Gut microbiome diversity as an adjuvant marker for immune function

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ABSTRACT

Background: The gastrointestinal (GI) tract represents our most intimate contact with the external environment. The GI tract is tasked with extracting the appropriate nutrients we need to thrive, maintaining a proper balance of helpful and harmful microbes, and acting as a conduit for waste removal.

Objective: This review aims to summarize a growing knowledge on the microbiome’s influence on the human body’s entire health and biological system.

Method: Selected, recently published literatures on studies related to gut microbiomes were studied and summarized.

Results: In essence, host’s mucin, protein, and bacterial polysaccharides create a unique mucosal biofilm that is home to various commensal and pathogenic organisms in the host intestine. Maintaining proper mucosal barrier function is vital for both GI and system-wide health. The lumen of the gut contains numerous entities that should never reach the bloodstream or lymphatic system. The mucosal barrier’s integrity is maintained by a single layer of tightly fitted columnar epithelial, and greater than 70% of the immune system is closely associated with the GI tract.

Conclusion: The microbiome helps the body produce specific vitamins and influences either innate or adaptive immune systems. The microbiome analysis has become one of a few adjuvant diagnostic tools in helping practitioners either combat disease or follow up therapy progress of their patients.

Keywords: gastrointestinal tract, biofilms, extracellular matrix, biopsy, mucins

Introduction

The protective barrier of the gastrointestinal (GI) layer is a critical function of our immune system; it is a distinct and interconnected function highly dependent on the microbial ecosystem and the host. The GI tract is the main frontier of the human body with the external environment. During their lifetime, an average person consumes approximately 35 tons of food, and bacteria and other microbes frequently outnumber the cells in our bodies. Originally believed to outnumber our cells by ten to one, this estimate has been refined to a factor of one, with human cells now accounting for only 43% of total body cells. When a prolonged and deliberate direct interaction of epithelial of the GI tract and microbiota, particularly the gut, it causes local inflammation and spreads complex systemic immunological and metabolic issues. It is exceedingly rare to find someone who does not have some form of GI dysfunction and has a chronic condition. On the other hand, individuals with significant GI disorders will exhibit systemic symptoms [1].

When digestion is compromised, a silent local inflammation may develop, escalating systemic problems or progressing to a more severe condition. Without addressing local gut problems, effective therapies for healing or managing the systemic problem may become ineffective or even exacerbate the local gut problem. It is critical for GI and systemic health to maintain a normal mucosal barrier in the GI tract. A selective barrier is an epithelium
mechanism that forms the tight junction connecting and sealing each intestinal epithelium cell. Over 70% of the immune system is found within the epithelium’s mucosa and intercellular space in a specialized lymphatic compartment. Due to its critical role in maintaining healthy immune system function, gut-associated lymphoid tissue (GALT) is inextricably linked to local and systemic health [2].

**Innate and adaptive immunity**

Our immune system defends us against foreign organisms and substances. Living organisms, microbial toxins and other microbial by-products, and other foreign substances are all examples of invaders. Immunity is classified into two distinct categories: Innate immunity, also known as naturally occurring immunity, is capable of recognizing and prepared to prevent microbes from entering host tissues and rapidly eliminating those that do. Adaptive immunity, also known as acquired immune response, requires lymphocyte expansion and differentiation in response to the pathogen to provide adequate defense; in other words, it acclimates to the presence of microorganisms. First-line immune defense regulated by innate immune response is provided by mucosal epithelial barriers and cells containing natural antimicrobial peptides (defensins and cathelicidin). In general, these functions prevent the entry of foreign organisms or chemical substances, microbial toxins, and other microbial by-products [3].

Suppose microbes penetrate the epithelial barrier of the gut lumen and enter the tissues or circulation. In that case, they trigger a non-specific immune reaction that induces a group production of specialized lymphocytes (e.g., natural killer (NK)-cells) and several plasma proteins (e.g., complement immune system). These immune mechanisms are naturally occurring and can recognize and react to specific microbes. As the first defense line against pathogenic infections, these immune responses augment adaptive immune responses that can adapt against various infections [4]. While each type of immunity has distinct functions, they both work to eliminate the offending agent and restore the body’s average balance.

**Microbiome ecosystem in the gut**

The microbiome is a total microbial organism found within all multicellular organisms. This group of organisms may include commensal or non-commensal bacteria, fungi, and viruses. Microbiota and microflora are synonymous. Additionally, the term microbiome is often associated with the comprehensive genomic information contained in these microbes. The human microbiome may be compared to the human genome [5]. The human microbiome changes in lockstep throughout an individual’s lifetime, with the human (as a multicellular organism) being a holobiont or hologenome. The term holobiont refers to a multicellular host and community of microbes related to it, including bacteriophage and other microcellular organisms. It can emphasize the host and its constrained symbionts and the variegation of nonobligatory symbionts and their compelling corporations within the host (Figure 1) [6].

Holobiont comprises multicellular organisms acting as a host together with symbiotic microbes. Some of these microbes can affect the phenotype of holobiont and evolve together with the host. Other factors affect the holobiont phenotype but do not coevolve with the host, and others do not affect the holobiont phenotype. All the microbiome found in the environment is not considered part of the holobiont [6]. Our various microbiomes develop in a predictable succession of species and functions from birth to old age, similar to other complex ecosystems [7]. Certain critical organisms in an earlier stage of microbiome development may be undetectable as a person matures, as their influence may last much longer than our ability to detect them. Immediately post-birth, the microbes from the external environment started as the initial microbial community of the gut. The infant’s gut microbial composition is strongly affected by their mother’s delivery method and initial food source selection [8]. It is well established that cesarean birth (C-section) alters the infant gut microbiome’s initial inoculation compared to vaginal delivery. Bifidobacterium and Bacteroides colonization are delayed in infants
born via C-section, and an initial microbiome
is frequently influenced by the mother's skin
microbiota [9,10]. This initial development
within the microbiome is thought to significantly
contribute to immune system dysregulation in
individuals born via C-section, increasing their risk
for certain allergic, inflammatory, and metabolic
disorders (part of the hygiene hypothesis) [11,12].

The intestinal epithelium: structure and
function

While it may seem counterintuitive to consider
the gut lumen external to the body, selectively
impenetrable barriers ensure it. As a result, the gut
barrier’s permeability functions as a critical interface
between the human body and the gut lumen milieu.
This barrier comprises a single columnar epithelial
layer dividing the lumen and the lamina propria,
capillaries, lymphatic system (lacteals), and smooth
muscle tissues below. The villi and microvilli of small
intestines protrude into the lumen during digestion,
optimizing nutrient absorption. Villi are absent in
large intestines; in contrast, goblet cells are more
abundant. These cells produce and maintain the
protective mucus layer with mucin synthesis and
secretion, which shield the large intestine lumen
from the toxicity of metabolites and other toxins
or pathogens found in semi-solid feces [13]. The
epithelium is a collection of large folded surfaces
with invaginations dubbed crypts of Lieberkühn [14].
The intestinal stem cells ascend through the zone
of transition, developing into intestinal epithelial
cells (IECs) at the epithelial layer crypts base. The
adult epithelial cell will eventually shed into the
crypt lumen apex (or villi in the small intestine)
[15]. To maintain the complex’s sophisticated
system of gut barrier function, IECs self-renew
continuously, replenished in three to four days,
and originate from a self-sustaining intestinal stem
cell (ISC) niche [16]. The GI tract act as a physical
barrier to identifying specific physiological benefits
related to a typical structure so that the GI tract
can function optimally. The intestinal epithelium
separates the luminal contents from underlying
tissue; the ICSs serve as a restrictive barrier held
together by tight intercellular junctions that prevent
foreign particles, e.g., microbes and antigens. It
coordinates various physiological processes, including
nutrient absorption, protection against pathogens,
and secretory functions. These diverse functions are
almost certainly dependent on diverse epithelial
cells. However, no comprehensive studies exist on
identifying epithelial types and their molecular
characteristics [17]. The gut epithelium comprises
multiple cell types that serve specific functions. Major histocompatibility complex (MHC) class II varies the distribution of IECs as non-conventional antigen-presenting cells within each bowel (Figure 2A, B). Enterocytes are the most prevalent intestinal epithelial cell responsible for micro/macronutrients and the absorption of water. By contrast, secretory cells (e.g., goblet and enteroendocrine cells) secrete mucins and hormones. Other IECs, dubbed Paneth cells, secrete antimicrobial factors protecting stem cells at the bottom of crypts of the small intestines [15,18]. Chemosensory tuft cells are required for helminth and M cell defense (Figure 3), and they play a vital task in the immune system’s recognition and eventual presentation of luminal antigens [19,20].

Microvilli are absent from colonocytes, the intestinal epithelial cells that line the colon. The distal GI tract contains the largest reservoir of microbes [21,22]; this may explain why the primary producer of mucus, the Goblet cell, is increasingly found higher in the distal GI tract, particularly near the distal colon.

The essential feature of the small intestine epithelium features the mucosal barrier covering the cells as the first defense mechanism. Compared to colon, the mucus layer in this part of the gut is thinner. The IECs express an innate immune receptor, although it’s less diverse than other cells [21].

Within the small intestinal barrier, enterocytes with microvilli secrete enzymes to help the microbiome and host transporter on fermenting carbohydrate and peptide chains. This process facilitates the absorption of macronutrients and micronutrients, secreting immunoglobulins [23]. A large structure of lymphoid called Peyer’s patches (PPs) is composed...
of aggregated lymphoid follicles encircled by the follicle-associated epithelium (FAE), which serves as an intersection between the GALT and the luminal microenvironment (Figure 2A) [24]. Microfold cells (M-cells) and goblet cells are IECs responsible for antigens transportation from the lumen to the multiple innate immune cells. The FAE produces fewer antimicrobial peptides, secreted IgA, and mucus which facilitates access to luminal antigens [25,26]. Specific IgA is formed by professional antigen-presenting cells (APC) that inspect microbial related to the epithelium, Peyer’s patches (B and T cells). Together they form IgA designated for antigens of the commensal microbial [27].

The M-cell pocket comprises macrophages, dendritic cells, and lymphocytes (B and T cells). It serves as a docking site for lymphocytes and other APC, shortening the distance traveled by transcytosis vesicles between the apical and basolateral surfaces [28]. The antigen is transferred from an M-cell to the underlying immune cell in the intestinal lumen via transcytosis, phagocytosis, or microvesicle shedding [29]. M cells may be able to sort transcytosis antigens selectively, and microvesiculation and the ability to encapsulate bacteria and toxins may provide an additional layer of defense against bacteria and toxins. Additionally, goblet cells may participate in luminal antigens’ movement to dendritic cells [30,31]. According to a previous study using live animal imaging, goblet cells in the small intestine epithelial layer pick up low-mass molecular antigens and transport

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them as goblet-cell-associated antigen passages (GAPs) to dendritic cells. The study explains their role in the preservation of microbial tolerance [31]. Another study also refuted that goblet cell-based microbiota sensing (via MyD88 signaling) is critical for regulating dendritic cell activation exposure to luminal substances (Figure 2A) [30].

Researchers now understand that cells such as enterocytes, goblet cells, and each type of IEC can evolve during the process of maturing and developing into specialized functions and be classified into different subsets (Table 1). At the culmination of colonic crypts, sentinel goblet cells can be found. These cells operate independently of the goblet cells located underneath them in the same vault. Its purpose is to demonstrate and detect neighboring bacteria and to initiate a fast, crypt-wide mucin dispense reaction to flush away irritating stimuli [32]. Two distinct tuft cells can express differently, i.e., the epithelial cytokine Tslp and immune marker CD45 [33].

Microbiome and host immunity

The intestinal microbiota is not uniform in composition [34]. The gut flora’s structure and composition are described as natural selection created by the host and their microbes, promoting interchangeable benefits and functional stability within the gut’s ecosystem. Five phyla of microbial are commonly reported as the vast majority of the diverse GI microbiota: Firmicutes, Bacteroidetes, Actinobacteria, Verricellomicrobia, and Proteobacteria [35]. When comparing small intestine and colon biopsy samples from healthy individuals, Leite et al. [36] discovered that various bacterial groups are enriched at various locations. In small intestine samples, Firmicutes and Actinobacteria were enriched in Bacilli. Bacteroidetes and the Firmicutes’ Lachnospiraceae family are more commonly found in colonic samples [36]. Along with differences in flora composition along the GI tract’s axis, microbial populations on the surface adherent and those in the luminal environment are distinct [37], and anaerobes bacteria are less found at mucosal surfaces than in the lumen compared to the aerobes.

Interactions between the host and microbe happen mostly on a surface covered with mucose, especially in the human intestinal mucosa. The intestine seems tolerant in bidirectional host–flora exchange and contains multifarious bacterial colony differs from the internal lumen ecosystem by a single epithelial cell layer. The flora exhibits metabolic activity comparable to an organ within an organ [38]. The fecal microbiome seems to continue diversified, as shown by a study that found severe infection of COVID-19 and SARS-CoV-2 were associated with change in fecal microbiome during the patients stay in the hospital. This finding may have implications for adjuvant strategies altering intestinal microbiota to mitigate disease severity [39].

A biosphere is essentially the environment in which bacteria live (some part of the human body). It is an ecosystem, and various species of bacteria, other microbes, and parasites coexist as competitors. Certain species are predatory, while others are parasitic. Additionally, species can choose to collaborate and combine their forces. Since birth, the gut microbiota evolves in lockstep with the organism and its metabolic and neurological programming; as a result, the development of this microbial community is critical for later life health [40,41]. Receptors capable of pattern recognition have a vital role in innate and adaptive immune responses. They are a critical mechanism for the organism’s immune system to communicate with the gut microbiome. From the microbiome’s point of view, triggering or cooperating disease is exceptionally reliant on host’s activation condition, genetic susceptibility, and the limit of certain microbe [42]. This decreases immune surveillance precision within the gut, allowing for an imbalance of commensal organisms, resulting in dysbiosis caused by host-derived genetics [43].

Numerous studies have shown that probiotics can enhance the abundance of microbe in the gut, promoting more mucus secretion and preventing the shattering of tight junction proteins by reducing lipopolysaccharides (LPSs) in the gut. LPS-induced regulatory inflammation and activation of endothelial, dendritic, and macrophage cells are mediated by Toll-like receptors (TLR 2, 4).
Additionally, reduced gut dysbiosis and intestinal leak due to probiotic therapy may help limit inflammatory biomarkers’ progression and abrupt immune activation. In turn, probiotics promote T-cell differentiation against Th2 and the production of Th2 cytokines, e.g., IL-4 and IL-10 [44].

**Immunomodulatory effects of the gut microbiome**

*Stimulating and maintaining balance of IgA production*

The tremendous amounts of commensal bacteria found in vertebrates’ lower intestines share numerous molecular patterns utilized by the innate immune system to perceive pathogenic bacteria [45]. IgA is required for IECs defense against microbial attack and maintaining an interchangeable interaction that benefits both host and commensal bacteria in the gut. This, in return, will allow a beneficial microbiome that promotes a healthy gut environment [46]. The intestinal mucosa serves as a physiological barrier for most microbes, as well as a pathogens bacteria and pathogens that invade the body. At least two distinct barriers comprise the homeostatic mucosal defense: epithelial and immunological barriers. Secretory IgA antibodies (SIgA) are the initial defense mechanism against antigens in the gut lumen [46]. Microbes promote IgA production that manages the translocation and neutralization of bacterial toxins on the surface of intestine mucosa. The barrier function of the mucosal layer is sustained by secretory IgA antibodies and antimicrobial peptides (AMPs) [47,48]. Dendritic cells (DCs) that develop as antigen-presenting cells are found in the intestinal mucosa and balance T-cell-dependent (TD) and T-cell-independent (TI) immune responses. DC population in the gut is heterogeneous, with distinct subsets inducing B cell IgA synthesis. The microenvironment has a strong influence on the characteristics of intestinal DCs, e.g., the metabolites of commensal bacteria and soluble factors from the epithelial cell [49]. IgA, which are homeostatic, is essentially polyreactive with a low affinity for antigens found on microbes, such as LPS, polysaccharides capsular membrane, and flagellin. A few commensal bacteria (20–50%) are covered with IgA [50,51].

**Maintenance of energy and homeostasis function through secretion of metabolites and nutrients**

Additionally, the gut microbiota plays numerous beneficial parts, e.g., in producing nutrition and metabolism. The organism utilizes short-chain fatty acid (SCFA) as a source of energy produced by intestinal bacteria from dietary fibers [52]. Apart from fermenting long-chain polysaccharides to be readily utilized by the host, intestinal bacteria also process multiple substrates, e.g., lipids, amino acids, and protein [53,54]. In the colon, dietary fiber is fermented by commensal bacteria to SCFAs needed by goblet cells and enterocytes. SCFAs also ferment vitamins (e.g., folate, biotin, riboflavin, vitamin B12 and K), acetate, butyrate, and bile acids [55].

**Direct bacterial/pathogen competition**

Another critical benefit conferred on the host intestine by the intestinal microbiota is protection against exogenous pathogen colonization, a phenomenon dubbed colonization resistance, and from indigenous pathobiont overgrowth (potential pathogenic symbionts of the microbiota) [56,57]. Commensal bacteria and archaea confer resistance on the host against pathogen infection. Colonization resistance occurs when intestinal bacteria form an epithelial barrier to keep out new bacteria or strains of the same species. Colonization resistance mechanisms, which control the microbiota’s ability to prevent the multiplication of pathogens, are complex, including competitive metabolic interactions, niche localization, and induction of host immune responses [58]. In turn, pathogens coevolve to counter colonization resistance. Surprisingly, the intestinal microbiota may also contribute nutrients to specific gut pathogens or directly contribute to the activation of virulence in pathogenic bacteria that would otherwise remain dormant. Additionally, commensal bacteria can indirectly aid in developing pathogenic infection resistance by producing antimicrobial peptides,
TH17 responses, and supporting the integrity of the epithelial barrier. An in vitro study using Caco-2 gut epithelial cells has shown Escherichia coli strain Nissle (E. coli Nissle) can stimulate the production of antimicrobial peptide β-defensin-2 in a time and dose-dependent manner, which may protect the mucosal barrier pathogenic bacteria [59]. As an example, microbiome-mediated direct inhibition colonization by immune-mediated competition of the Gram-negative organism B. thetaiotaomicron can promote the antimicrobial peptide RegIIIy synthesis that is predominantly active against Gram-positive bacteria [60–62]. Certain interactions require interbacterial competition and an active host immune system. For example, probiotic E. coli Nissle 1917 inhibits Salmonella enteric colonization by iron competition if the host produces the innate immune molecule lipocalin-2 that hampers iron availability [63].

**Cross-signaling pathway between microbiomes and innate immune cells**

The microbiome facilitates primary and secondary metabolism via mucosal surfaces by interacting with host intestinal epithelial cells. SCFAs in the colon resulting from indigestible polysaccharides fermentation act to modulate leukocyte functions, e.g., synthesis of proinflammatory and inflammatory cytokines (TNF-, IL-2, IL-6, and IL-10), eicosanoids, and chemokines (e.g., MCP-1 and CINC-2). These fatty acids can impact the leukocytes’ ability to move to inflamed areas and attack microbial pathogens [64]. The primary locations for priming adaptive immune cells in the intestine are the gut-associated lymphoid tissue (GALT) and gut-draining lymph nodes (LNs). Additionally, the small and large intestines contain smaller lymphoid aggregates (isolated lymphoid follicles and cryptopatches) referred to as solitary, isolated lymphoid tissues (SILTs) [65]. LPS is another immune regulatory molecule that maintains the hemostasis ecosystem in the lumen. LPS is an endotoxin found in a variety of microbes. It is a primary component that builds the outer layer of bacteria, which is involved in septic shock transmission (Figure 4) [66].

The glycolipid known as LPS can promote the immune response. Like others, LPS acts as a pathogen-associated molecular pattern (PAMP) and binds with TLR4, which initiates the transcription of proinflammatory cytokines. TLR4 is expressed as transmembrane proteins on the apical surfaces of mature intestinal epithelial cells [67]. Gram-negative bacteria will often depart from the LPS biosynthesis as their adaptive mechanism, which results in modifications in the type of acyl chains and the number of phosphates in lipid A of LPS.
TLR4 signaling activation can be alleviated by modifying LPS enzymatically. Additionally, the precise mechanism has been demonstrated using alkaline phosphatase (ALP) [66]. TLR1-9 is one of thirteen known TLRs in epithelial cells of humans’ gut [68].

Dysbiosis (alternatively spelled dysbacteriosis) is a microbial imbalance on or within the body. While dysbiosis is most prevalent in the digestive tract, it can occur on any exposed mucus membrane surface [69–71]. Low fiber, high fat, and simple carbohydrate diet lead to an imbalance in the microbiome’s diversity and cause dysbiosis. Disruption of the gut microbiota can lead to increased intestinal barrier permeability, resulting in low-grade systemic inflammation and promoting metabolic disorders. Metabolic endotoxemia that slowly builds up in obese conditions can accumulate blood LPS, inflammation, and insulin resistance through CD14/TLR4 signaling pathway [72–74]. The stimulation of innate NOD1 and NOD2 receptors activation is essential for keeping the resistance of peripheral insulin. Metabolic endotoxemia triggers obesity and insulin resistance [75]. An innate immunity receptor involved in energy production (NOD2) recognizes peptidoglycan in the bacteria cell membrane; its activation profile branches of cross-talk among the gut microbiota and metabolic diseases [76].

Dendritic cells (DC) are “professional” MHC II antigen-presenting cells that can activate and differentiate naive T cells in an unmatched manner (Figure 5). Additionally, they help establish and maintain immune tolerance under homeostatic conditions [77]. DCs are responsible for detecting the presence of microbial strangers and determining their potential for harm. DCs communicate this directly (cell to cell) or indirectly (cytokines) to systemic immune cells; this requires priming with a pathogen, cytokines, or specific tissues (e.g., gut epithelium). Priming of DCs with distinct T cell instructions results in the conversion of naïve Th0 cells to Th1 (CD4), Th2 (CD4), Th17 (CD4), and T-regulatory (CD4+ and CD25) cells [78].

Supporting and modulating the microbiome

Diet has a rapid and reproducible effect on the human gut microbiome. The microbiome’s diversity and activity reflected the differences between meat-based and vegetable-rich diets, indicating that carbohydrate and protein fermentation occur in trade-offs [79,80]. This modification is the most straightforward method of intervention [81]. Fiber aids in blood sugar regulation, binds and eliminates toxins, and acts as a prebiotic or food for the millions of beneficial bacteria that live in the gut. Indonesian traditional fermented foods such as tempeh and tauco are available in paste or slurry form and brem (rice wine). Fasting (intermittent caloric restriction) is another modulatory factor that alters microbiome diversity; Clostridium sp and Lachnospiracea significantly decreased after Ramadan fasting in two ethnic groups [82].

Increasing the variety of vegetables and fruits available will increase fiber consumption, which is associated with a diverse microbiome. This prebiotic food variant serves as a source of SCFA and has a natural selection effect on
the host microbiome, conferring optimal health benefits [83]. Butyrate (a member of the SCFA molecule family) has a variety of biological functions, including increasing mucus production and decreasing IEC permeability. It also acts as a histone deacetylase (HDAC) inhibitor, and a study shows its potential neurological impact in neurodegenerative diseases like Parkinson’s or Alzheimer’s [84]. Another straightforward method of modulating the microbiome is through physical activity/movement; evidence indicates that inactive people significantly increase certain bacteria [85].

Conclusion

Inflammation is an altercation of an infinite number of diseases. Inflammation in the gut caused by our diet will eventually result in dysbiosis, affecting the population and diversity of the microbiome. This condition eventually becomes the gateway to various systemic health problems that can be altered with a balanced, nutritious diet. This modification is the most straightforward method of intervention. Assume that adaptive immunity is “trained” in this manner by innate immunity through the mediation of APC, which occurs naturally through microbiome modification. In this case, the innate immune memory could also be manipulated therapeutically to promote healthy immunity. The body requires a certain amount of healthy inflammation, a necessary component of the immune defense system. When optionally balanced, the body takes sufficient immediate action to aid healing and then switches off the response when the threat has passed. However, when the immune system becomes imbalanced, the body enters a state of chronic inflammation, which can manifest as a minor symptom or something more serious.

Author contributions

Conceptualization, ML; Methodology, FC, ML; Investigation, ML; Resources, FC; Writing – Original Draft, ML, FC; Writing – Review & Editing, ML, FC; Supervision, FC.

Declaration of conflict of interest

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