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Intestinal Microbiota and Immunity: A Review

C. F. Egwuonwu[1], E. C. Evans[1] and A. L. Olokun[2*]

[1]Department of Biochemistry, Federal University of Technology Minna, Niger State, Nigeria.
[2]Department of Biological Sciences, Bingham University New Karu, Nasarawa State, Nigeria.

Authors' contributions

This research was carried out in collaboration between the three authors. Author CFE designed the study and wrote the first draft of the manuscript. Author ECE wrote the protocol while author ALO managed the literature. All authors read and approved the final manuscript.

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ABSTRACT

Microorganisms establish a symbiotic relationship at all stages of growth in man, beginning from birth to adulthood. They are found in every part of the body, and they participate in the immune system against pathogen-mediated immune responses. Their actions are elicited by secreting microorganism associated-molecular proteins (MAMPs) which they use as signalling molecules to activate a cascade of immunological responses within the host cell. They maintain the barrier function of the intestinal wall as well as prevent colonisation of the intestine by pathogens. Using their MAMPs, they bind to specific pattern recognition receptors (PRR) activating immune mediators in response to pro-inflammation by pathogens. These immune mediators are either induced or suppressed (in the case of overproduced immune response). Some of these symbionts elicit their action by anaerobic fermentation of dietary fibres into byproducts of short-chain fatty acids (SCFAs). These bacterial metabolites functions by binding to G-protein coupled reactions (GPCRs) on colonic macrophages and Dendritic cells (DCs) and contributed to the increased production of interleukin 10 (IL 10) in response to pathogen-mediated immune response. These unique immunological actions of intestinal microbiota, have shown that microorganisms are beneficial to the host as against the widespread belief that they are disease-causing agents.

**Corresponding author: E-mail: lanzyko07@yahoo.com;*

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1. INTRODUCTION

All higher animals are associated with a diverse microbial community that is composed mainly but not limited to bacteria. Their presence in all stages of human development creates a constant interaction between them and humans. Multi-cellular organisms exist as meta-organisms composed of both the macroscopic host and its symbiotic microbiota. With an estimated composition of 100 trillion cells, human symbionts outnumber host cells by at least a factor of 10 and express at least 10-fold more unique genes than their host's genome [1]. The number of microbial cells in the intestine alone outnumbers the number of human cells of the entire organism [2] on an average of 40,000 bacterial species [3], 9 million unique bacterial genes and 100 trillion microbial cells [4]. This complex community of microbes that include bacteria, fungi, viruses, and other microbial and eukaryotic species provide a tremendous enzymatic capability and play a fundamental role in controlling many aspects of host physiology. Several data confirm that gut microbiota is engaged in a dynamic interaction with the intestinal innate and adaptive immune system, affecting different aspects of its development and function [5]. Intestinal bacteria thrive in a stable, nutrient-rich environment but also serve beneficial functions to the host including energy salvage of otherwise indigestible complex carbohydrates, vitamin and micronutrient syntheses, competitive exclusion of pathogenic microorganism, and importantly, stimulation of immune development [6].

In the immune system, they prevent colonisation of the intestine by pathogens [7] where they maintain the barrier function of the intestinal wall. They promote the development of intestinal vascular bed [8], the nervous system in early childhood and its functioning in adults [9], and also a determining factor in the formation of mucosa-associated lymphoid tissue (MALT), as well as gut-associated lymphoid tissue (GALT) [10].

2. ENTRY ROUTE

The means via which microorganisms gain entrance into the human system is quite fascinating. There is sufficient evidence to suggest that the structure and composition of the gut microbiota vary systematically with ageing [11]. Changes in intestinal microbiota in infants are influenced by medical, cultural and environmental factors such as mode of delivery, type of infant feeding, gestational age, infant hospitalisation, and antibiotic use by the infant [12].

Before birth, it is commonly accepted that the intrauterine environment and newborn infant are sterile until delivery; some evidence shows the presence of bacteria in the intrauterine environment and suggests that these bacteria may influence the microbiota of the infant before birth [13]. The formation of the human gut microbiota begins during birth with colonisation by microorganisms from the mother and the environment. The mother probably represents the most influential external factor for the development of the infant's microbiome, due to intimate contacts during birth, nursing, and early feeding. In the first six months after delivery, the infant is colonised mainly with the presence of strains of *Bifidobacteria* and *Staphylococcus* [14]. The intestinal microbiota of the infant slowly develops and matures from a low diversity and complexity reaching an adult state at about age 3 [13].

Mode of delivery (vaginally or by cesarean section) has been demonstrated to have a strong influence on early gut colonisation particularly on the number of *Bifidobacterium* [15]. Analysis of the first fecal sample of newborn infants showed a strong relationship between the first microbial community of the digestive tract and the microbial community of either the mother's vagina (*Lactobacillus, Prevotella,* or *Sneathia*) in the case of vaginal delivery or the mother's skin (*Staphylococcus, Corynebacterium*, and *Propionibacterium*) in the case of cesarean section [16]. Work by Biasucci [15] showed that there was a significant difference between the microbial population of cesarean and vaginally delivered infants. *Bifidobacterium* numbers were significantly lower in cesarean born children, and the overall diversity of their microbiota appeared to be lower. This evidence demonstrates that the gut environment becomes populated by the first abundant microbial community it encounters, either the skin or the vaginal environment.

Mode of feeding is another strong influence in the development of the infant intestinal

Table 1. Microbiota in different sections of the gut

Anatomical location	Predominant bacteria
mouth	*Actinomyces*, *Arachnia*, *Bacteroides*, *Bifidobacterium*, *Eubacterium*, *Fusobacterium*, *Lactobacillus*, *Peptococcus*, *Peptostreptococcus*,
esophagus	*Streptococcus, Staphylococcus, Corynebacterium, Lactobacillus, Peptococcus*
stomach	*Lactobacillus, Streptococcus, Staphylococcus, Enterobactericeae, Peptostreptococcus, yeast*
small intestine	*lactobacillus, enterobacteria, enterococci, bifidobacteria, segmented filamentous bacteria.*
Colon	*bacteroides, lactobacillus, enterobacteria, enterococci, clostridia, methanogens*

microbiota. Healthy gut microbiota is frequently detected in breast milk, suggesting an important role of breast milk as a delivering system for gut bacteria [17]. Various studies have shown that breastfed infants show significantly higher counts of probiotic bacteria and lower counts of *Bacteroides, Clostridium coccoides* group, *Staphylococcus*, and *Enterobacteriaceae* as compared with formula-fed infants [18].

3. HOW GUT MICROBIOTA INTERACT WITH HOST IMMUNE SYSTEM

Numerous studies have confirmed that Gut microbiota and their byproducts are involved in one form of immune responses. They trigger the activation of multiple immune effectors against immunologic response by pathogenic microorganisms and even chemical-induced immunologic responses. Multiple immune effectors function together to minimise bacterial-epithelial invasion. These include the mucus layer, epithelial antibacterial proteins, and IgA secreted by lamina propria plasma cells. Compartmentalisation is accomplished by unique anatomic adaptations that limit symbiotic bacterial exposure to the immune system. Some microbes are sampled by intestinal dendritic cells (DCs). The loaded DCs move to the mesenteric lymph nodes through the intestinal lymphatic cell but do not migrate to distal tissues. This compartmentalises live bacteria and induction of immune responses to the mucosal immune system. Induced B cells and T cell subsets re-circulate through the lymphatic and the bloodstream back to mucosal sites, where B cells differentiate into IgA-secreting plasma cells.

4. HOW HOST CELL RECOGNIZES AND DIFFERENTIATES COMMENSAL AND PATHOGENIC MICROBES

Microorganisms on their own cannot elicit immunologic actions, but they achieve this using protein called Microorganism Associated-Molecular Proteins (MAMPs). With this protein,

Table 2. Ligand Microorganism associated-molecular protein (MAMPs) for Toll-like receptors (TLR), Nucleotide-binding oligomerisation domain (NOD)-like receptors (NLR) and G-protein coupled receptors (GPCR) and their location in the Intestinal epithelial cell (IEC)

Receptor	MAMPs	Location IN IEC
TLR 1	Triacyl lipopeptides	Surface membrane
TLR 2	Peptidoglycan, LTA	Surface membrane
TLR 4	Lipopolysaccharide	Baso lacteral membrane, Endosomal membrane
TLR 5	Flagellin	Baso lacteral membrane
TLR 6	Diacyl lipopeptide	Surface membrane
TLR 9	Cytosin-phosphate-guanosin oligodeoxy nucleotide (CpG-ODN)	Endosomal membrane
NLR1	Meso-Lanthionine meso-diaminopimelic acid	Cytoplasm
NLR 2	Muramyl dipeptide	Cyotoplasm
GPCR 41	Propionate	Cytoplasm
GPCR 43	Acetate and propinate	Surface membrane
GPCR 109A	Butyrate	Surface membrabe

the host cell recognises and differentiates them from pathogenic microbes. These MAMPs are specific to a particular receptor on the IEC which they bind to elicit their immunological responses. For example, receptors such as a Toll-like receptor (TLR) and nucleotide-binding oligomerisation domain (NOD)-like receptors (NLR) are used for signalling purposes. It is also worthy of note that these TLR and NLR have locations on the IEC (Table 2). Some are located in the epithelial cell, basolateral side of the IEC, and the cytoplasm. Also, the location of the receptor is important. If the receptor is considerably absent say on the EC, then the response to the ligand will be low or not seen and vice versa. Other receptors on the IEC are G-Protein coupled receptors (GPCR) 41, 43 and, 109A (Table 2). These GPCR are specific to short-chain fatty acids (SCFAs) that are products of the fermentation of dietary fibres by some symbionts. These SCFAs are acetate, butyrate, and propionate and by binding to these receptors, they initiate a cascade of reactions within the cell.

5. MICROORGANISMS INVOLVED IN IMMUNITY

The human gut houses numerous microorganisms but only a handful is actively involved in immunity. It is worthy of note that these microorganisms do not interact directly with the host due to an efficient protective barrier the host's epithelial cell posses preventing the uncontrolled access of bacteria [19] since they are foreign to the body. As earlier stated, they interact by secreting MAMPs that binds to their specific receptors on the IEC.

5.1 Segmented Filamentous Bacteria (SFB)

Segmented filamentous bacteria (SFB) are commensal bacteria that were first identified in the ilea of mammals. They selectively colonise the ilea shortly before weaning [20]. The first segment of the microbe possesses a nipple-like appendage, called a holdfast that projects into the plasma membrane of the enterocyte, without actually rupturing or penetrating the host cell wall [21]. The holdfast is made up of flagellin proteins-a globular protein that forms the filament in bacteria flagellum-which it secretes as its MAMP for signalling purpose. The flagellin of SFB as well as being used for signalling is also used as adhesins [21] and can penetrate the mucous layer lining the intestinal epithelium. Its presence in the gut has shown to have a profound influence on models of intestinal diseases as well as systemic immune-mediated diseases. According to Grönlund et al. [14] it can contribute to the colonisation resistance to the enteric pathogen *Salmonella enteritidis* which infects eggs and consequently humans if eggs are eaten raw or partly cooked. The presence of SFB and *Salmonella enteritidis* in the ileal epithelium of individual villi is mutually exclusive in the sense that SFB not only compete with pathogenic microbes for the binding spot on enterocytes by influencing glycosylation of enterocytes but also triggers a local response which hinders the ability of the pathogens to adhere to the epithelium and elicit their action. It has shown to potently induce immune responses in mammals [22] by its ability to produce IgA production as well as T_H17 immune responses. For SFB to elicit its immunologic action, it is necessary for it to bind to its specific receptors on the intestinal epithelial cell.

A study conducted by Kuwahara et al. [23] showed that SFB flagellin protein activates a signalling pathway in a Toll-like receptor (TLR) 5-dependent manner expressed by the $CD11c^{hi}CD11b^{hi}$ subset of intestinal dendritic cells. This activation invokes the production of IgA by stimulating intestinal epithelium cells and dendritic cells (DCs) to release of B cell-activating factor (BAFF) and A Proliferation-Inducing Ligand (APRIL) which induces IgA-producing B cells and plasma cells differentiation of the lamina propria to produce IgA [24]. IgA is secreted into the intestinal lumen where it alters the pathogenic microbiota composition and function. In addition, the binding of the flagellin protein to TLR 5 also induces the differentiation and proliferation of T-cell repertoire specifically the Th17 cells [25] which are pro-inflammatory cells that play important protective roles against bacterial and fungal pathogens while at the same time contribute to autoimmunity [26]. T_H17 cells regulate the gut microbiota community in an IL-22- and regenerating islet-derived protein 3γ (REGIIIγ)-dependent manner [27].

5.2 *Bacteroides fragilis* Polysaccharides

Bacteroides fragilis is an obligately anaerobic, Gram-negative, rod-shaped bacterium, whose primary known environmental reservoir is the human lower gastrointestinal tract [28]. It was shown to be involved in carbohydrate metabolism, which includes the degradation of dietary polysaccharides and the production of

surface capsular polysaccharides [29]. Its ability to express multiple polysaccharides has shown its involvement in enhancing immune responses [30]. Two of the capsular polysaccharides of *B. fragilis* are polysaccharide A (PSA) and B (PSB). These polysaccharides are zwtterionic polysaccharides (ZPS) having both positive and negative charges like peptides. Other ZPSs have been identified from other bacterial species, including type 1 *Streptococcus pneumoniae* capsular polysaccharide (CP1) and types 5 and 8 *Staphylococcus aureus* capsular polysaccharide but of all of the known ZPSs, PSA is the best characterised. PSA is the molecular protein used by *B. fragilis* to elicit its immunologic action.

PSA is capable of activating T cell-dependent immune responses that can affect both the development and homeostasis of the host immune system. *Bacteroides fragilis* protects from colitis induced by *Helicobacter hepaticus. H. hepaticus's* action in inducing inflammation is seen by its ability to induce the production of pro-inflammatory mediators: IL-17, IL-23, and tumour necrosis factor (TNF) by stimulating Th17 cell. As a result of this, functional maturation of Treg cells in a mammal is facilitated. PSA can proffer protection from the pro-inflammation of *H. hepaticus* by inducing an immuno-regulatory programme which involves activating a potent anti-inflammatory mediator: interleukin-10 (IL 10) in colonic Treg cells. This induction is seen by PSA's binding to TLR 2 on CD4+ Tcells. The balance between the pro-inflammatory Th17 cell responses to *H. hepaticus* and the regulatory T (TReg) cell responses to *B. fragilis* supports the control of intestinal inflammation [31].

5.3 *Lactobacilli*

Lactobacilli are gram-positive rods, primarily facultative or strict anaerobes [32], and non-sporulating [33]. They occupy a variety of niches which includes the gastrointestinal tract of humans and other animals; they line the mucosa of the mouth and vagina.

Lactobacilli have been shown to elicit innate and adaptive immune responses in the host. Its ability to secrete lipoteichoic acid (LTA) as a lactic acid bacteria aids it to bind to its pattern recognition receptors (PRR) expressed on immune cells and many other tissues including the intestinal epithelium [34]. In *vivo lactobacilli* have been successfully used to modulate inflammatory diseases, enhance barrier functions, and stimulate immunity against pathogenic microbes.

5.4 *Lactobacilli* against Pneumococcal Infection

Studies by Licciardi et al. [35] showed that *Lactobacilli* play a protective role against the pathogen *Streptococcus pneumoniae* (the *pneumococcus)* which is a predominant cause of pneumonia, meningitis, and bacteremia. This pathogen is a leading killer of children under age 5 and is responsible for the deaths of up to 2 million children annually [36]. Experimental data suggest that *lactobacilli* can influence the profile of microbial species in the nasopharynx to reduce *pneumococcal* colonisation [37]. This is achieved by preventing pathogens (*Pneumococci*) from attaching to and colonising the respiratory epithelium by associating with its specific cell surface receptors (Table 2) thereby enhancing mucus secretion and the production of secretory IgA. *Lactobacilli* interact with underlying dendritic cells (DCs) which signals the adaptive immune system to trigger a variety of effector cell types, including Th1, Th2, and Th17 as well as regulatory T cells and B cells depending on the local cytokine/chemokine released to destroy ingested microbes and kill the infected target cell. Furthermore, *lactobacillus* also maintains the epithelial barrier integrity by up-regulating the expression of specific tight junction proteins on damaged epithelium as a result of localised inflammatory responses following pathogen (*pneumococcal*) encounter an invasion.

5.5 *Lactobacillus* against Urogenital Infections *Bacterial vaginosis*

Lactobacilli as dominant members of the human vaginal microbiota play a protective role against urogenital infections [38]. A study by Reid [38], showed that it is the byproducts of lactobacillus metabolism that have an antagonistic effect against urinary and vaginal pathogens. This byproducts produced by specific strains of *lactobacilli* includes H_2O_2 (inhibits both Gram-positive and Gram-negative organisms), lactic acid (possess antimicrobial property and helps in maintaining the pH within 3.5-4.5 thereby not allowing a conducive environment for the growth of the pathogenic microbes), bacteriocins (a ribosomally synthesized antimicrobial peptides and bactericidal molecule which inhibits growth of the pathogen), biosurfactants (which inhibit

adhesion of the pathogen to the vaginal epithelium), and co-aggregation molecules (which blocks the spread of the pathogens) all function to inhibit the pathogen *Gardnerella vaginalis* [39]. Falagas et al. [40] also suggested that oral administration of different strains of *Lactobacilli* or its intra-vaginal administration can increase the numbers of vaginal *lactobacilli*, restore the vaginal microbiota to normal, and cure women of Bacterial vaginosis (BV).

5.6 *Lactobacilli* in the Prevention and Therapeutics of Colorectal Cancer

Lactobacillus is seen to be actively involved in the prevention and therapeutics of colorectal cancer (CRC). Its action against CRC is seen via two mechanisms:

1. By inducing inflammation involving lipoteichoic acid (LTA) (a zwitterionic glycolipid found in the cell wall of several Gram-positive bacterial strains) production which stimulates T cell to release IL10, IL12 and increases effector FOXp3+RORyt- Treg cells. LTA can stimulate DCs through Toll-like receptor 2, resulting in the release of IL-12 and regulatory, inflammatory cytokine IL-10 [35]. However, in 2005, [34], showed that disruption of LTA synthesis resulted in a *L. acidophilus* derivative that acts on intestinal immune cells to augment production of IL-10 in DCs, suppressed IL-12 levels, and significantly lessen the effect of dextran sulfate sodium- and CD4+CD45RB^{high} T cell-mediated colitis in mammals. These alterations of cell surface components of a strain of *Lactobacilli* provide a potential strategy for the treatment of inflammatory intestinal disorders and cancer therapy.
2. Activation of immunity by immune cells against the tumour cells, delay the onset of a tumour or increase the survival rate. Galdeano et al. [41] analysed the profile of cytokines induced by some LAB strains and observed that all *Lactobacilli* strains tested showed an increase in TNF-α, interferon-γ (IFN-γ) and the regulatory cytokine IL-10 resulting to immunomodulatory and antitumor effects by suppressing the proliferation of tumour cells and prolonging survival. The increase in survival was as a result of an increase in cellular immunity as reflected by the enhancement in the total numbers of T cells, NK cells and MHC class II+ cells, and CD4-CD8+ T cells [42].

5.7 *Bifidobacteria*

Bifidobacteria are among the prevalent groups of culturable anaerobic bacteria within the human and animal gastrointestinal tract, and among the first to colonize the human GIT, where they are thought to exert health-promoting actions, such as protective activities against pathogens via production of antimicrobial agents (e.g. bacteriocins) and/or blocking adhesion of pathogens, and modulation of the immune response [43]. Studies have shown the crucial role of the initial intestinal colonisation in the development of the intestinal immune system, and *bifidobacteria* could play a major role in this process [44].

In work done by Odile et al. [44], which sort to understand the effect of *Bifidobacterium* on the immune system, the work was aimed at determining the impact of different strains and species of *Bifidobacterium* on the T-helper 1 (T_H1)/T_H2 balance. They concluded that *Bifidobacterium*'s capacity to stimulate immunity is species-specific, but its influence on the orientation of the immune system is strain specific. They also stated that while some species had little or no effect on immunity some strains were able to induce T_H1 and T_H2 cytokines at the systemic and intestinal levels. Other strain induced a T_H2 orientation with high levels of IL-4 and IL-10, both secreted by splenocytes, and of TGF-β gene expression in the ileum. While some others induced T_H1 orientations with high levels of IFN-γ and TNF-α splenocyte secretions.

Other studies demonstrated the ability of different *Bifidobacterium* strains to activate DCs and to drive the differentiation of naïve T cells. Report by López et al. [45] supported the fact that specific food and commensal bacteria may play a role in balancing the development of Treg and Th17 cell compartments in the intestine through the existence of Treg cells with plasticity to show an effector function, secreting IL-17, or a regulatory action, suppressing activation of the immune system, depending on the environment and the nature of the stimuli [46]. Suppressing the activation of the immune system can clearly be seen when colonisation of the gut by bacteria such as *B. bifidum* LMG13195, favours a Treg polarisation, represents an attractive goal in the

prevention and treatment of inflammatory diseases characterised by an overreaction of the immune system, such as autoimmune diseases, asthma and allergy. Moreover, since Treg cells may be capable of IL-17 secretion under certain conditions, adaptive immune responses against mucosal extracellular pathogens cannot be impaired [45].

6. PRODUCTION OF SHORT-CHAIN FATTY ACIDS

Mammals rely on bacteria to break down indigestible dietary fibres [1]. These fibres are fermented by commensal bacteria into Short-chain fatty acids (SCFA) in the colonic lumen which includes acetate, butyrates and propionate. These short chain fatty acids (SCFA), regulate the size and function of the colonic Treg pool and protect against colitis in mammals Furusawa et al. [47] by binding to their specific G protein-coupled receptor 41, 43 and GPR109A for propionate, acetate and, butyrate respectively [48].

These SCFAs have been shown to be important in the control of allergic airway inflammation. In the study by Trompette et al. [49], they found that mice fed a high-fibre diet had increased circulating levels of SCFAs and were protected against allergic inflammation in the lung, whereas a low-fibre diet decreased levels of SCFAs and increased allergic airway disease. Specifically, increased levels of SCFAs lead to the enhanced generation of dendritic cell precursors and subsequent seeding of the lungs by DCs with high phagocytic capacity, which was accompanied by an impaired ability to promote Th2 cell effector function [49].

7. MICROORGANISMS INVOLVED IN FERMENTATION OF SHORT-CHAIN FATTY ACIDS

7.1 *Clostridium*

Clostridium is a spore-forming rod-shaped Gram-positive obligate anaerobes whose endospores have a distinct bowling pin or bottle shape. They inhabit the intestinal tract of animals, including humans and are also a normal inhabitant of the healthy lower reproductive tract of women [50].

It is of such bacteria capable of fermenting dietary fibres into SCFAs. Studies by Atarashi et al. [51] showed that clostridium species was able to enhance Treg cell which increased the production of IL10 a potent anti-inflammatory molecule. Nicholas and Alexander [52] proved that *Clostridia's* ability to ferment dietary fibres into SCFAs is responsible for the increase in Treg cells.

Despite being involved in roles that are beneficial to their host which includes maximising host utilization of nutrients, induction of host immune responses, and promotion of intestinal cell and mucosal development, evolving data has suggested that disturbances in this symbiotic relationship can result to microflora becoming pathogenic by acquiring virulence factors causing diverse conditions such as inflammatory bowel disease, irritable bowel disease, obesity, graft-versus-host disease, bacterial translocation illnesses, HIV immunopathogenesis, and possibly cancer [53]. Alternatively, bacteria are foreign to the host; though they can live normally as symbionts they can as well induce an immune response against the host cells if they directly encounter mucosal immune cells [2]. To prevent direct exposure of immune cells to the gut microbiota, the bowel wall is coated with a single layer of epithelial cells that provide an effective barrier preventing the uncontrolled access of bacteria to the bowel wall [20] and allowing symbionts to interact with host immune cells only via specific receptors on the IEC. If these protective mechanisms fail, bacteria can penetrate the bowel wall evoking inflammatory immune reactions such as those that occur in patients with inflammatory bowel disease (IBD) [54].

8. CONCLUSION

In conclusion, Gut microbiota has proven to be efficient against pathogen-mediated immune responses in various disease conditions, their ability in immunity can be harnessed to combat diseases of a kind.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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