome ecosystem are damaged or dysfunctional, the resulting inflammation and intestinal permeability can lead to a decline in immune function, the development of diseases, and the acceleration of biological aging.

Postbiotic Metabolites

Postbiotic metabolites, which have been called the new frontier in microbiome science,[14] are substances released by or produced through the metabolic activity of bacteria, which exert a beneficial effect on the host.[15]

A major paradigm shift is happening in microbiome science that is revolutionizing our understanding of how the gut microbiome functions and how it regulates health and aging. For decades, probiotic bacteria were thought to be the primary regulators of GI health, but the mechanisms weren't clearly understood. This mystery is being solved with the new understanding of the wide-ranging benefits of postbiotic metabolites. Postbiotic metabolites function in multiple ways to regulate the health of the microbiome ecosystem, and they also regulate many aspects of health throughout the body, including the immune system and the brain.

The MTA explains how probiotic bacteria produce postbiotic metabolites, how various postbiotic metabolites regulate different aspects of health, and what factors upset the microbial balance in the microbiome, resulting in changes that cause health problems and accelerate biological aging.

Consequences of Microbiome Disruption

Gut microbiome dysfunction initiates the following cascade of events, which explains why intestinal dysbiosis and inflammation accelerate biological aging: Dysbiosis: (1) causes intestinal inflammation, (2) which elevates levels of zonulin, (3) which degrade intestinal tight junctions, (4) which causes intestinal permeability, (5) which allows lipopolysaccharides (LPS) to enter circulation and causes systemic inflammation, (6) which suppresses the immune system and accelerates tissue damage, (7) which increases the risk of developing chronic degenerative diseases, and (8) which accelerates aging.

Dysbiosis is a term that denotes microbial imbalance in the microbiome ecosystem. A healthy microbial balance in the gut microbiome consists of approximately 85-90% beneficial bacteria and only about 10-15% bad bacteria.[16] When levels of bad bacteria become elevated, intestinal inflammation develops.[17]

Causes of Dysbiosis

Many factors can contribute to microbiome malfunction; however, the most common and most serious causes are microbial imbalance,[18] gluten-induced inflammation,[19] antibiotics,[20] poor diet,[21] and stress.[22] The fact that these factors are so prevalent explains why microbiome dysfunction is so prevalent and is a major factor that accelerates biological aging.

Antibiotics have saved millions of lives, but they can also have serious adverse effects. Antibiotics dramatically alter the bacterial composition of the gut microbiome in animals, children, and adults, which causes dysbiosis and often leads to additional health problems.[23] The overprescribing of antibiotics continues to be a major health problem.[24]

In addition to antibiotics, other classes of microbiome-disrupting drugs include oral contraceptives, NSAIDs, corticosteroids, antipsychotics, antacids, proton pump inhibitors, H2 receptor antagonists, statins, metformin, laxatives, opioids, selective serotonin reuptake inhibitors (SSRIs), and antidepressants.[25,26]

Other factors can also have a detrimental effect on the gut microbiome such as C-section birth, lack of breastfeeding, poor sleep, a sedentary lifestyle, stress, environmental toxins such as heavy metals and pesticides, and an unhealthy diet.[27-30]

Stress and Microbiome Dysfunction

The gut-brain axis is a bidirectional communication highway that enables the gut and the brain to constantly communicate with each other. In the past few years, the mechanisms explaining how stress causes microbiome dysfunction and intestinal permeability have been elucidated. This directly links stress with microbiome dysfunction and accelerated aging.

The brain responds to chronic stress by releasing corticotropin-releasing factor (CRF), which binds to mast cells in the GI tract. Mast cell activation results in the release of protease enzymes, which degrade the epithelial tight junctions, resulting in intestinal permeability.[31] Thus, the brain-gut stress response helps explain why people with chronic stress, such as PTSD and psychiatric disorders, have high rates of intestinal permeability and damage to their gut microbiome.[32,33]

Inflammation results from the same factors that cause dysbiosis: too many bad bacteria, gluten, antibiotics, poor

diet, and stress. When any of these factors occur, the level of intestinal inflammation increases, which elevates levels of zonulin, which leads to intestinal permeability.[34]

Zonulin is a protein produced in the intestinal tract in response to inflammation; it was discovered by the Harvard pediatrician Alessio Fasano. Fasano states that zonulin is "the only human protein discovered to date that is known to reversibly regulate intestinal permeability by modulating intercellular tight junctions."[35] Zonulin disassembles or destroys tight junction proteins, which results in intestinal permeability or leaky gut. The discovery of zonulin explains how dysbiosis and inflammation cause intestinal permeability, which results in health problems and the acceleration of biological aging.

Tight junctions are the spaces between the epithelial cells that line the intestinal tract. Proteins located on the surface of epithelial cells function metaphorically like Velcro.[36] The tight junction proteins stick together to form a semipermeable barrier, which regulates the absorption of nutrients, water, and other beneficial compounds while preventing pathogenic and/or inflammatory compounds from entering systemic circulation. Healthy tight junctions are critical for maintaining good health.

Intestinal permeability results when intestinal tight junctions are damaged or degraded, which enables unwanted, harmful substances, such as LPS, to leak into systemic circulation. An increasing amount of data is linking dysbiosis and intestinal permeability with a wide range of diseases and accelerated aging.[37,38]

The Microbiome Diet

Probiotic bacteria require two main categories of compounds in food to produce postbiotic metabolites: dietary fibers and polyphenols. Humans don't possess the enzymes needed to digest most types of dietary fibers and polyphenols. Hence, these compounds pass through the GI tract unchanged. However, when they reach the colon, they are the food for the probiotic bacteria. Bacterial fermentation of nondigestible dietary fibers and polyphenols results in the production of a wide range of postbiotic metabolites with various types of biological activity.[39]

In *The Mind-Gut Connection,* world-renowned gastroenterologist and microbiome scientist Emeran Mayer, makes the following statement: "Your bacteria use the information stored in their millions of genes to transform food into hundreds of thousands of metabolites."[40]

A review article published in 2002 reported that over 22 000 postbiotic metabolites have been identified in the scientific literature.[41] It's unrealistic to attempt to name and list the health-regulating effects of thousands of probiotic, bacterially produced, postbiotic metabolites that been identified thus far. The following list covers the most researched and understood postbiotic metabolites to date.

Short-chain fatty acids (SCFAs). Acetic, propionic, and butyric acids are postbiotic metabolites that are classified as short-chain fatty acids. They provide a wide range of health benefits.[42]

Antimicrobial peptides (AMPs). AMPs exert a wide range of inhibitory effects against pathogenic bacteria, fungi, parasites, and viruses. AMPs range in size from 10-60 amino acids and currently 3180 AMPS have been identified and are listed in the Antimicrobial Peptide Database.[43,44]

Essential Nutrients. The following essential nutrients are produced by probiotic bacteria: B-vitamins—thiamine, riboflavin, nicotinic acid, pantothenic acid, pyridoxine, cobalamin, folic acid, and biotin; vitamin K; and various amino acids.[45-47]

Neurotransmitters. Neurotransmitters include gamma-aminobutyric acid (GABA), norepinephrine, and acetylcholine.[48]

Antioxidants. Numerous strains of probiotic bacteria have been shown to produce metabolites with antioxidant activity, but these effects are highly strain specific.[49] A unique strain of probiotic bacteria named *Lactobacillus fermentum* ME-3 has been shown to synthesize substantial amounts of glutathione. Thus, glutathione is a postbiotic metabolite produced by *L. fermentum* ME-3. Glutathione's multiple functions are so critical to health that it has been identified as a biomarker of aging.[50,51] The article "***Lactobacillus fermentum ME-3: A Breakthrough in Glutathione Therapy***" was published in the Aug/Sep 2022 issue of *Integrative Medicine: A Clinician's Journal* (IMCJ).[52]

Exopolysaccharides (EPS). EPS are branched, long-chain sugar polymers produced primarily by lactic acid bacteria that exert a wide range of beneficial properties.[53]

Urolithins. These bioactive metabolites are produced from bacterial metabolism of polyphenols.[54]

Cell wall fragments. These fragments contain substances that influence immune function(s).[55]

Cell-free supernatant (CFS). CFS is the liquid media in which bacterial cells grow.[56]

Intestinal Permeability

As mentioned previously, Dr. Fasano discovered that zonulin is a protein that is produced by intestinal epithelial cells in response to inflammation.[35] Zonulin disassembles intestinal tight junctions.[57] Thus far, zonulin is the only compound that has been discovered that has the ability to destroy intestinal tight junctions, which results in intestinal permeability.[58]

Fasano's discovery is very important because it provides the mechanism that links dysbiosis and intestinal inflammation to intestinal permeability, the development chronic degenerative diseases, and accelerated aging.[59]

Disease and the Gut

Twenty-five hundred years ago, Hippocrates, who is called the father of medicine, is credited with saying, "All

disease begins in the gut." A few exceptions to this rule exist—getting tetanus from stepping on a rusty nail, inhaling a toxic gas, and being born with a genetic abnormality. Hence, it's more accurate to state, "Most chronic diseases begin in the gut."

Multiple factors can trigger intestinal inflammation. However, according to Fasano, the two most powerful triggers for intestinal inflammation—which cause the elevation of zonulin, the destruction of intestinal tight junctions, and the development of intestinal permeability—are gluten and microbial imbalance—too many bad bacteria.[60]

Zonulin is now recognized as a biomarker of aging. In older people, elevated levels of zonulin are associated with increased levels of inflammation, reduced muscle strength, and increased frailty.[61]

The MTA proposes that disruption of the gut microbiome is a primary cause of disease and accelerated aging. Scientists still have much to learn, but the fundamental mechanisms that regulate this process are now understood.

As this article previously discusses, bacterial imbalance/dysbiosis and intestinal inflammation cause the elevation of zonulin, which disassembles intestinal tight junctions, leading to intestinal permeability. Each of these factors, which disrupt the gut microbiome, are associated with the major age-related diseases, including cancers and cardiovascular, metabolic, neurological, and inflammatory diseases.[62-64]

An individual's diet is the most important factor that regulates the health of his or her gut microbiome.[65] If people don't feed their probiotic bacteria well, they won't thrive and survive, and equally important, an individual's bacteria won't be able to produce the postbiotic metabolites that regulate many aspects of health.

This article previously mentioned that the two primary food groups for probiotic bacteria are dietary fibers and polyphenols. The best sources of these probiotic foods are fruits and vegetables. This explains why a plant-based diet is critical for microbiome health. Other types of foods, such as whole grains, nuts, seeds, herbs, and spices also contain microbiome-supporting fibers and polyphenols.

Nutritional Disaster

Studies have reported that 90-95% of American children and adults don't meet the recommended intake of dietary fiber.[66,67] Similar disparities have been reported regarding dietary polyphenols. Plant-based foods are the primary source of polyphenols. One study reported that 91% of American adults don't consume adequate daily amounts of vegetables and 88% of adults don't consume adequate amounts of fruits.[68] Data from the 2005-2006 National Health and Nutrition Examination Survey (NHANES) reported that 80% of Americans fall short in the consumption of virtually every color category of polyphenol-containing foods.[69] The results of these studies are disturbing because they indicate that most people are living with a malnourished microbiome, which increases the risk of developing dysbiosis and intestinal permeability.

Frequency of Dysbiosis

The studies reviewed above reveal that most people aren't consuming adequate amounts of the types of foods, fruits and vegetables, that are required to support a healthy microbiome. The standard American diet, also called the Western diet, which is traditionally high in fat, sugar, and refined carbohydrates and low in fiber, induces unfavorable changes in intestinal bacteria, which are associated with dysbiosis.[70]

GI complaints are one of the most common reasons people see their physician. Results from a large national survey reported that nearly two-thirds of Americans suffer from GI symptoms.[71] Most Americans are not consuming adequate amounts of dietary fibers and polyphenols, which results in dysbiosis, a weakened immune system, and increased risk of many diseases.

Inflammaging

Chronic inflammation is now recognized as a fundamental cause of progressive decline in metabolic, physiological, and immunological function, which results in accelerated biological aging. The term inflammaging was created to address the fundamental link between inflammation and aging.[72] Learning how to prevent the inflammation that results from GI bacterial imbalance and intestinal dysbiosis is a key component in the MTA.[73]

Lipopolysaccharides (LPS): Biomarker of Aging

LPS are part of the structure of the outer cell wall of gram-negative bacteria, which reside in the GI tract of all humans. However, when dysbiosis, inflammation, and intestinal permeability occur, LPS leaks into the body. When LPS enters systemic circulation, it is a highly toxic substance that causes the release of pro-inflammatory cytokines in cells throughout the body. LPS has been correlated with numerous chronic, age-related diseases.[74]

In a double-blind, placebo-controlled, crossover human clinical trial, participants were administered either a low-dose of LPS or a placebo via intravenous infusion. The dose of LPS (0.6 ng/kg) was so low that the volunteers weren't aware of any symptoms. Blood tests revealed that the people who received the low dose of LPS had a substantial increases in inflammatory markers—a 25-fold increase in tumor necrosis factor-alpha (TNF-α) and a 100-fold increase in interleukin-6 (IL-6). They also had a 21% decrease in insulin sensitivity and a 32% increase in homeostatic model assessment-insulin resistance (HOMO-IR), which is a marker of insulin resistance. This study revealed that low levels of LPS, which don't cause symptoms, are causing chronic inflammation, which is associated with accelerated aging.[75]

A Healthy Microbiome

A healthy microbiome requires: (1) a diverse range of probiotic bacteria; the healthy human gut microbiome is estimated to contain from 500-1000 species of bacteria,[76] and (2) a diet that supplies a diverse range of fibers and polyphenols, which enables gut probiotic bacteria to produce a diverse range of postbiotic metabolites.

You *can't* create a healthy, diverse microbiome by taking commercial probiotics! When commercial probiotics are ingested, those bacteria generally don't colonize in the intestinal tract. Hence, ingested probiotics are limited in their ability to promote intestinal health and prevent disease.[77]

The *only* way an individual can create a healthy, diverse microbiome is by consuming a diverse range of plant-based foods that provide a diverse range of dietary fibers and polyphenols. This supports the growth and proliferation of a diverse range of the person's innate bacteria, which results in the production of a diverse range of postbiotic metabolites.[78]

This article's author has created an eight-minute YouTube video that teaches people a time-saving method of creating a salad that contains 16 different kinds of fiber and polyphenol-rich vegetables that promote a healthy gut microbiome. This video is *Ross' Salad Buzz.* You can watch it by searching for the terms **Ross Salad Buzz**.

Healing the Microbiome

Many people purchase commercial probiotics with the goal of reducing GI dysbiosis-related symptoms and improving their microbiome. As noted previously, studies report that from 90-95% of American children and adults don't consume adequate amounts of dietary fibers and polyphenols. In fact, Americans fall seriously short in both quantity and diversity of the foods that probiotic bacteria need. This raises the question of how much benefit people actually get when they ingest commercial probiotics.

Many companies that market probiotics have conducted studies that report that people who take their brand of probiotic gain various health benefits. However, other studies report that ingested probiotics generally don't colonize and remain in the body. Instead, they pass through and are eliminated from the body in stools. In one meta-analysis of seven randomized, clinical trials (RCTs), the authors reported finding, "a lack of evidence for the impact of probiotics on fecal microbiota composition in healthy adults."[79]

The paradigm shift in microbiome science emphasizes that it's not the probiotic bacteria, but rather, the postbiotic metabolites that are primarily responsible for regulating the health of the microbiome ecosystem and conferring health benefits to the host.

Case Against High Dose Probiotics

Balance and diversity are important traits for the health of ecosystems. This holds true for the Amazon rain forest, coral reefs, and the human gut microbiome. Greater biodiversity equates to greater strength and resilience, and this is especially true for the human gut microbiome.[80]

People often think more is better. Consequently, we see commercial brands of probiotics with 50, 100, and 200 billion CFUs per dose. Taking a probiotic that contains a large amount of one or several strains of probiotic bacteria actually works *against* balance and diversity. Ingesting a high dose of one or several strains of probiotic bacteria may trigger the immune system to launch an alarm reaction.

Scientists in one study compared the immune responses after administration of a high dose and a low dose of *Lactobacillus acidophilus*. In their conclusions, the authors stated, "Probiotics can be ineffective or even detrimental if not used at the optimal dosage for the appropriate purposes."[81]

Probiotics vs Postbiotics

When probiotics are taken orally, those bacteria must survive the harsh acidic environment in the stomach. If they survive, when they reach the colon, they are likely entering a hostile environment where the pH level is from 10 to 100 times too alkaline.[82] And, when they arrive in the colon, they must locate dietary fibers and/or polyphenols and begin the process of converting them into postbiotic metabolites. This all takes time.

Directly ingesting postbiotic metabolites is a much faster and more effective method of reducing symptoms of intestinal distress compared to ingesting probiotic bacteria. Postbiotic metabolites will *immediately* begin to reduce inflammation, kill pathogens, help restore the proper pH, and enhance immune function.

In *The Gut-Immune Connection,* Emeran Mayer states, "Taking the popular and highly advertised short cut of popping a daily supplement pill containing billions of colony-forming units (CFUs) will not do the job."[83]

Postbiotic Metabolites

Interest in postbiotics is growing rapidly because they provide a wide range of health benefits, and consequently, they have been called the new frontier in microbiome science.[84]

The pharmaceutical, food, and cosmetic, and the natural products industries are increasingly focusing on the development of products containing postbiotic metabolites for several reasons. Postbiotic metabolites are safer to administer than live bacteria and they are more stable and have longer shelf lives.[85]

Although numerous companies have begun marketing products with the term postbiotic metabolites or postbiotics on the label, most of these products contain probiotics with just one or several postbiotic metabolites included in the formulation.

Multiyear Fermentation Processes

Iichiroh Ohhira was a world-renowned microbiologist who developed a multiyear fermentation manufacturing process that can produce over 500 postbiotic metabolites. That manufacturing process mimics the fermentation processes result in the production of postbiotic metabolites in the GI tract (primarily in the colon).

Cell-culture studies and animal and human clinical trials have been published that reveal that oral ingestion of Ohhira's probiotics can provide a wide range of health benefits. A detailed explanation of Dr. Ohhira's multiyear fermentation process is available in a booklet, ***Dr. Ohhira's Probiotics & Postbiotic Metabolites***,[86] which is available from the following link: *www.naturalpharmacist.net/ohhirabook*

Postbiotic metabolites are the new frontier in microbiome science. The industry of postbiotic metabolites is in its infancy, and much research still needs to be done. However, hope exists that postbiotic metabolites will be therapeutically useful to improve microbiome health, enhance overall health, and slow down the process of biological aging, thereby facilitating increases in lifespan and healthspan.

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