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The Immune Symphony Conducted by the Microbiome: A Review

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Abstract
The human gut microbiota, comprising trillions of bacteria, viruses, fungi, and other microorganisms, forms a highly dynamic ecosystem essential for host health. It plays a pivotal role in the development, regulation, and functioning of the immune system. Microbial metabolites, including short-chain fatty acids (SCFAs), bile salts, and tryptophan derivatives, influence mucosal defense, immune cell maturation, and inflammation control. Current evidence from animal models, particularly germ-free (GF) mice, and human studies highlights the significance of gut microbial exposure in immune development. Factors such as age, diet, antibiotics, and geography shape microbial composition, which in turn regulates immune cell signaling pathways and activates pattern recognition receptors (PRRs). Findings demonstrate that a balanced and diverse microbiota is critical for immune homeostasis, while dysbiosis impairs immune regulation. Both innate immune cells (dendritic cells, macrophages) and adaptive immune cells (T and B lymphocytes) are influenced by gut microbes through molecular and metabolic interactions. GF mice consistently show immature immune systems, emphasizing the indispensable role of microbiota in immune maturation. The gut microbiota is fundamental in maintaining immune balance and systemic health. Disruptions in microbial diversity contribute to immune-related diseases, while therapeutic interventions such as probiotics, prebiotics, and fecal microbiota transplantation show promise in restoring microbial equilibrium. Continued research into host–microbiota interactions offers innovative opportunities for microbiome-based therapies targeting immune-mediated disorders.

Introduction

The microbiota, a broad and varied microbial ecology found in the human body, colonizes the skin, mouth cavity, and gastrointestinal tract, among other surfaces. The gut microbiota is one of them that is an attracted topic of research because of its enormous effects on host immunity, metabolism, and general health. Trillions of microorganisms, e.g. bacteria, fungus, archaea, fungus and protozoa present in the gut microbiota, with bacteria being the most prevalent kind[1]. In a dynamic and reciprocal relationship, Immune system and gut microbiota control immunological responses, and the immune system modifies microbial composition to preserve homeostasis[2]. To differentiate harmful invaders from benign commensal microorganisms, this interaction is essential. Immunological cell training, immune tolerance, gut barrier integrity, and inflammatory response modulation are all made possible by the microbiota. The lack of gut bacteria, causes immune system inadequacies, such as undeveloped gut

associated lymphoid tissue (GALT), reduced T cell populations, poor antibody production, and greater susceptibility to infections according to studies conducted on germ-free (GF) mice, who are reared in sterile surroundings and lack a microbiome. This demonstrates how crucial gut microorganisms are in determining immune function[3].

The generation of metabolites is a significant way that gut microbiota affects immunity. Butyrate, acetate, and propionate which are short-chain fatty acids (SCFAs) are formed when beneficial bacteria digest dietary fibers[4]. Furthermore, tryptophan is converted by gut microorganisms into indole derivatives, which alter mucosal immunity and lessen excessive inflammation by activating the aryl hydrocarbon receptor (AhR). Secondary bile acid synthesis also aids in controlling immune cell function, such as T cell differentiation and macrophage polarization. Numerous immune-related diseases, such as inflammatory bowel disease (IBD), rheumatoid arthritis (RA), allergies, and asthma, have been connected to dysbiosis, or microbial imbalance[5]. An excess of harmful bacteria or a reduction in the diversity of the gut microbiota can contribute to the development of disease by causing immune dysregulation and persistent inflammation[6]. Likewise, elevated Th17-driven inflammation in rheumatoid arthritis has been linked to an excess of *Prevotella copri*. Researchers are looking at treatments that target the microbiome to alter immune responses considering the mounting evidence linking the microbiota and immune system. These include of dietary changes, fecal microbiota transplantation (FMT), probiotics, and prebiotics[7].

Promising methods for treating immune-mediated illnesses include precision microbiome-based immunotherapies and modified bacterial strains. The very complex relationships between gut microbiota and the immune system are examined in this review, with particular attention paid to the function of gut microorganisms in innate and adaptive immunity, the influence of microbial metabolites, disorders linked to dysbiosis, and treatment approaches meant to restore microbial balance. Novel microbiome-based treatments to improve immune function and avoid immunological-related illnesses will be made possible by an understanding of these pathways[8].

Gut Microbiota Diversity and Composition

The gastrointestinal tract is home to a diverse collection of bacteria called the gut flora or gut microbiota[9]. Protozoa, fungi, viruses, bacteria, and archaea make up this category, with bacteria being the most common[10]. While an imbalance (dysbiosis) is associated with a number of immunological-related and metabolic illnesses, a balanced and diversified microbiota is essential for preserving immune homeostasis, nutrition metabolism, and defense against infections[11].

What is contained in the gut microbiome?

Due to the advancement of microscopes, Antonie van Leeuwenhoek was the first one who have written description of the gut microbiota in the late seventeenth century. As he studied various environmental samples, Leeuwenhoek discovered what he called animalcules-bacteria and protozoa. Two centuries later, mechanistic studies of microbial physiology and the ability to "see" without the use of microscopes were made possible by developments in the culture of bacteria[12].

These bacterial fingerprints and the recently developed PCR technique were used to create time-consuming, low-resolution cultivation-independent methods like denaturing gradient gel electrophoresis (DGGE), which revealed the amazing diversity of the microbiome as bands on a gel. With the advent of new platforms in the 20th century, millions of amplicons could be sequenced simultaneously[13]. The creation of impartial platforms built on metagenomics, or "shotgun" sequencing and sequencing of a sample's DNA fragments, has built upon next-generation sequencing techniques and enabled two significant advances in our understanding: increased microbiome taxonomic resolution, which enables community members' strain levels and perceptions of the extreme expanse of genetic material, such as the enormous antibiotic resistance.

Through the imaging of organisms invading the host, microbial cultivation, and finally culture-independent methods like denaturing gradient gel electrophoresis, next-generation sequencing, and multi-omics techniques like metagenomics, meta-transcriptomics and metabolomics, we have gained an understanding of the gut microbiome. Characterization of microbial membership, gene content, and metabolic activity over the whole community has been made possible by the combination of cultivation- dependent and -independent methods[14].

Bacterial phyla as gut microbes

Five primary bacterial phyla dominate the human gut microbiota, and each one has unique functions in host immunity and metabolism.

Firmicutes

This phylum, which includes helpful genera like *Lactobacillus*, *Clostridium*, *Ruminococcus*, *Faecalibacterium*, and *Eubacterium*, makes about 60–80% of the gut flora. Short-chain fatty acids (SCFAs) e.g. such butyrate, can be generated by a variety of Firmicutes species and support immunological modulation, gut barrier integrity, and anti-inflammatory reactions[15].

Bacteroidota

Bacteroidetes participate in immunological regulation and glucose metabolism. For instance, the polysaccharide A (PSA) generated by *Bacteroides fragilis* stimulates the development of regulatory T cells and inhibits inflammatory reactions.

Actinobacteria

Bifidobacterium,

a member of the phylum Actinobacteria is crucial for the colonization of an infant's gut which promotes pathogen resistance, immunological development, and mucosal barrier function. SCFAs, which control inflammation and immune cell activity, are produced when dietary fibers are fermented by *Bifido bacterium*[16].

Proteobacteria

These bacteria, which include *Salmonella*, *Helicobacter* and *Escherichia* are found in smaller amounts in a healthy gut but have the potential to develop into opportunistic pathogens. Gut dysbiosis, inflammatory bowel disease (IBD), and metabolic problems are linked to elevated levels of Proteobacteria[17].

Verrucomicrobia

The phylum Verrucomicrobia contains the helpful bacteria *Akkermansia muciniphila*, which breaks down intestinal mucus, improves the function of the gut barrier, and has anti-inflammatory qualities[18]. Type 2 diabetes, inflammatory diseases, and obesity are associated with lower levels of Akkermansia.

Factors Influencing Microbiota Diversity

Disease resistance and immunological modulation depend on the variety of gut microbiota. Age and developmental stages, including infancy, are two factors which affect the conformation of the microbiota. Newborns' gut microbiota is dominated by *Lactobacilli* and *Bifidobacteria*, which aid in the development of immunological tolerance. Low er microbiome diversity and a higher risk of allergies and autoimmune illnesses are observed in infants born via caesarean section or fed formula[19]. Being an adult, diet, environment and lifestyle choices all contribute to the establishment of a stable and diversified microbiota.

As people age, the composition of their microbiota ch anges. Firmicutes and Bacteroidetes tend to decrease while Proteobacteria increase. This can cause immunological dysregulation and inflammation[20].

Another element affecting the composition or conformation of the microbiome is nutritional intake and diet. A diet high in fiber, encourages the growth of bacteria that produce SCFA, improving immunological and intestinal health. Proteobacteria and harmful Firmicutes are increased in a high-fat, high-sugar diet, which causes inflammation and metabolic disorders.

According to Zmora *et al.,* (2018)[21], probiotics found in fermented foods like kefir, kimchi, and yoghurt help to preserve the equilibrium of microorganisms in the gut. Antibiotics have the power to significantly alter the gut microbiota's makeup, decreasing microbial diversity and making people more vulnerable to opportunistic illnesses like *Clostridium difficile*. Antibiotic overuse, especially in early childhood, is associated with autoimmune disorders, allergies, and immunological dysregulation[22].

Immune Function and Microbiota Diversity

The immune system's formation, regulation, and operation are all significantly influenced by the gut bacteria. Maintaining immunological homeostasis, fostering immune tolerance, and protecting against infections all depend on a highly diversified microbiome. On the other hand, immunological dysregulation, persistent inflammation, and a higher risk of metabolic and autoimmune disorders have all been connected to decreased microbial diversity. Both innate and adaptive immunity are influenced by the interactions between immune cells and gut microorganisms, which would increase the body's capacity to fight off infections without triggering unwarranted inflammation. By avoiding over activation, which can result in inflammatory illnesses, microbial diversity maintains the equilibrium of the immune system[23].

By teaching immune cells to differentiate between benign antigens and dangerous pathogens, commensal microorganisms aid in the development of immunological tolerance. This is the only one way that the gut microbiota supports immune function[24]. Intestinal epithelial cells' tight connections are maintained by a varied microbiota, which inhibits pathogen invasion and systemic inflammation. Butyrate, a short-chain fatty acid generated by helpful bacteria like *Faecalibacterium prausnitzii*, improves the function of intestinal barrier and controls immunological responses. The synthesis of pro- and anti-inflammatory cytokines is controlled by a balanced microbiome. By blocking NF-κB signaling and encouraging IL-10 secretion, SCFAs like butyrate and propionate reduce excessive inflammation and avert autoimmune reactions[25].

Developmental process of gut microbiota and host immune system

Our favorable mutualistic connection with our microbiota has been established via hundred thousand years of co-evolution, whereby the microbiota supports several physiological processes of the host in exchange for food and habitat. In addition to helping with food digestion and fermentation, which is crucial for the synthesis of some vitamins, the microbiota is also important in protecting the body from infections. Some even release antimicrobial peptides to intentionally discourage competition. To stop harmful germs from infecting hosts, a steady microbiota and mucus layers are necessary[26].

The optimal development of the immune system depends on early microbial colonization, according to recent research on germ-free (GF) mice. An animal's capacity to fight off dangerous bacteria is weakened by a lack of microbiota, which causes less immune cells, including intraepithelial ab T cells receptors CD8C cells, CD4C LP T-cells, and IgA-producing plasma cells, as well as smaller mesenteric lymph nodes, PP, and undeveloped intestinal mucosal immunity. The absence of microbiota produced GF mice with an unstructured spleen and lymph nodes with disorganized B- and T-zones, as well as lower serum levels of IgG compared to mice raised in conventional housing, among other findings that suggested housing conditions affecting microbiota colonization caused immune alterations[27].

Moreover, GF mice had less functional CD4C CD25C Tregs and fewer intestinal microorganisms. The balance between Foxp3C Tregs and interleukin (IL)-17 which produce effector T helper cells inside the gut to be reliant on the gut microbiota composition and to need signals from intestinal bacteria. The generation of a very varied metabolite repertoire by the microbiota because of the anaerobic fermentation of residual food in the digestive track is one way the bacteria may regulate host physiological processes. SCFAs, which enter the body by epithelium of intestine and by making interaction with host cells to affect immunological responses and disease risk, are the main byproducts of the bacterial fermentation of fibers in the colon[28].

SCFAs are thought of as advantageous metabolites with anti-inflammatory qualities, and they serve a variety of regulatory roles in host physiology and immunology. The amount of SCFA in the colon is affected by the microbial makeup of the digestive tract and the amount of fiber consumed[29]. Bacteria that can hydrolyze cellulose and xylan can be encouraged by a diet high in fiber. It is also studied that a high population of *F. prausnitzii* and other bacteria producing short chain fatty acids may shield the host from non-infectious intestinal illnesses and inflammation[30].

Accordingly, investigations have linked Crohn's disease (CD) and other inflammatory bowel disorders (IBDs) to reduced abundances of *F. prausnitzii*. Histone deacetylases (HDACs), which are inhibited by SCFAs, encourage an anti-inflammatory cell phenotype that is essential for preserving immunological homeostasis. The modulation differentiation of Treg by butyrate tells us how the immune system is affected by microbiota through epigenetic control. This led to epigenetic modifications that enhanced Treg regulatory ability and boosted Foxp3 induction[31].

It has been demonstrated that GF mice which is colonized with Bacteroides the taiotao micron or *F. prausnitzii*, which produce SCFA, produced mucus and goblet cell differentiation *in vivo*. Intestinal epithelial goblet cells in vitro responded to SCFAs by upregulating mucin gene transcription. In a similar vein, several SCFAs help IECs form tight junctions, and colonization having a *Bifidobacterium longum* strain that generates high amounts of acetate provided defense against the deadly enteropathogenic infection with *Escherichia coli* O157:H7. This demonstrates how SCFAs can support integrity of IEC and prevent

lethal toxins from entering the bloodstream from the gastrointestinal lumen[30].

Although the exact mechanism by which composition of microbiota controls immunological homeostasis is not known, recent research indicates that the presence of species of bacteria might alter responses of immune system by promoting the growth of lymphocyte subtypes. The microbiota reconstitution of germ-free mice with *Bacteroides fragilis*, modified Schaedler flora, and *Clostridium* sp. promotes the accumulation of IL-10C Tregs inside colon of these animals whereas segmented filamentous bacteria helps in promoting the growth of Th17 cells in mice and cause the release of IL-17 and IL-22. These findings suggest that immune regulatory mechanisms depend on the recognition of microbial stimuli[32].

Mechanisms of host's gut microbiome impact

Determining the processes behind the microbiome's impacts on the host is a difficult undertaking because of the microbiome's immense taxonomic, genetic, and metabolic diversity. These effects might be direct, where the host is impacted by the composition and function of the microbiome, or indirect, where microbe–microbe interactions influence these aspects. Here, we concentrate on the direct molecular processes via which the host is influenced by the gut microbiota. To assist in considering such relationships, we offer three conceptual frameworks that are not mutually exclusive. The chemical makeup of the entity mediating the host impact is examined in the first frame; this can include anything from complex glycolipids to minute metabolites. It includes the mechanisms that each entity mediates, which can include genotoxic agents, host pathway signaling, or energy substrates[33]. Where the crucial interaction with the host taking place is, that is, where is the molecule and where is it operating, according to the second spatial frame? This includes substances that move far through the blood or lymphatic system as well as those that operate at the luminal junction with intestine of epithelium. For instance, a microbial product's local impact on the intestinal epithelium might have distant consequences through the production of endocrine factors like hormones or cytokines, afferent neurons that are related to the immune cell migration or central nervous system. Function is the third frame. Two facets of these relationships that are frequently overlooked in this subject should be considered while thinking about function[34].

First, even while a microbial component x can interfere host's phenotypic y, it does not always mean that the bacterium has "intent"; when the microbiological component is only a waste product, for instance, the bacteria may not get any advantage from the phenotype of host in any way. The function's impact on the microbes, hosts, and maybe both parties' fitness comes in second. The process of evolution, including the possibility of co-evolution, may be defined by assigning fitness to a specific function throughout life cycle and circumstance. Specific cities and redundancies are related to function[35]. The process of each microbe-derived item determines whether it is specific to the community or individual bacteria. Different microorganisms may contribute to the same cause on the microbial side. Two distinct microbial organisms may trigger the same host signaling cascade on the host side, resulting in functional redundancy and comparable consequences. Now that we have this framework, we will talk about three main types of microbial entities that mediate direct relation between the host and gut microbiome: metabolites, ligands of pattern recognition, and compounds that act through impacts on adaptive immunity[29,36,37].

Pathogen resistance as an example of a deconstructing mechanism

We now go back to the example of resistance of pathogen to show how several different direct (microbe) and indirect (host reactions) pathways might mediate microbiota effect on a single host's phenotype. MAMPs derived from gut microbiota can trigger the development of antimicrobial molecules including the lectin RegIII that inhibits vancomycin-resistant Enterococcus, via activating PRR signaling pathways, such as via TLRs[38]. PRRs' innate regulation of adaptive immunity also governs T- and B-cell responses as ant pathogenic, for instance, fungal MAMPs' activation of C-type lectin receptors aids in the coordination of TH 17 cells which are anti-fungal. Primary metabolites from the gut microbiota, can trigger coupled receptors of G-protein to synchronize type-2 immune-mediated defense against worms[29].

Similarly, tryptophan metabolites generated from bacteria can agonies the aryl hydrocarbon receptor, causing IL-22 to be produced. This, in turn, can induce the generation of antimicrobial peptides[39]. In a mechanism called disease tolerance, the microbiome can also change the harmful effects of infections at the cellular level as well as tissue levels on the host in

addition to altering pathogen load. For instance, it may prevent skeletal muscle atrophy and cachexia[40].

Conclusion

Among other surfaces, the skin, oral cavity, and gastrointestinal tract are colonized by the microbiota, a diverse and extensive microbial ecology present in the human body. One of these, the gut microbiota, has garnered a lot of attention due to its profound impacts on host immunity, metabolism, and overall health. The gut microbiota is made up of trillions of microorganisms, the most common of which being bacteria, viruses, fungi, archaea, and protozoa. These microbes and their host have a symbiotic relationship that affects immune system development, balance, and function. The immune system gut microbiota regulates immunological responses in a dynamic and mutually reinforcing connection, with the immune system altering microbial composition to maintain homeostasis. The microbiome facilitates immunological cell training, immune tolerance, gut barrier integrity, and control of the inflammatory response. Studies on GF mice, which are raised in clean environments and lack a microbiome, have shown that the absence of gut bacteria results in immune system deficiencies, including underdeveloped gut- associated lymphoid tissue, lower T cell populations, inadequate antibody production, and increased susceptibility to infections. This illustrates the importance of gut microbes in regulating immune activity. One of the most important ways that gut microbiota influences immunity is through the production of metabolites.

Using the ability of computing to identify patterns and causation, we must concurrently measure microorganisms, metabolites, and microbial and host activities to increase our causal knowledge of the gut's microbial ecology. From the standpoint of human health, studies should aim to measure and elucidate the contributions of immunopathology of host as well as tolerance, environmental factors, and microbial membership to health of host and illness. Lastly, the direction of our knowledge on the gut microbiota depends on how we consider and synthesize information about it and how biologists, doctors, and the public can communicate to advance the field and improve our basic level understanding of the gut microbiome.

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Author Contribution

Atika Ahmad conceived the idea and designed the contents for the preparation of review draft, Muhammad Ahtisham Jamil helped and supervised the preparation of this review article.

Conflict of Interest

Authors declare no conflict of interest.

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