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Research Article

The Protective Role of Commensal Bacteria in Intestine

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Abstract

Commensal bacteria have co-evolved with the host species to dominant the microbial community in the gastrointestinal tract. Intestinal symbiotic bacteria affect various aspects of host healthy status. Germ-free animals are usually associated with weaker immunity and higher susceptibility to disease. This review briefly summarizes the roles played by commensal bacteria in protecting the host and the mechanisms involved from the host point of view. Overall, these mechanisms can be divided into three actions including maintaining physical intestinal barrier function, stimulating production of host defence components, and modulating cellular immunity.

Keywords: Anti-microbial peptide • Bacteria • Cellular immunity • Immunoglobulin's • Intestinal barrier

Introduction

The relationship between the host and commensal bacteria is the product of long-term and complex coevolution [1]. In this largely symbiotic relationship, the host provides a habitat for different microbial species that in turn benefit host health through various host- microbe interactions. The human gastrointestinal tract is an extensive interface exposed to the environment and colonized by trillions of microbes dominated by bacteria, with more than 1000 bacterial species [2]. Gastrointestinal symbiotics not only serve as a foreign organ by contributing to host nutrition and energy homeostasis, but also assist in the development and maintenance of the host immune system [3]. Perturbation in microbiota has been reported in chronic gastrointestinal, neurologic, and metabolic diseases such as Inflammatory Bowel Disease (IBD), type 2 diabetes, atherosclerosis, allergy, and even colon cancer [4]. Protection of host cells achieved by commensal microbes is an extremely complex process involving many different factors and mechanism, such as competing for nutrients [5], producing microbes-derived anti-microbial properties [6], and regulating the host immune system [7]. This review will focus on the role of commensal bacteria in regulating host immune system, summarising the various mechanisms involved from the host perspective. These mechanisms can be divided into three actions including maintaining physical intestinal barrier function, stimulating production of host defence components, and modulating cellular immunity. Commensal bacteria help maintain host physical barriers through stimulating the production of mucins and tight junctions to protect the host from pathogenic and viral intrusion. Commensal bacteria also stimulate production of host defence molecules like anti-microbial peptides and immunoglobulins that can kill invading pathogens, and finally commensal bacteria can modulate cellular immunity by regulating the number, differentiation, migration, and downstream signaling of immune cells

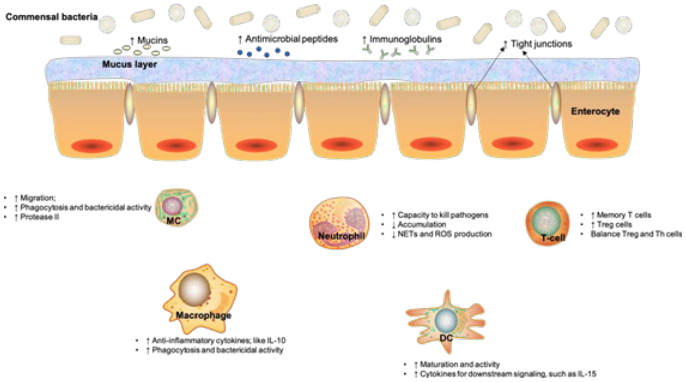

Figure 1. The protective function of intestinal commensal bacteria. MC: Mast cell; DC: Dendritic cells; Treg cells: Regulatory T cells; Th cells: Helper T cells; NETs: Neutrophil Extracellular Traps; ROS: Reactive Oxygen Species. .

Maintain function of physical intestinal barrier

Mucus and Mucin: The mucus layer in the intestine serves as the first line of defence against the environment and prevents the intestinal epithelial layer from direct contact with microorganisms, thereby protecting the intestinal epithelial barrier from pathogenic attack and helping to maintain intestinal homeostasis [8]. Goblet cells secrete hydrated mucin molecules that are crucial components of mucus formation. However, mucins are also substrates for microbes and can be degraded by bacteria such as Helicobacter pylori Helicobacter pylori [9] and Akkermansia muciniphila [10]. Previous studies highlight how one action by commensal bacteria to protect the host involves stimulating mucin synthesis that helps restore mucin levels degraded by pathogenic bacteria. For example, an in vitro study by Mack et al [11], found that Lactobacillus plantarum increased Muc2 and Muc3 mRNA levels in HT29 human goblet-like cells and suppressed adherence and invasion of pathogenic Escherichia coli (E. coli) O157:H7. These findings are in agreement with a more recent study by Mack et al [11] where Lactobacillus strains adhered to HT29 cells, induced Muc3 gene transcription and translation, increased extracellular Muc3 mucin production, and blocked adherence of enteropathogenic E. coli E2348/69. Another study investigating a mixture of probiotic bacterial agents (VSL#3), also reported an increase in Muc2, Muc3, and Muc5AC mucin gene expression and secretion in HT29 cells [12].

The exact mechanisms involved in protection of the host physical intestinal barrier by commensal bacteria remain unknown, however the mechanisms appear to depend on the ability of commensal bacteria to adhere to the mucus layer, facilitate interactions with host cells, and stimulate mucin production [13]. Probiotic bacteria may also compete for binding sites with pathogenic microbes essentially limiting the binding of invading pathogens to the mucus layer. However, it has also been proposed that mucin secretion induced by commensal bacteria is not dependent on adhesion but facilitated by molecules secreted by bacteria. For instance, findings from an in vitro study showed that VSL#3 bacterial conditioned media stimulated secretion of mucin more than the VSL#3 bacteria [14]. In another study, Lactobacillus acidophilus A4 cell extracts significantly increased Muc2 expression in HT29 cells [15]. Ulcerative colitis patients present with decreased thickness of the mucus layer, particularly in the active inflammation sites [16]. Hence, understanding the mechanisms involved in protection of intestinal

barrier integrity by commensal bacteria will aid in the development of clinical treatment to restore and improve gut barrier function in patients.

Tight junction: Tight Junctions (TJ) modulate intestinal barrier integrity and are essential for intercellular adhesion. TJ mainly comprised of transmembrane proteins, such as occludin and claudin, adaptor proteins, such as Zonula Occludens 1 (ZO-1), regulatory proteins, and transcriptional and post-transcriptional regulators [17]. These TJ proteins work together to maintain intestinal barrier integrity, prevent entry of pathogens, regulate passive transport of molecules, and limit free exchange of apical and basolateral components across membranes [18]. Paracellular permeability and Transepithelial Electrical Resistance (TER) are indicators of intestinal integrity and barrier function. Many factors, including cytokines, chemicals, pathogens, and stress, can compromise the intestinal barrier by decreasing TER and increasing paracellular permeability that can allow pathogen invasion and infection. Changes in TJ composition and structure are usually associated with IBD and can impact TJ function. For example, increased gut permeability is characteristic of inflammatory bowel diseases and is present in patients with Crohn's disease before clinical relapse [19]. Loss of ZO-1 and increased intestinal permeability was reported in mice treated with Dextran Sulfate Sodium (DSS) prior to exhibiting intestinal inflammation.

In animal studies involving a DSS induced mouse model of colitis, reduced levels of TJ protein, enhanced epithelial injury, and higher mortality were observed in germ-free mice compared to control mice with normal microbiota [20]. Interestingly, transplanting human faecal commensal microbiota into germ-free mice restored intestinal barrier structure and function to normal levels, and also reduced susceptibility to intestinal injury [21]. In more precise studies, treatment with commensal bacteria have been investigated to help maintain intestinal barrier integrity by regulating production of TJ proteins [22,23]. Several in vitro studies have also confirmed in vivo findings, for example Lactobacillus casei modulated ZO-1 expression, restored reduced TER, and increased epithelial permeability induced by cytokines in a Caco-2 cell model [15]. Another study by Resta-Lenert and Barrett [24] demonstrated that both live Streptococcus thermophilus and Lactobacillus acidophilus induced occluding and ZO-1 expression, increased TER, and decreased permeability of human intestinal epithelial cell lines, thus protecting intestinal epithelial cells from the infection of enteroinvasive E. coli, compared with controls containing culture media and inactive bacteria.

Stimulate defence components production

Antimicrobial peptides: Defensins and cathelicidins are two major families of antimicrobial peptides secreted by innate leukocytes, like macrophages and epithelial cells, or stored in intracellular compartments, like neutrophil granules and Paneth cells [25]. Defensins and cathelicidin are cationic peptides that play important roles in the host defence system by directly killing invading pathogens, or by modulating innate and adaptive immune responses, including chemokine production and pro-inflammatory cytokine production [25]. Deficiencies in antimicrobial peptides, like defensins, contribute to IBD development and are associated with a higher risk of pathogen invasion [26,27]. Activation of microorganism-sense Pattern Recognised Receptors (PRRs) like Toll- Like Receptors (TLRs), can trigger synthesis of antimicrobial peptides through signalling pathways such as Nuclear Factor Kappa B (NF-kB) and Mitogen-Activated Protein Kinases (MAPKs) [28]. In a Caco-2 cell model, E. coli [29] (EcN) and Lactobacillus plantarum stimulated secretion of human β-Defensin 2 (hBD-2) and increased expression of TLRs [30,31]. These host responses to bacteria have also been investigated clinically. For instance, a clinical trial showed that faecal levels of hBD-2 protein significantly increased in healthy participants administered Symbioflor 2 (a mixture of several commensal E. coli strains) twice daily for three weeks, compared to the control group who received placebo treatments and did not exhibit any changes in hBD-2 protein levels [32].

Immunoglobulin: Immunoglobulin A (IgA) is the dominant non-inflammatory antibody in mucosal surfaces and can be distinguished as serum IgA and Secretory IgA (SIgA) [33]. IgA translocates to the surface of epithelial cells where it binds to a Polymeric Ig Receptor (pIgR) before being secreted as SIgA. The pIgR receptor is expressed on the basolateral surface of epithelial cells and functions as an antibody transporter [34].

Release of SIgA protects the intestinal epithelial barrier from microbial pathogens and antigens through various mechanisms. For example, SIgA prevents pathogens and antigens from adhering to intestinal epithelial cells by forming hydrophilic shells repelled by epithelial-glycocalyx. SIgA can also bind receptors expressed on immune cells to activate antimicrobial activity, anti- or pro-inflammatory responses, or immune exclusion. Furthermore, SIgA plays a crucial role in preventing invasion and infection, and maintaining intestinal microbiota homeostasis by directly binding and neutralizing virulence factors [35]. IgA was shown to present lower level in germ-free animals but were rapidly restored by microbial colonization [36]. Mice pre-treated with Bifidobacterium also showed four-fold higher levels of rotavirus-specific IgA in serum, compared with control mice 28 and 42 days after rotavirus inoculation [37]. The importance of commensal bacteria and IgA was also highlighted by another study where Lactobacillus casei increased anti-Shiga toxin IgA antibodies in a rabbit model of Shiga toxin-producing E. coli infection and reduced morbidity [38].

Immunoglobulin G (IgG), another abundant and important immunoglobulin in mucosal immunity, helps to protect the mucosa from pathogens and maintains mucosal homeostasis [39]. The impact of bacteria on IgG has been explored less than IgA, however a study by Ansaldo reported upregulation of B cell-generated IgG through CD4+ T cells in mice in response to Akkermansia muciniphila [40].

Regulate immune cells and cell-mediated immunity

Mast cells: Mast Cells (MCs) play an important role in allergic reactions, and also participate in inflammatory processes, tissue repair, and angiogenesis [41]. Mast cells are very early and rapid responders to viruses, toxins, and other pathogens by detecting and recognising detrimental signals through cell-surface PRRs [42]. Evolution has equipped MCs with various responses to resistant invading pathogens including secretion of bioactive mediators, such as protease, cytokines, and chemokines, formation of MC-extracellular traps, and phagocytosis [43,44]. In a study by Kunii et al, intestinal commensal bacteria promoted migration of MCs from the blood to the intestine [45]. In another study, reduced levels of mucosal MCs, and protease II produced by MCs, were measured in intestinal lymph from rats treated with antibiotics [46]. However, even though activation of MCs inhibit pathogens, it also contributes to intestinal barrier dysfunction [47]. Notably, Lactobacillus casei [48] reversed MC activation and inhibited other MC mediators induced by enterotoxigenic E. coli K88, thus maintaining integrity of the intestinal barrier [48].

Macrophages: Macrophages (MPs) act as scavengers and maintain intestinal homeostasis through phagocytosis of microbes and apoptotic cells. In addition to phagocytosis, MPs also secrete cytokines and chemokines to regulate downstream signalling and play a role in initiating adaptive immunity, like presenting antigens to T cells. Macrophages can be characterized into two types, Macrophages 1 (M1) and 2 (M2). The first type, M1, are involved in inflammation and express pro-inflammatory cytokines, like Tumour Necrosis Factor-α (TNF-α) and Interleukin-6 (IL-6), in response to pathogens. The second type, M2, produce anti- inflammatory cytokines, like Interleukin-10 (IL-10), and promote tissue repair and growth [49]. Activation of MPs is essential for defence against invading pathogens and for removal of pathogens. The role of commensal bacteria in modulating MPs has been well studied. For

example, decreased numbers of MPs were observed in the colon of germ-free mice, while pre-treatment of MPs with Lactobacillus increased phagocytosis and bactericidal activity against pathogens such as S. aureus, S. typhimurium, and E. coli. Bacteria can also modulate production of cytokines by MPs, as evidenced by a study where a single strain of Clostridium butyricum stimulated production of IL-10 by intestinal MPs in inflamed mucosa alleviating experimental colitis in mice [50].

Neutrophils: Neutrophils are produced in Bone Marrow (BM) and are the most abundant leukocytes in blood. These immune cells are attracted to various chemical signals and are among the first responders to migrate towards inflammatory sites. Similar to MCs, neutrophils protect the host through phagocytosis and release of cytokines, however neutrophils also release granular proteins, Reactive Oxygen Species (ROS), and Neutrophil Extracellular Traps (NETs) [51]. Neutrophils isolated from antibiotic-treated and germ-free mice displayed a significantly reduced capacity to kill pathogens, compared to neutrophils from control mice [52]. The activation of neutrophils is essential for killing invading pathogens, however excessive immune response by neutrophils can promote tissue damage. The commensal bacteria Bifidobacterium longum 51A has been shown to alleviate the inflammatory response and decrease neutrophil recruitment and accumulation in an experimental gout murine model [53]. Another study proposed that probiotic Lactobacillus rhamnosus GG inhibited formation of NETs induced by chemicals and Staphylococcus aureus, consequently reducing ROS production and preventing destruction of surrounding cells [54]. Different neutrophil responses to probiotic bacteria have been reported by several studies [55-57]. The precise pathway and response to bacteria, however, still need more investigations. Subsequently, further studies are needed to better understand the mechanisms and signalling pathways involved in neutrophil responses to bacteria.

Dendritic cells: Dendritic Cells (DCs), also known as antigen presenting cells, are in constant communication with other cells by direct cell-cell contact mediated through cell-surface proteins, or via distant interactions involving cytokines. Immature DCs exhibit high endocytic activity but limited capacity to activate T cells when compared to mature DCs. However, once activated by contact with an antigen, immature DCs mature and migrate to lymph nodes where they present antigens to T cells and antibody-producing B cells. Importantly, antigen presentation induces the adaptive immune response, thus mature DCs serve as messengers between innate and adaptive immunity. A studied showed that treatment with Bifidobacterium animalis ssp. lactis 5764 efficiently induced maturation of DCs from bone marrow that was accompanied by an improvement in acute intestinal inflammation [58]. Plasmacytoid DCs (pDCs) are a subset of DCs and play an important role in viral resistance. The administration of I strain plasma showed the capacity to improve the decrease in pDC activity caused by heat stress in a mice model [59]. Notably, commensal bacteria sometimes do not only have an impact on DCs themselves but influence other downstream innate immune cells. Natural Killer (NK) cells are a type of cytotoxic lymphocytes. In a study involving germ-free mice, NK cells exhibit reduced antiviral activity associated with compromised antiviral immunity due to failure of DCs to release cytokines, such as IL-15 required for NK cell priming [60].

T cells: T cell responses are initiated by Antigen-Presenting Cells (APCs) such as macrophages and dendritic cells. Once activated, T cells develop into memory T cells and several distinct types of effector T cells including Helper T (Th) cells, Regulatory T (Treg) cells, and cytotoxic T cells. In addition to the ability of upregulating memory T cells by oral administration of Bacillus subtilis [61], several studies have shown that commensal bacteria are also involved in regulating immunity mediated by Treg cells. Treg cells play a crucial role in immune tolerance and prompting termination of the immune response to avoid autoimmunity and excessive damage to the body that can be caused by this physiological state [62]. Treatment with Bifidobacterium infantis increased the number of Treg cells, and alleviated intestinal damage caused by Salmonella infection [63]. Moreover, treatment with Bacillus fragilis induced Treg cells to secrete IL-10, thus protecting the host from damage caused by Helicobacter hepaticus infection [64]. In contrast to Treg cells which suppress immune response, Th cells differentiate into several subtypes with different roles to stimulate immune responses by other immune cells. However, the excessive activation of Th can contribute to autoimmunity and inflammation [65]. Hence, the balance between Th cells and Treg cells are crucial in maintain immune homeostasis [66]. Certain Lactobacillus species, for example, Lactobacillus acidophilus [67] and Lactobacillus casei [68] balance Treg and Th17 cell populations and stimulate expression of cytokines leading to reduced intestinal inflammation and 1,2-Dimethylhydrazine (DMH)-induced colorectal cancer. Another study showed that Bifidobacterium Infantis effectively attenuated chemotherapy-induced intestinal mucositis by decreasing Th1 and Th17 response, and by increasing CD4+ CD25+ Foxp3+ Tregs response [69-71].

Conclusion

This review briefly summarised the protective roles commensal bacteria play in regulating and maintaining the host immune system. Interactions between bacteria and the host not only enhance host defence system, but also regulate cellular immune response. Understanding how commensal bacteria benefit the host can provide insights into treatments targeting various diseases. The roles commensal bacteria play in host protection have been extensively studied; however the precise mechanisms, mediators, and pathways involved are still unclear. Short chain fatty acids, the main products of bacterial fermentation of undigested dietary fibre in the intestine, have been a major focus in this field of research reported by many studies as protective mediators. In addition, bacterial cell wall components, like peptidoglycan and lipopolysaccharide, have also been identified by host cell-surface PRRs in the induction of immune responses. Moreover, both Gram-negative and Gram-positive bacteria can produce membrane vesicles that contain many bioactive components that modulate the host immune system. The precise roles of these mediators and the mechanism involved require further investigation.

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