

Article

The Immune-Microbiota Axis

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Abstract: This document explores the "Immune-Microbiota Axis," highlighting how trillions of microbes act as essential trainers for our immune system. It examines how modern, hyper-sanitized lifestyles and antibiotic overuse deplete microbial diversity, leading to autoimmune disorders and allergies. By understanding this synergy, medical science is moving toward personalized treatments that utilize our "second genome" to optimize health. Modern medicine now recognizes that a patient's microbial diversity—not just a balance of "good vs. bad" bacteria—determines the success of treatments like vaccines. Overusing antibiotics is like a "scorched-earth" policy; it wipes out the diverse microbial communities that are foundational to our survival and long-term health

Keywords: Immunity, innate immunity, acquired immunity, vaccination, microbiota, immune microbiome cross talk.

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1. Introduction

The role of the infinitely small in nature is infinitely large."— Louis Pasteur. In the past, Greek and Ayurvedic medicine thought of health as "humoral balance." But William Harvey's discovery of blood circulation changed that and led us to modern physiology. We now understand that health is a complicated interaction between the brain, nerves, and hormones, which work together to control immunity. It's no longer just the absence of pain; it's a dynamic balance of our physical, mental, and social lives, shaped by our DNA, infections, and the choices we make every day. The Microbiome: Our "Second Genome" We are ecosystems that walk around. There are trillions of microbes in our bodies, and their DNA is 100 times more than ours. That's why they are called our "Second Genome." These organisms are active partners that break down fibers and make important vitamins. Materials and methods:

This article is a review-based study. The information presented is from reputable scientific journals, medical textbooks, and research papers (such as Nature, Science, and PLOS Biology). It analysed secondary data to understand the impact of the "immune-microbiota axis."

2. Literature Review:

1. Louis Pasteur: He was the first to recognize the importance of "very small" microbes.
2. William Harvey: He laid the foundation for modern physiology by discovering blood circulation.
3. Belkaide and Hand (2014): They have conducted significant research on the role of microbiota in immunity and inflammation.

Discussion& Result

Immunity: A complex biological system. The word immunity comes from the Latin *immunitas*, meaning freedom from disease. Immunity is the ability of our body to recognize and fight harmful pathogens, thereby protecting us.

Immunity has two types.

1. Innate immunity
2. Acquired immunity

Innate Immunity: Innate immunity is a nonspecific defense that is present at birth. It is achieved by forming various barriers against foreign agents in our bodies. There are four types of barriers within innate immunity.

Some specific features of Innate immunity

- Acts within minutes
- First line of defense
- No need for previous interaction with the pathogen
- No specific
- No immunological memory

The mechanism of innate immunity: The innate immune system begins with the recognition of an enemy (microbe), in which specific and conserved patterns on the surface of microbes, called MAMPs (microbial-associated molecular patterns), bind to specialized PRRs (pattern recognition receptors—proteins on immune cells that detect microbes) on our cells. These PRRs are germline-encoded (inherited in our genes) and detect the enemy immediately without prior recognition; the most famous of these are Toll-like receptors (TLRs—well-known PRRs), which, upon binding to an enemy, trigger signaling pathways within the cell, leading to the production of cytokines (molecules that send signals in the immune system) and antimicrobial enzymes that help eliminate pathogens. Furthermore, this entire system relies on four major barriers: physical, physiological, cellular, and cytokine, which together form the body's first and strongest defense wall.

Innate immunity consists of four barriers.

1. Physical or Anatomical Barrier: Our skin is the first barrier; its outermost layer, the stratum corneum, is made of dead cells and protease inhibitors that block and kill bacteria. Our internal surfaces, like the respiratory and GI tracts, are lined by a mucosal barrier. In the respiratory system, goblet cells trap incoming germs through sticky mucus, while ciliated epithelium acts like a conveyor belt, sweeping them out of the body.
2. Physiological Barrier:

Fever is a strategic maneuver by our immune system to create a "bad environment" within the body to stop the enemy with physiological barriers. When pathogens release exogenous pyrogens (toxins), our cells signal the hypothalamus to release endogenous pyrogens (such as interleukin-1), which "reset" the body temperature and stop the growth of the microorganism. Additionally, the pH of various body parts, such as stomach acidity, and the lysozyme enzyme present in secretions (such as tears and sebum), destroy the enemy's cell walls and kill them.

Cellular Barrier: At the cellular level of innate immunity, PMNs (neutrophils), monocytes, and macrophages are our body's front-line soldiers. When an infection occurs, WBC numbers rapidly increase, and monocytes arrive at the affected site, where they transform into larger, specialized macrophages to clear viruses and debris. This process, called phagocytosis, begins with "chemotaxis" signals—signals that draw cells toward the enemy. Opsonins (such as C3b and antibodies) then surround the enemy, making it easier for the cells to capture and destroy it. The phagocyte then expands its pseudopodia to engulf the enemy, forming a phagosome, from which lysozyme and respiratory burst (oxygen radicals) combine to completely destroy it. Interestingly, our gut microbes keep these phagocytes "active," as research has shown that the phagocytes of "germ-free" animals are quite stiff and weak. Non-Phagocytic cell: (e.g., natural killer cells) This is a large, granular lymphocyte

cell. In addition to phagocytes, another type of cell, natural killer (NK) cells, kills virus-infected and tumor cells in the body by forming perforin-lined pores (holes created by a protein called perforin) in the plasma membrane of target cells (i.e., infected cells). Water enters through these pores, causing the diseased cells to swell and rupture.

- (4) Cytokine Barriers: The final and essential component of innate immunity is the cytokine barrier, in which interferons (antiviral proteins) play a major role. When a cell is infected by a virus, it releases proteins composed of 270 amino acids that stimulate neighboring cells to produce "translation inhibition proteins" (T.I.P.s), thereby inhibiting viral growth. Interferons are species-specific and make cells resistant to viral infections. While they are used not only for viral prophylaxis, INF- α has also been successfully used to eliminate tumors and treat Kaposi's sarcoma in AIDS patients.

Acquired Immunity: Acquired immunity, also known as adaptive Immunity. is our body's "pathogen-specific" (targeted to particular germs) defense system that relies on familiarity and memory. Its four most important characteristics are: Diversity: It can recognize millions of different pathogens. Self/non-self-discrimination: It knows how to distinguish between the body's own cells and an external enemy (otherwise it attacks its own body). Memory: This is its most important feature. When a pathogen first enters, the response is slow (primary response), but its "data" is stored. The next time the same enemy is encountered, the immune system recognizes it and launches a powerful attack, called a secondary or anamnestic response.

Primary Immune Response: As soon as the antigen enters the body, a "lag period" begins, during which our immune system recognizes the enemy and prepares its "battle strategy." After this, activated T-cells and B-cells enter the battlefield as effector cells; T cells launch a direct attack, and B cells (plasma cells) act as antibody factories. Initially, IgM antibody levels rise slowly, then fall once the enemy is eliminated. However, during this battle, some B-cells transform into "memory cells" that permanently store the enemy's "mugshot" (identity) in their database, so that the next time a "lag period" is not needed and an immediate attack can be launched.

Secondary immune response: When the enemy (antigen) attacks again, memory cells break the "lag period" and activate the immune system. Initially, existing antibodies are used up fighting the enemy, a phase known as the "negative phase," but this is followed by a massive and powerful "explosion" of IgG antibodies that are even more effective than before. This entire process is carried out jointly by B lymphocytes (which form the army of antibodies) and T lymphocytes (which assist the B cells)—which is why booster doses help peak immunity.

IMMUNE SYSTEM IN THE BODY

The human immune system consists of –The immune system is characterized by its recognition, response, and memory—all of which play critical roles in transplantation, allergy, and autoimmune diseases. It is developed in two specific organs:

1. Primary Lymphoid Organs (The Training Grounds) Lymphocytes are born here and acquire their "antigenic specificity": Bone Marrow: The primary organ where all blood cells (T and B cells) are produced. Thymus: This organ, near the heart, provides the microenvironment for the maturation of T-lymphocytes. (Note: It is large during childhood but shrinks by puberty.)
2. Secondary Lymphoid Organs (The Battlefield): When lymphocytes mature, they encounter antigens in secondary organs, where clonal proliferation begins. Among these organs, the spleen acts as a blood filter and RBC reservoir, while lymph nodes capture antigens from tissue fluid and trigger an immune response. Furthermore, 50% of our body's lymphoid tissue is composed of MALT (mucosa-associated lymphoid tissue), which includes important defensive structures such as the tonsils, appendix, and Peyer's patches.

Our body has two types of active immune system based on these two types of lymphocytes:

- (1) C.M.I.S (Cell-mediated immune system) or Cellular immunity
C.M.I.S is based on 60-70% T-cells

When pathogens enter the body, macrophages are the first to react, secreting cytokines and interleukins that activate T cells.

1. **Helper T-cells:** When helper T-cells are activated, they give the hapless immune system a "wake-up call," spurring killer T-cells and B-cells into action. At this stage, these cells begin to form specific clones, a process called clonal selection. They also release lymphokines (chemical signals) that summon white blood cells (WBCs) to the affected site to fight the enemy.
2. **Killer T-cells:** As soon as helper T-cells sound the alarm, killer T-cells (also known as CD8+ T-cells) spring into action. Think of them as the "special forces" of our immune system. Their primary function isn't to fight bacteria in the blood, but to find and destroy our own cells that have been hijacked by viruses or that have become cancerous.

Killer T-cells function like a "targeted strike." They recognize an enemy cell and release two powerful weapons: perforins (which pierce the cell membrane) and granzymes (which enter the cell through those holes and trigger apoptosis, or cell suicide). This prevents the virus from spreading further, and macrophages do the rest of the cleanup. After the battle, regulatory T cells (Tregs) become "peacekeepers." They use signals such as IL-10 to calm the immune response so the body is not harmed. Our gut microbes train these cells in "immune tolerance." If this balance is disrupted, the body attacks its own tissues, organs, and cells, leading to autoimmune diseases (such as IDDM Type 1 or rheumatoid arthritis). **Memory T-cells:** These are the "veterans" of our immune system. Instead of engaging in battle, they store data about the enemy. They neither kill pathogens nor produce antibodies; instead, they act as a database. When the same enemy returns, even years later, they transform into foreign effector cells, triggering a powerful anamnestic response.

(2) **Antibody-Mediated Immune System or Humoral Immunity:** B-lymphocytes are the "missile launchers" of our immune system. When they receive the "green light" from helper T-cells, they transform into plasma cells. These cells don't go to the battlefield themselves; instead, they sit in the lymph nodes and release millions of Y-shaped protein weapons called antibodies (immunoglobulins). These antibodies "tag" enemies throughout the body so they can be eliminated. Biochemically, these antibodies are glycoproteins similar to the "gamma globulins" in our blood serum (in a healthy body, the ratio of albumin to globulin is 2:1). They are called "immunoglobulins" because they are round proteins (globulins) that function as part of the immune defense. **Antibody Structure:** The biochemical structure of an antibody is a distinctive "Y" shape, composed of two heavy (H) and two light (L) polypeptide chains—hence the name H₂L₂. These chains are joined together by disulfide bonds. The two ends of this molecule fit together like a "lock and key" with the antigen, forming an antigen-antibody complex. There are five types of antibodies in the human body. **Function:** **Agglutination, IgG:** 75-80% of the total antibody count. Its molecular weight is 146,000. IgG is the only antibody that passes the placenta, providing passive immunity to the fetus and protecting body fluids. **IgA:** 10% of the total antibody count. Its molecular weight is 170,000. Found in colostrum, saliva, and mucus. It protects the outer surface of our body. **IgM:** 5-10% of the total antibody count. Its molecular weight is 960,000 (heaviest). It is the first antibody to form. It is found in large quantities in blood plasma and protects the bloodstream.

IgD: 1-3% of the total antibody count. 185,000. It helps activate B cells to initiate an immune response.

IgE: 0.05% is high. 188,000 (smallest). Found in. Forms bonds with mast cells; plays a key role in allergic reactions.

Vaccination and Immunization: The fundamental principle of vaccination and immunization is to inoculate our immune system's memory. This history and technology can be understood through three prominent figures: **Pioneers of Protection** **Edward Jenner (Father of Immunization):** In 1796, Edward Jenner noticed something interesting: women who milked cows (milking) didn't develop smallpox after contracting cowpox. To test this, he gave a boy a cowpox scar, and strangely, the hair remained unaffected by the smallpox virus. This is where the concept of "vaccination" began. **Louis Pasteur** then took this work further and discovered a way to "kamzor" (inactivate) enemy germs (pathogens), leading to the first successful vaccines for diseases like chicken cholera and anthrax. **Emil von Behring**

(Father of Passive Immunization): He demonstrated that antibodies could be transferred from one animal to another. The Modern Frontier Today, we are in the age of recombinant DNA technology, where we use bacteria and yeast as "vaccine factories." A prime example is the hepatitis B vaccine, which is produced using transgenic yeast. This technology allows us to produce vaccines in much shorter timeframes, in much larger quantities, and at a higher quality.

Types of vaccination:

Live Vaccines (Natural/Attenuated)	Killed vaccines (Inactivated)	Toxoids (Subunit Vaccines)	Recombinant Vaccines	Antigen (Subunit Vaccines)
<ul style="list-style-type: none"> • Small Pox • Rota Virus 	<ul style="list-style-type: none"> • Salk Polio (IPV) • Whooping Cough(pertussis) 	<ul style="list-style-type: none"> • Tetanus (TT) • Diphtheria (DT) 		<ul style="list-style-type: none"> • Hepatitis-B

Microbiota: These microbes were previously called microflora because they were mistakenly considered part of the plant kingdom, but after the five-kingdom classification, they were placed in the Monera and are now known as microbiota. A baby grows up in a sterile environment in the mother's womb, but after birth, it is exposed to trillions of microorganisms, which can be positive, harmful, or neutral. In the human body, these microbiotas are of two types: resident (always present) and transient (present for a time).

1. Resident microflora: These live in our bodies forever, until death. They are closely associated with a specific location. If they are removed, they reoccupy that location. They do not harm us; rather, they benefit us.
2. Transit microflora: These microflorae are not permanent residents of our bodies, but rather come and go. As long as the resident microflora is healthy, they do nothing. However, when the resident microflora goes awry, it can affect our bodies and even cause illness. For example, MRSA (methicillin-resistant *Staphylococcus aureus*) in the skin, *E. coli*, etc.

Humans acquire their normal microflora at birth. Although we can survive without it, a balanced microbiota of bacteria, protozoa, fungi, and viruses (which reside on our skin and inside our bodies) is essential for optimal health. Our bodies contain more microbes than our own cells (10¹³–10¹⁴) and can now be analyzed in depth with modern technology. Our gut is their largest market and the "Academy of the Immune System," where they teach our immune system the difference between friend and foe. Anaerobic (oxygen-free) microbes are also the most abundant in the skin and respiratory tract. While transit microflora can be removed with cleaning, resident microflora remains an integral and valuable part of our bodies.

Approximate distribution of microorganisms in the body:

Skin - 2%

Urogenital tract - 9%

Oral cavity and throat - 15-16%

Gut/Large Intestine - 60%-70%

Normal Skin Microflora: The skin is our body's largest organ and a strong barrier. The microflora that lives on it—including bacteria, fungi, and viruses—functions as a complex community, mostly beneficial to us. The habitat and number of these microbes on the skin (colonization) depend on each individual's specific "ecology"; factors such as skin topography (location), endogenous changes in the body, and the external environment (environment) determine which microbes will dominate where.

Urogenital Tract Microbiota: The Urogenital tract microbiota refers to the small community of microbiota that inhabits the human urogenital tract. Recent studies show that the kidneys, ureters, and urinary bladder are normally sterile. In humans, the urogenital tract in women is more populated than in men because women have a shorter urethra and are dominated by the vaginal microbiota. Examples of urogenital microbiota include *Corynebacterium*, *Streptococcus*, *Staphylococcus epidermidis*, and small amounts of *E. coli*. Men sometimes also have *Lactobacillus*. This urogenital microbiota protects the tract

by maintaining an acidic pH and preventing pathogen growth. Oral microbiota: Our oral microbiota consists of an entire ecosystem of bacteria, fungi, viruses, and protozoa that live in different parts of the mouth: Teeth and gums: *Lactobacillus* and *Streptococcus sanguinis* are found on the surface of the teeth (dental plaque), while beneath the gums (*gingival sulcus*) are fungal species like *Treponema denticola*. Tongue and cheeks: The back of the tongue (dorsum) is home to anaerobic bacteria like *Bacteroides*, while the inner lining of the cheeks (buccal mucosa) is occupied by *Streptococcus mitis*.

Role of Normal Microbiota: Our relationship with resident microbes ranges from beneficial and neutral to potentially harmful if they migrate to the wrong organs. These microbes provide colonization resistance by occupying space and nutrients, effectively blocking pathogens. They act as a vitamin factory, synthesizing essential nutrients like Vitamin K and B12, while engaging in chemical warfare by producing lactic acid and natural antibiotics (bacteriocins) to kill invaders. Furthermore, they serve as a "gym" for the immune system, stimulating lymphatic tissue and activating the complement pathway to keep our defenses alert. Hygiene Hypothesis: Our immunity requires a profound "apprenticeship" with soil and microbes during childhood. When we over-sterilize or clean our bodies, the immune system doesn't get a chance to distinguish between friend and foe. This "over-protection" actually weakens our defense system, increasing the risk of diseases like allergies in the future. The truth is, our immune system improves only when it completes its "training" by living with microbes.

Dysbiosis and Disease: When our bodies have fewer "good" bacteria and more "bad" bacteria, this imbalance is called dysbiosis (or dysbacteriosis). This term was coined by A. Nissl in 1916. Remember, this is not a separate disease, but a "clinical laboratory syndrome" that results from pre-existing intestinal or endocrine disorders. Causes and Effects: Causes: The biggest contributors are excessive antibiotic use, poor lifestyle habits, aging, and climate change. Effects: Disruption of this balance increases the risk of allergies, asthma, digestive problems (such as IBD and obesity), and even mental health and metabolic diseases (such as Type 2 Diabetes).

Factors Influencing Our Microbial Allies

Our microbiota changes with our lifestyle. Key factors that influence its balance (eubiosis) include: Diet and antibiotics: A high-fiber diet promotes good bacteria, while processed foods and excessive use of antibiotics eliminate our "resident friends," paving the way for pathogens. Sanitization paradox: Excessive cleaning leaves our immune system "under-educated"; some exposure to microbes is necessary for immune training. Life and stress: Delivery method (normal vs. C-section), aging, and mental stress (via the gut-brain axis) affect the number and signature of our microbes. Relation of Immune System and Microbiota: "The relationship between the immune system and microbiota isn't limited to just 'living'; it's a constant 'biochemical dialogue.' The immune system and microbiota interact. In microbiology, we call this relationship immune-microbiome cross-talk. Imagine that our immune system is an army, tasked with protecting our bodies from our enemies, i.e., pathogens. But how does the immune system know who is a friend and who is a foe? Microbiota helps in this. It acts as an instructor. It trains our immune system to distinguish between friend and foe and, by targeting the enemy, protects our bodies from pathogens. All communication between the immune system and the microbiota occurs through chemical signals.

1. Chemical messengers (SCFAs): When our gut microbiota digests fiber, it releases short-chain fatty acids (SCFAs) (such as acetate, butyrate, and propionate), which are not only essential for energy but also important signaling molecules. These SCFAs regulate immune cells by binding to their GPR41/43 receptors, with butyrate specifically stimulating regulatory T-cells, so the immune system knows when to remain silent and when to attack.
2. Training peacekeepers (T-reg cells):

One of the microbiota's most important functions is to train regulatory T cells. This is facilitated by SCFAs, which act as the immune system's "police," preventing it from attacking its own cells. This helps control inflammation and prevents autoimmune diseases. (3) Toll-like receptors (TLRs): Handshake: Our immune system has several receptors called Toll-like receptors that monitor microbes by sensing specific proteins on them. TLRs recognize specific PAMPs (pathogen-associated molecular patterns) on

microbes. This is a kind of handshake. Our immune system is very sensitive. TLRs teach the immune system tolerance to beneficial bacteria and prevent it from reacting. (4) GALT (Gut Associated Lymphoid Tissue): This is the class of the immune system. GALT is located in our gut, where microbes and the immune system meet. It serves as a training ground where immune cells (T-cells and B cells) learn to recognize which bacteria are friends and which are foes. In this way, the microbiota interacts with the immune system, helping it mature.

Clinical Insight:

Why Antibiotics Might Mute Your Vaccine:

Source: *Hagan et al. (2019), Stanford University.*

Observation: Antibiotic-induced dysbiosis leads to a weakened response to the Influenza vaccine.

Mechanism: Loss of microbes \longrightarrow Absence of Flagella \longrightarrow No TLR5 stimulation \longrightarrow Reduced IgG production.

Clinical Significance: Gut microbes act as "Natural Adjuvants," enhancing the body's ability to build vaccine-mediated memory.

Conclusion

Our immune system isn't just an "army" fighting the enemy; it's an "intelligent system" that's constantly learning and improving. The rise of autoimmune diseases and allergies in today's world is proof that, in our obsession with "cleanliness," we've lost the ancient "instructors" (microbes) that taught our cells the difference between friend and foe. Our immunity isn't static; it's a training ground that our microbiota constantly updates.

The focus of future medicine won't be simply eliminating pathogens, but restoring the body's "systemic balance." We'll need to rethink our lifestyles and the indiscriminate use of antibiotics so our immune system doesn't become "de-skilled." We need to see ourselves as an ecosystem, not a single organism. The gist of the article is that "health isn't the absence of bacteria, but the presence of the right bacteria."

We and our microbes are two characters in the same story, living off each other. The future will be "personalized medicine," in which treatments are tailored to a patient's microbiome profile. We are entering a century where we will prioritize friendship and "biological diplomacy" rather than killing the enemy.

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